Erasmus Universiteit Rotterdam

# Handling uncertainty: a plea to systematically assess the real-world cost-effectiveness of expensive outpatient medicines

## Cost-effectiveness review and critical evidence appraisal for pharmaceutical products potentially benefitting most from unrevised reimbursement in the Netherlands

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# Dedication

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# Abstract

**Objective:** Outpatient medications with high expenditures are not structurally monitored on their real-world cost-effectiveness at a post-reimbursement moment in the Netherlands. Concurrently, an increased uncertainty is observed on key reimbursement criteria at the time of decision making. Aim of the study was to investigate the feasibility and desirability of a periodic re-assessment procedure for reimbursed expensive outpatient medicines in the Netherlands.

**Methods:** Imatinib, pegfilgrastim, and adalimumab were analysed as case studies once at the time of reimbursement decision making (labelled t=0) and once at present in 2011 (t=1). For t=0, grey literature was obtained from the website of the Dutch reimbursement agency. For t=1, a systematic literature review of economic evaluation studies was performed in the databases of MEDLINE via PubMed; the Cochrane Library; the Centre for Reviews and Dissemination, including the NHS Economic Evaluation Database; and the Cost-Effectiveness Analysis Register (www.cearegistry.com) from inception to May 2011. Bibliographies of related articles were assessed and the three marketing authorisation holders contacted directly to identify additional (un-)published studies. Based on the Dutch pharmacoeconomic guidelines, a data-collection form was compiled. Numerical scores were assigned to individual studies on their relevance and quality for the Dutch setting. Incremental cost-effectiveness ratios were converted and inflated to 2010 Euros (€), the base year of costs in this study.

**Results:** At t=0, uncertainty prevailed for the criteria effectiveness and quality of life in 5 of the 8 reimbursement advices available. In the extreme, the absence of appropriate data rendered the assessment of a reimbursement criterion impossible. Concurrently, economic considerations played no visible role in the final reimbursement decision. At t=1, 49 full economic evaluation studies qualified for inclusion and appraisal. The amount and timeliness of studies suggest that a re-assessment of drugs after ≤4 years would be very possible. They were of fair relevance to be considered for the Dutch setting. Reimbursement seemed, ceteris paribus, cost-effective in all officially assessed indications. Use in other (unregistered) conditions or therapy lines were more often regarded as cost-ineffective. Four indications in imatinib had neither reimbursement advice nor published economic evaluations.

**Discussion:** Today's dichotomous reimbursement system is insufficient to meet the changed needs of decision making under uncertainty. The cost-effectiveness review of international economic evaluations was based on second-best data with validity concerns. Publication and funding biases cannot be excluded. Using international studies with heterogeneous designs, methods, resource utilisation, and costs bears inherent limitations. Outcomes can merely suggest improvements without optimising healthcare resource allocation for the Netherlands. A formalised re-assessment procedure for expensive outpatient medicines with real-life cost-effectiveness data seems desirable. The national reimbursement authority should demand outcomes research from manufacturers for all reimbursed expensive medications. Considerations to be taken into account include, inter alia, a transparent process, clearly defined criteria and definitions, stakeholder involvement, and political will to enforce the possible consequences of a review, which consist of continuous or conditional reimbursement, drug price alterations, or delisting.

**Keywords**: cost-effectiveness; decision making; uncertainty; systematic review

# Contents

# List of abbreviations

**AED**: access with evidence development
**ALL**: acute lymphoblastic leukaemia
**AS**: ankylosing spondylitis (Bechterew's disease)
**ATC**: Anatomical Therapeutic Chemical classification system
**AWBZ**: Exceptional Medical Expenses Act [*Algemene Wet Bijzondere Ziektekosten*]
**BI**: budget-impact
**CBA**: cost-benefit analysis
**CBG**: Medicines Evaluation Board [*College ter beoordeling van geneesmiddelen*]
**CD**: Crohn's disease
**CEA**: cost-effectiveness analysis
**CED**: coverage with evidence development
**CFH**: Medicinal Products Reimbursement Committee [*Commissie Farmaceutische Hulp*]
**CMA**: cost-minimization analysis
**CML**: chronic myeloid leukaemia
**CUA**: cost-utility analysis
**CVZ**: Health Care Insurance Board [*College voor zorgverzekeringen*]
**DDD**: defined daily dose
**DFSP**: dermatofibrosarcoma protuberans
**DMARD**: disease-modifying antirheumatic drug
**EE**: economic evaluation
**EMA**: European Medicines Agency
**EPAR**: European Public Assessment Report
**EQ-5D**: EuroQol – 5 Dimensions
**FK**: Dutch National Drug Formulary [*Farmacotherapeutisch Kompas*]
**FN**: febrile neutropenia
**G-CSF**: Granulocyte colony-stimulating factor
**GIPdatabank**: Database of costs and utilisation for outpatient drugs in the Netherlands
**GIST**: gastrointestinal stromal tumours
**GVS**: Medicines Reimbursement System [*Geneesmiddelenvergoedingssysteem*]
**HES&CEL**: advanced hypereosinephilic syndrome or chronic eosinophilic leukaemia
**HICP**: Harmonised Indices of Consumer Prices
**ICER**: incremental cost-effectiveness ratio
**JIA**: juvenile idiopathic arthritis
**List 1A**: mutually interchangeable outpatient medicines clustered in the GVS
**List 1B**: not mutually interchangeable outpatient medicines in the GVS
**List 2**: outpatient medicines in the GVS (both Lists 1A and 1B) whose reimbursement depends on pre-set conditions
**LYG**: life-years gained
**MDS/MPD**: myelodysplastic myeloproliferative diseases
**MED/HE**: medical or health economics journal
**MoH**: Minister of Health [*Minister van Volksgezondheid, Welzijn en Sport*]
**MTX**: methotrexate
**N/A**: not applicable
**na**: not available
**NICE**: National Institute for Health and Clinical Excellence
**NL-TQS**: Netherlands Total Quality Score
**NSAID**: non-steroidal anti-inflammatory drug
**NWO**: The Netherlands Organisation for Scientific Research [*Nederlandse Organisatie voor Wetenschappelijk Onderzoek*]
**NZa:** Dutch Healthcare Authority [*Nederlandse Zorgautoriteit*]
**PASI**: Psoriasis Area and Severity Index
**PP**: plaque psoriasis
**PsA**: psoriatic arthritis
**QALY**: quality-adjusted life year
**QoL**: quality of life
**RA**: rheumatoid arthritis
**RVZ**: Council for Public Health and Health Care [*Raad voor de Volksgezondheid en Zorg*]
**Rzv**: Health Insurance Regulation [*Regeling zorgverzekering*]
**Stcrt**: *Staatscourant* (official State Journal)
**T=0:** time of reimbursement decision making
**T=1:** time of the present (2011)
**TNF**: tumor necrosis factor
**UC**: ulcerative colitis
**ZonMw**: The Netherlands Organisation for Health Research and Development [*Zorgonderzoek Nederland Medische Wetenschappen*]
**Zvw**: Health Insurance Act [*Zorgverzekeringswet*]

All abbreviations used in this thesis have been listed here unless it can reasonably be assumed that they are well known (like e.g., mathematical operators; currencies; countries), or they have been used only once in a table or appendix, in which case the abbreviation is defined in the comments at the end of the table or figure.

Abbreviations translated from Dutch regarding reimbursement were taken from the English version of the official CVZ website (http://www.cvz.nl/en/) and recent CVZ documents published in English.

# Chapter 1

## Introduction

Reimbursement applications of new pharmaceutical innovations are increasingly characterised by uncertainty at the moment of decision making regarding (long-term) effectiveness, cost-effectiveness and budget-impact. This uncertainty maintains in the Netherlands during the life-cycle of the majority of medicines, which is controversial for at least expensive outpatient medications. They are not (yet) structurally monitored or re-assessed on their real-life cost-effectiveness at a post-reimbursement moment (Steenhoek and Koopmanschap 2010:1711).

In May 2011, the Dutch Minister of Health[1] Schippers proposed her ideas to temporarily include new innovative medications in the publicly funded benefit package to the House of Representatives of The Netherlands (*Tweede Kamer der Staten-Generaal*). Final inclusion in the reimbursement system would be conditional on the obligation to assess the real-life cost-effectiveness of the medication after a certain period of time (Minister of Health, Welfare and Sport 2011).

Rationale for this proposal forms the tension reimbursement decisions face in light of the applications of new innovations for serious and severe diseases, but accompanied with high costs and an uncertain therapeutic added value. This may lead to a time-consuming decision making process, which cannot be in the interest of the patients and marketing authorisation holders. Her proposed changes to the reimbursement system would be able to offer more legal instruments (like e.g. price-volume agreements) in improving cost containment while safeguarding the access to new innovations in a reasonable manner (which get the possibility to demonstrate their added value).

This tension corresponds directly with issues perceived by the Dutch reimbursement advisory body *College van Zorgverzekeringen* (Health Care Insurance Board, CVZ), which communicated in one of its reports in collaboration with the Netherlands Organisation for Health Research and Development (*Zorgonderzoek Nederland Medische Wetenschappen*, ZonMw) the difficulty of finding the golden way in the course of controlling (by critically testing new innovations) and accessibility (by facilitating the access to new and promising innovations) (ZonMw and CVZ 2007:18).

The root of the problem the Minister tries to tackle is the limitation of today's dichotomous 'yes or no' reimbursement system. The current system implicitly assumes that enough knowledge is available on the relative therapeutic value (read: effectiveness) at the time of decision making, and that enough knowledge is available about the costs and benefits of new drugs in comparison to existing alternatives. The Minister realised that this is more often not the case as new innovative drugs (or the conditions they are indicated for) tend to be very complex or aim at very small patient populations. Accordingly, sufficient information is often absent at the time of decision making.

Today's two-tiered system bears the risk that a reimbursed medicine could show an insufficient added value at a later point; with the costs created so far leading to increased insurance premiums and, in the worst scenario, a medicine assumed effective could turn out to be malicious.[2] Contrary, a medication

1 For clarification: the Dutch Minister of Health is known in other jurisdictions as Secretary of Health. The Ministry of Health is equivalent to the Department of Health; it forms part of the government and is responsible for matters related to health, welfare and sports in the Netherlands.

2 This scenario became already reality a few times in the past. Painful historical reminders for the necessity of deliberate registration and reimbursement procedures form the examples of thalidomide (Contergan®/ Softenon®) in the 1960s, and more recently refocoxib (Vioxx®) and benfluorex (Mediator®) in the 2000s.

could be denied reimbursement given the lack of sufficient information but would later prove its added value and was unjustifiably withheld from patients.

Under the new system, these drugs may be included under strict conditions and on a temporary basis. In other words: the Minister wants to enhance the current reimbursement system with a third option: "yes, if". By re-assessing innovations after provisional reimbursement (e.g. care that is currently either included with the benefit of the doubt or denied in light of insurmountable concerns), a reasonable benefit package management would be substantiated (CVZ 2009a:2,9; Leer et al. 1999:87).

## 1.1 Historical context

In the Netherlands, the idea of temporarily including (expensive) pharmaceuticals to the benefit package is not new. In 1997, the predecessor of the CVZ (the *Ziekenfondsraad*, Dutch for: Health Insurance Council) suggested to establish a third list in the Dutch medicines reimbursement system (GVS) – List 1C – intended for new expensive outpatients medications with uncertainty on the effectiveness that would be temporarily reimbursed (ZFR 1997:16,28).[3] The idea was back then rejected based on concerns of societal unrest from uplifting the reimbursement status of an already included medicine; that the temporary admission would only mean to postpone the final decision; the additionally required financial resources; and that the evaluation of the therapeutic value would require a controlled setting, which may lead to delays in the availability to all patients (ZFR 1999:9).

Since 2002, expensive inpatient medications were included on a list featuring medications that qualify for national subsidies to hospitals so as to help finance that care and ensuring patients' access (Steenhoek and Koopmanschap 2010:1709): the NZa (*Nederlandse Zorgautoriteit*, Dutch Healthcare Authority) policy guidelines 'Expensive drugs' and 'Orphan drugs' (CVZ s.d.; CVZ 2008a). In 2006, this regulation was amended with the condition that new expensive intramural pharmaceutical innovations would be re-assessed on their real-life cost-effectiveness and appropriate use four years after their temporary uptake. Outcomes research forms the basis for this obligation. The list features today about 46 drugs with the first three being delisted recently in July 2011 due to the absence of the required dossier and anticipated lower costs than expected (NZa 2011). The three delisted drugs are still reimbursed but paid from the budget of the hospitals (and thus without national subsidies). Albeit the cessation of the policy guidelines is planned for the end of 2011, the temporary aspect under the condition of conducting outcomes research will be preserved. Per 01 January 2012, all existing and new expensive inpatient drugs will be designated for temporary inclusion by ministerial order.

Following the implementation of this system, a broader awareness for temporary inclusion and re-assessing pharmaceutical innovations was raised in academic and political circles.

Uyl-de Groot and Giaconne recommended to perform outcomes research for expensive drugs or perhaps all new drugs while being temporarily reimbursed in 2005 (Uyl-de Groot and Giaconne 2005:396). In 2007, Koopmanschap and Steenhoek anticipated a rising policy interest in expensive outpatient medicines when the NZa policy guidelines were amended with the obligation for outcomes research (Koopmanschap and Steenhoek 2007:21). In 2009, Poley, Stolk and Brouwer also advocated for the temporary inclusion of (expensive) new outpatient medicines and predicted the introduction of such a system in the near future (Poley et al. 2009:8). In 2010, Steenhoek and Koopmanschap raised

3 List 1B of the positive list includes in essence drugs with a therapeutic added value and no similar alternative, which qualify for a higher (premium) pricing. This in contrast to List 1A that clusters mutually interchangeable drugs by means of reference pricing. For more details on the Dutch reimbursement system, see e.g. Oostenbruggen et al. 2005; Schut and Van de Ven 2005; and Schaefer et al. 2010.

once more attention for the continuing absence of a structured re-assessment of cost-effectiveness for expensive outpatient pharmaceuticals (Steenhoek and Koopmanschap 2010).

Today's Minister of Health proposed in January 2007 a parliamentary motion to the then governing parties that requested to propose a regulation on the temporary inclusion of promising innovations in the benefit package under the condition that during a certain time period, the therapeutic added value and cost-effectiveness would be demonstrated (Tweede Kamer der Staten-Generaal 2007). The background of that motion formed indications of difficulties for new promising innovations to find the way into the benefit package. Then-Minister Klink commissioned the CVZ and ZonMw to research whether such a regulation would be possible and to come up with a joint-solution, which resulted in the foundation of an innovation desk (since June 2011 accessible via www.zorgvoorinnoveren.nl) run by the CVZ; ZonMw; and NZa that, respectively, advice over care (whether or not covered); stimulate and fund research; and applies policy guidelines for funding health care (CVZ 2007; 2009a:13).

The same report also commented on the current possibility for temporary reimbursement in cases of compassionate use. The Minister of Health was observed as making only limited use of this type of funding due to, inter alia, the past experience of pseudo-claims; the political sensitivity to decisions of terminating funding; and the possible health damage for patients previously being treated who cannot afford the costs themselves or receive reimbursement by a third party (CVZ 2007:14).

In December 2009, the CVZ issued another report on provisionally reimbursing new innovative care. It inventoried the existing public and private opportunities for funding and demonstrated that all except the policy guidelines for expensive medications were not connected to the obligation of gathering additional information on the (long-term) effectiveness and safety of new interventions (CVZ 2009a:19). It also acknowledged international developments in a variety of countries, among which the UK, Germany, the USA, Canada, Spain, Australia, Sweden and France. Although given different names (of which 'access [or coverage] with evidence development' (AED/CED) the most prominent), in all jurisdictions are the same interventions (mostly drugs) subject to the investigation (CVZ 2009a:21). A strengthened international collaboration was the logical conclusion for the future.

## 1.2 Units of analysis

The Minister of Health specified two undesired scenarios: the wrongful reimbursement of inefficient care, and the wrongfully exclusion of care with added value. She made clear that her focus will rest on preventing the possible exclusion of new, innovative innovations that seem most promising to her in achieving the highest gain for patients in terms of high quality; low costs; and fast access to new interventions (Minister of Health, Welfare and Sport 2011).

Also, the CVZ documented in its report from 2009 on provisional reimbursement that the priority should be given to new innovative care, owing to the inherent uncertainty of innovations regarding (long-term) effectiveness and safety, and care with uncertainty on its (cost-)effectiveness (CVZ 2009a:9,22). In addition, conditional reimbursement could be considered as standard practice for expensive medications to tackle off-label use (CVZ 2009a:22).

Based on these two observations, a selection for medications was made for this study. First, it seems interesting to investigate potentially inefficient, yet reimbursed medications given the lower attention by the Minister. Second, it seems appealing to focus on drugs with high uncertainty on their (cost-)effectiveness, which should be fulfilled for most expensive medications as pharmacoeconomic evidence is only mandatory for outpatient medicines applying for inclusion on List 1B of the GVS since 2005.

Pharmaceuticals with high expenditures may be able to fuel the rising healthcare expenditures that force cost containing action, while the opportunity costs of funding expensive treatments may translate into health foregone for other patients (Eichler et al. 2004:521). Combined with the inevitable scarcity of resources, allocative choices have to be made among a competing set of health care technologies. Whilst expensive inpatient drugs are already subject to a systematic re-assessment procedure, expensive outpatient medicines are not.

In the Netherlands, outpatient pharmaceutical medicines have no formal definition for being considered expensive (a fact speaking for itself!). Researchers from the institute of Health Policy & Management in Rotterdam suggested adapting the definition of expensive inpatient medicines for their outpatient counterparts (Steenhoek and Koopmanschap 2010:1711). Inpatient drugs are defined as expensive in case they fulfil two criteria:

1.) their costs per day are at least ten times higher than the average costs of drugs per day;

2.) their total costs must be at least 0.5% of the total costs of all medicines (CTG, 2002).

Based on this definition, the CVZ provided an unpublished spreadsheet identifying 25 outpatient medicines as expensive for the Netherlands for the period 1989 to 2010 (based on GIPdatabank.nl).

In 2010, 18 drugs fulfilled the criteria of above mentioned definition for expensive (see *Table 1*). Their forecasted total expenditure amounts to about €770 million. Therapeutics with the Anatomical Therapeutic Chemical (ATC) Classification code 'L' (i.e., antineoplastic and immunomodulating agents) were most prevalent (9/18) and accounted in total for more than half of all reimbursement costs of expensive drugs in 2010 (66.7% with €516 million). The total amount of users was 163,000 for all 18 drugs, with 68,000 accounting for drugs of ATC-code L (i.e. 42%). In total, all expensive outpatient medicines amount to almost one-fourth of total pharmaceutical expenditures in 2010 (22%).

For the study presented here, it seems desirable to make a selection among these drugs. It seems appealing to select medicines with a high expenditure as the potential to benefit from an unrevised reimbursement would likely be the highest (or an indicator for benefitting in the past). At the same time, the likelihood for a large amount of economic evaluations is high given the anticipated trade-off for pharmaceutical companies to either lower their prices or invest in evaluation research to justify a value based pricing (Claxton et al. 2011). For these reasons, adalimumab (Humira®, reimbursement volume €170 million) as the most expensive outpatient medication is chosen, next to pegfilgrastim (Neulasta®, €41 million) and imatinib (Glivec®, €36 million) as fifth and sixth most expensive in 2010.

All three cases belong to the group of antineoplastic and immunomodulating agents (i.e., ATC-code L) and might therefore not be representative for the entire group of expensive medications. It can be argued that an analysis based on the ATC-code improves the external validity of the research as the costs of medicines differ greatly between different ATC groups (Light and Warburton 2011:37). However, the aim of this study is to demonstrate exemplary the feasibility of a re-assessment procedure. Neither the classification of a drug, nor underlying properties like the amount of users; defined daily doses (DDDs); or indications should prohibit a priori the decision of whether or not to re-assess an expensive medicine with uncertainty in essential reimbursement criteria.

**Table 1**: Outpatient drugs fulfilling expensive inpatient definition in 2010 (forecasts of reimbursed costs from unpublished CVZ spreadsheet)

| Medicine (generic name) | ATC-code | Total costs (1=€1 million) | Costs/DDD (1=€1) | Users |
|---|---|---|---|---|
| *Reference 2010 (threshold values)* | - | *17.92* | *4.87* | - |
| erythropoietin | B03XA01 (antianemic preparation) | 24.4 | 10.95 | 10,215 |
| darbepoetin alfa | B03XA02 (antianemic preparation) | 33.1 | 10.33 | 12,499 |
| bosentan | C02KX01 (antihypertensive) | 21.0 | 121.64 | 639 |
| somatropin | H01AC01 (hormone) | 51.5 | 31.36 | 4,423 |
| octreotide | H01CB02 (antigrowth hormone) | 20.6 | 44.88 | 1,977 |
| tenofovir disoproxil & emtricitabine | J05AR03 (HIV antiviral combination) | 25.6 | 19.47 | 4,958 |
| emtricitabine, tenofovir disoproxil, efavirenz | J05AR06 (HIV antiviral combination) | 31.5 | 31.58 | 3,422 |
| immunoglobulins, normal human, intravascular | J06BA02 (antiinfective) | 22.0 | 375.82 | 1,174 |
| imatinib | L01XE01 (antineoplastic) | 35.9 | 88.02 | 1,288 |
| leuprorelin | L02AE02 (hormone) | 18.9 | 5.33 | 13,036 |
| goserelin | L02AE03 (hormone) | 23.4 | 6.61 | 13,856 |
| pegfilgrastim | L03AA13 (immunostimulant) | 41.0 | 80.18 | 6,732 |
| interferon beta-1A | L03AB07 (immunostimulant) | 41.3 | 20.18 | 2,959 |
| etanercept | L04AB01 (immunosuppressant) | 143.7 | 40.32 | 12,162 |
| adalimumab | L04AB04 (immunosuppressant) | 169.8 | 43.39 | 12,453 |
| tacrolimus | L04AD02 (immunosuppressant) | 21.0 | 13.36 | 5,143 |
| lenalidomide | L04AX04 (immunosuppressant) | 20.7 | 179.73 | 662 |
| quetiapine | N05AH04 (antipsychotic) | 27.4 | 4.83 | 55,465 |
| Total | - | 772.9 | 1,128 | 163,063 |

Medicine names and ATC-codes obtained from ATC/DDD Index 2011 of the World Health Organization (WHO), accessed via http://www.whocc.no/atc_ddd_index/

## 1.3 Objective of the study

This study concentrates on the uncertainty of reimbursement at the time that decisions are made and performs a re-assessment that aims for the reduction. The purpose of this study is to investigate whether a systematic review procedure for expensive outpatient drugs after a given period of time would be feasible and desirable.

## 1.4 Research questions

Q1: *How certain is the evidence for clinical and cost-effectiveness among selected outpatient drugs at the time a positive reimbursement decision was made?*

Q2: *How certain is the evidence for cost-effectiveness among selected outpatient drugs at present (May 2011)?*

Q2.1: *(How) did cost-effectiveness evidence develop over time?*

Q2.2: *How well do economic evaluation studies comply with essential criteria proposed in this thesis as NL-TQS (based on, inter alia, the Dutch guidelines for pharmacoeconomic research and the criteria of Drummond)?*

Q3: *Is the positive reimbursement decision in light of the new evidence still legitimate?*

Q4: *How would a review tend to change the decision?*

Q5: *Under which conditions is it feasible and desirable to implement a review procedure?*

## 1.5 Frame of reference

To enable decision makers in taking sound action, they need to be informed about the difference in value-for-money a set of alternatives can generate. This information supports the best allocation of money in the interest of the public, if decisions are made with a honest motivation and based on an explicit, substantiated framework.

Economic evaluation studies are increasingly seen as a capable and reliable tool in assessing the value of (new) health technologies (Oostenbruggen 2005:225). They form a cornerstone of the scientific discipline named 'Health Technology Assessment', which "developed to support purchasing or coverage decisions" (Canadian Coordinating Office for Health Technology Assessment 2005:4).[4] Conducting explicit health technology assessments are seen to help create a consistent and transparent reimbursement process (Oostenbruggen 2005:225); thereby following the rationale of evidence-based policy and decision making (Mugford et al. 2010:1-4). This concept was named in 1999 by the Dutch Ministry of Health as guiding principle for the then-founded CVZ (Luijn 1999:1294).

The CVZ as advisory body is responsible for assessing reimbursement applications and issuing advices to the Minister of Health in the Netherlands, and is since its origin involved in (pharmaco-) economic evaluations. Correctly, the Minister of Health mandated CVZ's predecessor already in 1997 to compile pharmacoeconomic guidelines (CVZ 2004a:1). It is noteworthy that pharmacoeconomic dossiers deal in essence with an economic evaluation study.

In 1999, the first pharmacoeconomic guidelines were issued as standardised format for future cost-effectiveness dossiers (ZFR 1999). These guidelines were subject to a review after the initial first ten reimbursement dossiers containing a (then-voluntary) pharmacoeconomic report for a new drug were received (CVZ 2004a). In 2005, the guidelines were reviewed and updated (CVZ 2005). Since January 2005, pharmacoeconomic dossiers form an obligation for reimbursement applications that apply for inclusion on List 1B of the positive list.

Then-Minister of Health Borst-Eilers instructed already in 1999 the CVZ to evaluate the guidelines after the first 10 pharmacoeconomic drug dossiers were obtained on their usefulness and applicability in practice, next to whether the guidelines would also be applicable for a review of existing drugs (CVZ 2005:2). The CVZ confirmed the use for existing drugs and even indicated a weighted preference for certain criteria (CVZ 2005). However, since this confirmation was given at the same time that the new, updated guidelines were proposed, the attention was subsequently drawn away from the further unspecified ministerial plan to review reimbursed medicines. The focus remained (justifiably) on the applicability of the updated guidelines for new medical innovations.

The 2006 updated guidance was changing on substantial parts; e.g. reducing the total amount from 19 to 11 guidelines by merging items and transferring them to other procedural documents of the reimbursement application. Rationale was – next to updating guidelines to the current state of scientific art – to stratify guidelines based on procedural and methodological aspects (CVZ 2005:10). The CVZ even stated the disclaimer that the guidelines cannot be read without the two documents 'Manual for cost research' and 'Procedure for requesting drug reimbursement' (CVZ 2006a:1).

Based on this background, a context-specific checklist is developed in this thesis to assess economic evaluation studies on their quality and relevance for the Dutch setting. The 1999 Guidelines were regarded as suitable for evaluating existing drugs; yet, they are in a certain sense outdated. Therefore,

4 Health technology assessment is sometimes referred to as the 'fourth hurdle' for drugs to effectively access the market, alongside the three harmonised criteria for a successful licensing (i.e. safety, quality and efficacy) (Hutton, 2006).

the comments from the update in 2005 will be incorporated, next to other useful sources. A detailed explanation on the checklist compilation can be found in *Appendix 1*.

The instrument gives those factors in line with the Dutch guidelines more weight; thereby, it adopts the appealing approach of quantifying the quality and relevance of economic evaluation studies. The Secretary of the CFH communicated in the appendix of the document evaluating and updating the first Guidelines that the CVZ used so far no weighting of the factors, while indeed desirable (CVZ 2005:51).[5] Moreover, the secretary of the CVZ even started to give an attempt to differentiate weighting according to different criteria (CVZ 2005:59-60); thus showing sympathy for the idea of giving more weight of one criterion over the other. Those comments were picked-up and translated into specific weights.

The instrument will derive one single numerical outcome that is labeled "*Dutch Total Quality Score*" (abbreviated as "*NL-TQS*"). The NL-TQS ranges from 0 to 50 with an acknowledged ceiling effect at the bottom (less sensitive given the pre-selection on studies). An interval is proposed for individual studies from 0-10, 11-20, 21-30, 31-40, and 41-50. Corresponding labels could be 'very poor', 'poor', 'moderate', 'fair', and 'good'. However, all studies seem worth to be considered as this numeric measure does not intend to exclude articles but to indicate on their specific relevance (and quality) for the Dutch setting. Exclusion took place based on pre-defined criteria.

As remarked for other quantitative instruments, quantifying international studies is no easy or universal task and needs adjustment to specific settings (Stearns and Drummond 2003). The quantitative outcome of the constructed checklist is therefore only used as indicator for the qualitative relevance of studies for the Netherlands. The checklist is not intended to replace existing lists or instruments; rather, it could be used as basis to develop a framework for revising the cost-effectiveness evidence of (expensive) reimbursed drugs.

## 1.6 Structure of the thesis

In Chapter 2, the methodology is outlined for the study. Chapter 3 introduces the three selected (pharmaceutical) cases for analysis. Chapter 4 investigates the (un-)certainty at the time of reimbursement decision for these drugs. Chapter 5 investigates the cost-effectiveness at present. Therefore, the first section (5.1) looks on the development of cost-effectiveness evidence to clarify whether a review would be possible. The second section (5.2) investigates the compliance of international economic evaluation studies with criteria regarded important and incorporated in the NL-TQS. The third section (5.3) presents the cost-effectiveness results from the included studies. Chapter 6 tracks whether the positive decisions made are justified ex-post and whether a change in reimbursement should be recommended. Chapter 7 provides considerations regarded important for the re-assessment procedure. Chapter 8 discusses the findings in light of the limitations of this study.

5 In Dutch: "Daarnaast dient opgemerkt te worden dat het CVZ tot op heden geen prioritering heeft aangebracht in de richtlijnen. Een prioritering of weging van de richtlijnen is wenselijk om uniformiteit en transparantie in de totstandkoming van de eindconclusies ten aanzien van de onderbouwing van de doelmatigheid van geneesmiddelen te bevorderen." CVZ 2005, Appendix 1: p.18 (p.51 of the whole document).

# Chapter 2

## Methodology

To answer above mentioned research questions, a retrospective literature study was conducted. Scientific (peer-reviewed) articles and grey literature were gathered online. The Cochrane Handbook for Systematic Reviews of Interventions guided the systematic analysis (Higgins and Green 2011).

A statistical analysis of the policy documents was considered and dismissed based on the restricted amount of observations for the expensive drugs in 2010 ($N$=18) that would likely result in a low statistical power. For the same reason, the choice of drugs can be seen as limitation. However, this research is not investigating why certain drugs are the most expensive ones. Although this would be an interesting additional research question; this thesis accepts certain outpatient drugs as being expensive and questions the legitimacy of the positive reimbursement decision.

A statistical analysis of the outcomes of the economic evaluation studies would be theoretically possible; however, methodological heterogeneity would most likely bias the outcomes enormously. The appeal of a quantitative approach is reflected in the compiled NL-TQS instrument, which strives to assign a value to each individual economic evaluation study. However, the numerical expression is intended as supplementary alongside existing methodologies and instruments that rather reflects the relevance of studies for the Dutch setting than making a selection among them.

### 2.1 Analysis process

Initially, information was gathered about the general characteristics of the pharmaceutical products, their indications, annual amount of users and costs, the date of registration and reimbursement, and any special feature like conditional reimbursement or orphan drug designation. Data was collected from various websites of the CVZ (document archive on their homepage; a comprehensive database on all registered drugs in the Netherlands called *Farmacotherapeutisch Kompas*; and the Drug Information System *GIPdatabank* that features data on expenditure and utilisation of drugs in the Netherlands), the national authorisation body called *College ter Beoordeling van Geneesmiddelen* (CBG; in English: Medicines Evaluation Board), and the European Medicines Agency (EMA).

Secondly, all relevant advisory reports compiled by the CVZ on reimbursement applications were gathered and examined. These reports contain information on the interchangeability of new with existing pharmaceuticals, the therapeutic value in case a drug is not interchangeable, and considerations on budget-impact and cost-effectiveness if the new medicine is assessed as having an added or similar therapeutic value. The reports were taken as proxy for the moment of decision making although, strictly speaking, the Minister of Health makes the final decisions. Nevertheless, the decisions of the Minister are in almost all cases following the advices issued by the CVZ.

Third, target searches were performed in the PubMed (U.S. National Library of Medicine) database to identify relevant economic evaluation studies. (Inter-)national literature was obtained with the following search terms: ‘cost effectiveness’, ‘cost utility’, ‘cost benefit’, ‘cost minimization’, ‘economic evaluation’, ‘pharmacoeconomics’, and ‘health economics’; next to the particular generic and brand name. Economic evaluations found were cross-checked with the Cochrane Library from the Cochrane Collaboration, the University of York Centre for Reviews and Dissemination (CRD) databases, including the NHS Economic Evaluation Database (NHS EED), and the Cost-Effectiveness

Analysis registry from the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center (www.cearegistry.org). Moreover, drug marketing authorisation holders were directly contacted to access additional published and/or unpublished material.

All database searches were done from inception to May 2011. To differentiate between the period before and after reimbursement decision in the Netherlands, the reimbursement decision as published online in the official State Journal *Staatscourant* by the Minister of Health is used as cut-off date. All studies were stratified according to that date and presented either at the moment of decision making (t=0) if the economic evaluation(s) could have been considered at the time of assessment, or at the present (t=1) following final reimbursement decisions.

The labels chosen for the two different dates are abbreviated with 't=x', where x is not representing the amount of years but used as dichotomous figure differentiating the time when decisions were made (t=0) and the present (t=1). It should not be confused with the conventional writing of 't=4' for inpatient expensive medications, which indicates the mandatory re-assessment after 4 years. The reasons are of practical nature: first, it was unclear at the beginning of the study whether a review after 4 years would also be feasible for outpatient drugs; second, the review studied retrospectively from a fixed date in 2011 and the time to the moment of initial reimbursement varied for the drugs (with 2 years for one indication of adalimumab up to 10 years for the assessment of imatinib).

## 2.2 Study inclusion selection

Included economic analyses contained only full economic evaluations of the type of cost-effectiveness (i.e., a comparison of the costs of two treatments with their effectiveness and reported as e.g. cost per life-year gained), cost-utility (comparing the costs of two treatments with their effectiveness in terms of for quality-adjusted life years gained), cost-benefit (a comparison of costs and the monetary valuation of effects), and cost-minimization (compares only the costs of two alternative treatments with similar outcomes) (Drummond et al. 2005).

Prospectively designed exclusion criteria ranged from studies not involving humans; abstracts, posters and presentations without complete full-text publication; review articles without new, independent economic evaluation; all cost comparison studies and cost analyses as all partial economic evaluations; articles mentioning cost-effectiveness only as future research opportunity; case reports; expert opinions; comment articles; editorials; letters to the editor; any duplications; and written in a different language than English, Dutch (two studies included for imatinib) or German (one for pegfilgrastim).

No restriction in terms of disease or indication was made, allowing to detect possible studies on off-label use. However, only studies published in peer-reviewed journals were considered as relevant. In cases of uncertainty, the website of the journal was accessed and searched for claims of a peer-review approach. The restriction to high quality evidence is chosen given their widespread acceptance and validity, and in order to minimise potential bias.

All titles and abstracts of included studies were reviewed. Articles which were unclear in their relevance were obtained in full-text. Reference lists of articles were investigated for additional relevant material. This search was repeated until no more relevant articles were identified. Full-text articles were retrieved for all potentially relevant studies. A careful examination of each individual article ensured that the inclusion criteria were met.

## 2.3 Data collection

The data were abstracted and catalogued in a data-collection form with Microsoft Excel based on the pre-specified criteria of the NL-TQS, including general information of the articles like the author(s), title, journal name, journal classification (medical or economical), year of publication, and country setting; next to the items of the checklist compiled for appraising international studies on their relevance in a country-specific way and that is based on the national Pharmacoeconomic Guidelines of the CVZ for the Netherlands from 1999 and the update from 2006; the Consensus on Health Economic Criteria (CHEC-) list from 2005 (Evers et al. 2005); the Quality of Health Economic Studies (QHES) instrument from 2003 (Chiou et al. 2003); and the Drummond checklist (Drummond et al. 2005).

Globally, the studies were examined on their study design; methodological elements; use of modelling techniques; costs; benefits; uncertainty of analysis; validity of conclusions, presentation, transparent reporting; contextual embedding; ethical implications; and disclosures of funding and conflict of interests. Studies were ordered per indication, treatment line, and comparator.

To enhance comparability of outcomes, two ways of presentation were chosen: first, the values as documented in the currency and base year mentioned in the study itself; second, values reported in other currencies than the Euro were converted into the Euro by applying a currency exchange rate derived from the Dutch Central Bank (*De Nederlandsche Bank*); in addition to a conversion to 2010 Euros (€) for all studies via the Harmonised Indices of Consumer Prices (HICP) from the European Central Bank for the Netherlands.[6] Although a sub-item on health is included in the HICP, the overall score on all-items is used for inflation as other, non-medical cost factors are also recognised as important and required in the Dutch setting (considering the societal perspective and productivity losses). Where the base year was not stated, the year of publication was chosen for compensation. This liberal assumption is benefitting studies since the time between publication and conduct of a study or base year can differ greatly (thus affecting the conversion rate and real value). The outlined approach was inspired by a similar method applied by Doan et al. (2006) in a review for the United States.

To minimise errors and fallacy, several studies were examined simultaneously by more than one person; as was the overall process of this study supervised. Abstracted data were frequently discussed in periodic meetings between the principal supervisor (MK) and the first author (FS) of the study. No blinding to any information was applicable.

Lastly, a disclaimer seems appropriate. The careful interpretation of the presented economic evaluations is emphasised as the compared studies were conducted in various countries with heterogeneous methodologies, settings, and requirements. The reader should keep in mind that results only estimate an approximation of reality and need to be interpreted with the appropriate care.

6 The Harmonised Indices of Consumer Prices (HICP) is an economic indicator that measures price changes and inflation over time for the euro-zone, the European Union, the European Economic Area, and other countries. It is the official measure for consumer price inflation in the euro-zone and used for the monetary policy of the euro area and the assessment of inflation convergence as required by the Maastricht criteria. (see http://epp.eurostat.ec.europa.eu/portal/page/portal/hicp/introduction; accessed last on September 26, 2011).

# Chapter 3

## General introduction to selected pharmaceutical cases

This chapter aims at introducing the three expensive pharmaceutical products chosen for analysis (i.e., imatinib, pegfilgrastim, and adalimumab). The focus lies on their indications, procedural steps of registration and reimbursement, and any special characteristics. In the rest of this article, the abbreviations for the indications introduced here will be used.

### 3.1 Case 1: Imatinib

Imatinib (Glivec®, Novartis Europharm Ltd.) is a protein-tyrosine kinase inhibitor that helps control cell division by blocking specific enzymes known as tyrosine kinases, located in some receptors on the surface of cancer cells that stimulate them to divide uncontrollably (EMA, 2011a).

In 2001, marketing authorisation was granted by means of the centralised procedure for the entire EU, which was renewed in 2006 (EMA 2011a). The main indication forms:

- chronic myeloid leukaemia (CML, a type of cancer with uncontrolled growth of the white blood cells). Originally licensed for the chronic phase of the disease if it is not responding to interferon alpha and in the advanced phases of the disease (called accelerated phase and blast crisis) in 2001, this indication was shortly after extended with first-line treatment in 2002 [both under the premise that patients are not eligible for a bone marrow transplant].

During the last ten years, the indications of imatinib were extended with six other related malignancies (information derived from the European Public Assessment Report (EPAR) for Glivec®, EMA 2011a):

- gastrointestinal stromal tumours (GIST, cancer in the supporting tissues of the stomach and bowel) in 2002 and 2009 [unresectable and after surgical intervention, respectively];
- acute lymphoblastic leukaemia (ALL, cancer in which lymphocytes multiply too quickly) in 2006;
- myelodysplastic myeloproliferative diseases (MDS/MPD, production of large numbers of abnormal blood cells) in 2006;
- advanced hypereosinophilic syndrome or chronic eosinophilic leukaemia (HES&CEL, another type of white blood cells, eosinophils, grow uncontrolled) in 2006;
- and dermatofibrosarcoma protuberans (DFSP, cancer in the tissue beneath the skin) in 2006.

All indications considered adults, with CML additionally being licensed for children.

Standard treatment in CML before the advent of imatinib formed immunotherapy with interferon-alpha, and in case patients were not eligible for a bone marrow transplant. For GIST and DFSP, the only possible alternative treatment formed surgery (EMA 2005, 2007a). Accordingly, imatinib was authorised in diseases that cannot be removed with surgery, have spread in the body, or who were likely to reoccur after surgical removal (EMA 2011a). For ALL and MDS/MPD, conventional chemotherapy, a bone marrow transplant, and radiotherapy were considered as alternative treatments. For HES&CEL, no satisfactory alternative was available at the time of registration (EMA 2007b).

Imatinib was granted an 'orphan designation'[7] for all six of its indications in 2001 (CML, GIST) and 2005 (the others) as it complies with the definition set by the European Medical Agency for orphan drugs and in the absence of (more) effective alternative treatments.[8]

For CML, ALL and MDS/MPD, the designation was granted under the assumption that imatinib "could be of potential significant benefit for the treatment of [CML;ALL;MDS/MPD], because it may act in a different way to other drugs/than the available methods [CML;MDS/MPD] and[/or] it might improve the long-term outcome of the patients [CML;ALL;MDS/MPD]. This assumption will have to be confirmed at the time of marketing authorisation" (EMA 2007c, 2007d, 2007e). For GIST, DFSP, and HES&CEL, it was anticipated that imatinib might "help in slowing down or stopping the further growth of the cancer cells" (EMA 2005, 2007a, 2007b).

Eventually, the Minister of Health followed the reasoning of the CFH as presented in the advisory report of the CVZ from November 2001. Imatinib is placed on List 1B of the Dutch national formulary since 2002, granting premium-priced reimbursement to a drug with added therapeutic value (Stcrt 2001: no.25074). Without the additional listing on List 2, the extended indications were exempted from an assessment by the CFH.

**Table 2:** Registered and reimbursed indications for imatinib

| | Orphan designation recognition procedure | | | Timeline reimbursement decision making procedure | | | | CVZ assessment components | | | | MoH decision |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Indication | COMP opinion | Orphan designation | Registration date# | Application to MoH for GVS | CFH assessment | CVZ advice | MoH enforcing reimbursement§ | Interchange -able | Therapeutic value | Budget Impact | Pharmaco-economics | Inclusion GVS (List 1A/1B/2) |
| *CML* | 19/12/2000 | 14/02/2001 | 07/11/2001 | 03/08/2001 | 13/11/2001 | 13/11/2001 | 01/01/2002 | No | Added | €2.7M p/a | na† | 1B |
| *GIST* | 07/09/2001 | 20/11/2001 | 24/05/2002 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| *ALL* | 13/07/2005 | 26/08/2005 | 13/09/2006 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| *DFSP* | 13/07/2005 | 26/08/2005 | 13/09/2006 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| *HES&CEL* | 19/08/2005 | 28/10/2005 | 28/11/2006 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| *MDS/MPD* | 10/11/2005 | 23/12/2005 | 28/11/2006 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

COMP: Committee for Orphan Medicinal Products, CML: chronic myeloid leukaemia, GIST: gastrointestinal stromal tumours, ALL: acute lymphoblastic leukaemia, DFSP: dermatofibrosarcoma protuberans, HES&CEL: advanced hypereosinophilic syndrome or chronic eosinophilic leukaemia, MDS/MPD: myelodysplastic myeloproliferative diseases, N/A: not applicable, na = not available, M = million, p/a = per annum

# Central registration via EMA, but national reimbursement assessment and enforcement.
† No pharmacoeconomic dossier included as imatinib was assessed by the CVZ before 2005.
§ Reimbursement is enforced when a ministerial notice is published in the State Journal 'Staatscourant' (Stcrt), the official record of the Dutch government on new laws and other governmental announcements like the managing of the Lists of the medicines reimbursement system (GVS). In the announcements, a date is defined since when the enforcement of reimbursement is valid. Those dates are depicted here. Reference source for CML: Stcrt 2001 no 250. Accessible online via https://zoek.officielebekendmakingen.nl/, accessed last on 3 August 2011.

7 Pursuant to Article 3 of the Regulation (EC) on Orphan Medicinal Products by the European Parliament and Council, medicines can be granted an orphan designation in case they are used for the treatment of life-threatening or chronically debilitating conditions that affect no more than five in 10,000 people in the European Union, or in case the medicines would be unlikely to be developed without economic incentives for the return on investments; in addition, no satisfactory alternative method is existent or is inferior to the new innovation (European Union. Regulation (EC) No. 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999 and Commission Regulation (EC) No. 847/2000 of 27 April 2000).

8 1,471 registered Dutch users of imatinib in 2010 represent 0.88 patients per 10,000 inhabitants (0.000089% of the total population, counting with 16,615,394 inhabitants of the Netherlands in 2010 according to the CBS).

## 3.2 Case 2: Pegfilgrastim

Pegfilgrastim (Neulasta®, Amgen Europe B.V.) is an immunostimulant that belongs to the group of 'granulocyte colony-stimulating factors'. These growth factors are registered for the reduction of the risk and duration of (febrile) neutropenia (FN) as induced by chemotherapy. Contraindicated is the use in chronic myeloid leukaemia and myelodysplastic syndromes (EMA 2011b).

In general, neutropenia acts cytotoxic (cell-killing) and is characterised by low levels of a certain type of white blood cells (called neutrophils) as induced by chemotherapy. The occurrence of neutropenia with fever is called febrile neutropenia (EMA2011b). This form of disease can increase the risk of infections and other side effects that require a hospital admission (e.g. bone pain). Therefore, the quality of life, survival rate, and total costs seem to benefit from preventive treatment that stimulates haematopoietic blood-cell growth.

Pegylated filgrastim (pegfilgrastim) is a variant of filgrastim with a prolonged duration of action due to a decreased renal clearance mechanism. Marketing authorisation was granted for the EU in 2002, valid for an unlimited period (EMA 2011b). This exception must be seen in light of the proven efficacy and effectiveness of filgrastim and the absence of any pharmacological meaningful difference between the two drugs. Pegfilgrastim has an improved administration scheme that suffices with one administration per cycle of chemotherapy instead of daily as with filgrastim (CVZ 2002:3).

Since 2003, pegfilgrastim is clustered together with filgrastim and lenograstim on List 1A of the Dutch positive list (Stcrt 2003: no.2314). Additionally, it is also registered for List 2, point 11, which states conditions for reimbursement of granulocyte colony-stimulating factors[9].

**Table 3:** Registered and reimbursed indications for pegfilgrastim

| | | Timeline reimbursement decision making procedure | | | | CVZ assessment components | | | | MoH decision |
|---|---|---|---|---|---|---|---|---|---|---|
| Indication | Registration date# | Application to MoH for GVS | CFH assessment | CVZ advice | MoH enforcing reimbursement§ | Interchange-able | Therapeutic value | Budget impact | Pharmaco-economics | Inclusion GVS (List 1A/1B/2) |
| *Neutropenia* | 22/08/2002 | 11/2002 | 12/2002 | 12/2002 | 02/2003 | Yes | Similar | N/A | N/A | 1A + 2 |

N/A: not applicable, na = not available

# Central registration via EMA, but national reimbursement assessment and enforcement.

9 Granulocyte colony-stimulating factors are intended only for insured patients that (a) are treated with chemotherapy for a malignant condition and have a medical indication registered under the Medicines Act; (b) are treated with ganciclovir for cytomegalovirus retinitis caused by AIDS and have a medical indication registered under the Medicines Act; (c) are being treated for a severe congenital, cyclic or idiopathic neutropenia; (d) have for this drug an unregistered indication and suffer from a disease that appears in the Netherlands not more than in 1 of 150,000 inhabitants, while the efficacy of that drug in that indication is scientifically proven and in the Netherlands for that condition is no treatment possible with any other for that disease registered drug.

## 3.3 Case 3: Adalimumab

Adalimumab (Humira®, Abbott Laboratories Ltd.) is a recombinant monoclonal antibody (the first fully human) that reduces inflammation and related symptoms by blocking the biologic activity of an antigen in the body called 'tumor necrosis factor' (TNF, also known as TNF-alpha) (EMA 2011c:2). A centralised marketing authorisation was granted by the European Commission first in 2003 and renewed for an unlimited period in 2008 due to the adequately and sufficiently demonstrated quality, safety and efficacy (EMA 2011c:4).

Adalimumab belongs to the biological response modifiers, often shortened to 'biologic' drugs (Chiou 2004:307). Unlike chemically synthesised agents, these medications are produced from living organisms (Koo 2005). Previously, the two biologics infliximab (Remicade®, Janssen Biologics B.V.) and etanercept (Enbrel®, Pfizer Ltd.) were centrally authorised in 1999 and 2000 (EMA 2011d, 2011e), and reimbursed the same years (Stcrt 2000: no.187).

The main indication of adalimumab concerns since 2004:

- moderate to severe active rheumatoid arthritis (RA; joint inflammation), after inadequate response to different non-biologic disease-modifying antirheumatic drugs (DMARDs). In 2005, that indication was extended with recently diagnosed RA patients who were untreated with methotrexate (EMA 2011c).

Other extended indications are (information derived from the EPAR of adalimumab, EMA 2011c):

- active and progressive psoriatic arthritis (PsA; joints inflammation accompanied by red, scaly patches on the skin) in 2005;
- severe active ankylosing spondylitis (AS; inflammation in the joints of the spine) in 2006;
- moderate to severe Crohn's disease (CD; an inflammatory bowel disease) in 2007;
- moderate to severe chronic plaque psoriasis (PP; red, scaly patches on the skin) in 2007;
- active polyarticular juvenile idiopathic arthritis (JIA; rare childhood condition of multiple joint inflammation) in 2008 [first indicated for adolescents aged 13-17 in 2008; then for children aged 4-12 in 2011].

The last indication was the only treatment not solely authorised for adults. However, all indications are limited to patients with inadequate response or intolerance to alternative therapies, or contra-indications (except for first-line treatment in severe RA) (EMA 2011c:2).

The Minister of Health agreed in all cases with the reasoning of the CFH as presented in the advisory reports of the CVZ. Adalimumab is placed together with etanercept (and infliximab) on List 1A of the Dutch national formulary since 2004 (Stcrt 2004: no.15). In addition, adalimumab is also restricted by List 2 (point 33) that contains all above listed indications.[10]

10 Adalimumab is intended only for insured patients of: (a.) eighteen years or older with active rheumatoid arthritis and an inadequate response or intolerance to treatment with various disease-modifying antirheumatic drugs, including at least methotrexate, unless there is a contraindication for methotrexate; (b.) eighteen years or older with active and progressive psoriatic arthritis when the response to previous disease modifying antirheumatic drugs has been inadequate; (c.) eighteen years or older with severe active ankylosing spondylitis in which there is inadequate response to at least two NSAIDs at maximum doses and other conventional treatment; (d.) eighteen years or older with Crohn's disease where there is inadequate response to maximal use of corticosteroids and/or immunosuppressants, or who do not tolerate such treatments or where a contra-indication exists; (e.) eighteen years

**Table 4:** Registered and reimbursed indications for adalimumab

| | | Timeline reimbursement decision making procedure | | | | CVZ assessment components | | | | MoH decision |
|---|---|---|---|---|---|---|---|---|---|---|
| Indication | Registration date# | Application to MoH for GVS | CFH assessment | CVZ advice | MoH enforcing reimbursement§ | Interchange-able | Therapeutic value | Budget impact** | Pharmaco-economics | Inclusion GVS (List 1A/1B/2) |
| *RA* | 08/09/2003 | 10/2003 | 11/2003 | 12/2003 | 01/2004 | Yes | Similar | N/A | N/A* | 1A + 2 |
| *PsA* | 08/2005 (2008) | na† | 09/2005 | na† | 12/2005 | [Yes] | Similar | na† | N/A | 1A + 2 |
| *AS* | 06/2006 | 07/2006 | 07/2006 | 08/2006 | 10/2006 | [Yes] | Similar | 'Probably not more costs' | N/A | 1A + 2 |
| *CD* | 06/2007 | 07/2007 | 08/2007 | 09/2007 | 06/2008‡ | [Yes] | Similar | 'Unclear' | N/A | 1A + 2 |
| *PP* | 12/2007 | 02/2008 | 02/2008 | 04/2008 | 06/2008 | [Yes] | Similar | 'Budget neutral' | N/A | 1A + 2 |
| *JIA* | 08/2008 | 12/2008 | 01/2009 | 02/2009 | 04/2009 | [Yes] | Similar | 'Barely more costs' | N/A | 1A + 2 |

RA: rheumatoid arthritis, PsA: psoriatic arthritis, AS: ankylosing spondylitis, CD: Crohn's disease, PP: plaque psoriasis, JIA: juvenile idiopathic arthritis, N/A: not applicable, na = not available

# Central registration via EMA, but national reimbursement assessment and enforcement.
* No pharmacoeconomic dossier included as adalimumab was clustered on List 1A together with etanercept.
** No budget-impact analysis required for a drug that is clustered on Lists 1A and 2 but whose extended indications were not the first to be registered in the GVS.
† Only the pharmacotherapeutic assessment report of the CFH available.
§Enforced by official publication in the State Journal 'Staatscourant' (Stcrt). Reference sources for RA: Stcrt 2004 no 15; PsA: Stcrt 2005 no 242; AS: Stcrt 2006 no 194; CD: Stcrt 2008 no 107; PP: Stcrt 2008 no 107; JIA: Stcrt 2009 no 69. All accessible online via https://zoek.officielebekendmakingen.nl/, accessed last on 3 August 2011.
‡ Crohn's disease was first mentioned in an updated version of List 2 in the same announcement that also plaque psoriasis was mentioning. No dating back of enforcement could be found. A more thorough search did not reveal an earlier published announcement. In the CVZ advice for CD was a consultation round among stakeholders mentioned during the drafting of that report, which might be responsible for the delay; in addition, that drug was compared with the only recently in the GVS included infliximab (uptake in June 2007).

For adalimumab, the CVZ was required to assess several off-label applications due to the inclusion in List 2. Conditions have to fulfil three criteria to qualify for reimbursement: the prevalence of that particular (non-registered) condition needs to be lower than one in 150,000 citizens of the Netherlands; the efficacy for the intended use needs to be scientifically demonstrated; and no treatment should be possible anymore with any other for that disease registered medication in the Netherlands [List 2, section 33 'Adalimumab'; accessed 03/08/2011].

All non-registered indications in common were a therapy-resistant, serious, rare condition that the manufacturer did not request reimbursement for out of economical reasons. As noted by the CVZ, the off-label use must be regarded as last resort therapy for end-stage patients (CVZ 2008b:4).

However, only severe sight threatening, treatment-resistant uveitis was considered a rational off-label use of adalimumab (CVZ 2007a). All others use was assessed as not (yet) rational, mostly due to lacking scientific evidence and not the prevalence criterion or the availability of alternative technologies (severe, therapy-resistant sarcoidosis; [CVZ 2008d] severe, therapy-resistant hidradenitis suppurativa; [CVZ 2008b] therapy-resistant Takayasu's arteritis [CVZ 2009c]; therapy-resistant Wegener's granulomatosis [CVZ 2009c]; and therapy-resistant Behçet's disease [CVZ 2010d]).

or older with moderate to severe chronic plaque psoriasis where there is inadequate response, intolerance or an absolute contraindication to PUVA, methotrexate and cyclosporine; (f.) with active juvenile idiopathic arthritis with polyarticular course, with inadequate response to one or more disease modifying antirheumatic drugs, or (g.) those with an unregistered indication for this product and suffering from a disease that in the Netherlands is less frequent than 1 in 150,000 inhabitants, the efficacy of that drug in that indication is scientifically demonstrated and in the Netherlands is no treatment possible with any other for that condition registered drug.

# Chapter 4

## Certainty at the time of reimbursement decision making (at t=0)

### 4.1 Introduction

In this section, the focus rests on the (un-)certainty prevailing at the time of reimbursement decision making as documented in the publicly available advices of the CVZ to the Minister of Health. Data available for decision making at t=0 were subdivided into a therapeutic and economic part, following the structure of reimbursement dossiers. This section intends to illuminate:

> Q1: *How certain is the evidence for clinical and cost-effectiveness among selected outpatient drugs at the time a positive reimbursement decision was made?*

Medications are presented in an integrative manner to enhance readability. Given that official advices were not issued for all indications, t=0 is an aggregated endpoint that equals the year 2001 for imatinib; 2002 for pegfilgrastim; and 2003 to 2009 for adalimumab (RA 2003; PsA 2005; AS 2006; CD 2007; PP 2008; and JIA 2009).

#### Therapeutic value

The therapeutic value is determined by the CFH through compiling a *Farmacotherapeutisch rapport* (Pharmacotherapeutic Report). Medicines intended for clustering in the reference pricing system (i.e., List 1A) are assessed on their 'interchangeability' with already reimbursed pharmacological comparators to detect similar clinical features; medicines intended for List 1B are assessed to determine a therapeutic *added* value. Extended indications require a new CFH assessment in case the drug is restricted conditionally by List 2.

Interchangeability is tested for new drugs and comparators by investigating whether both are 1.) indicated for the same disease; 2.) used for patients of the same age; 3.) requiring a similar route of administration; and 4.) showing similar clinical features (Health Insurance Regulation, Rzv; art. 2.40).

If interchangeability is rejected, or the manufacturer claims for an added value, the CFH determines the therapeutic value of the new medication in comparison to the standard (or usual) treatment of care (CVZ 2010a:2). Until 2010, the therapeutic value was determined by the CFH according to seven criteria: (1) efficacy; (2) effectiveness; (3) quality of life; (4) side-effects; (5) applicability; (6) ease of use; and (7) experience. Since 2010, the CFH compressed the criteria 1 to 3 in one new criterion labelled 'intended effects'; criterion 4 was re-named into 'unintended effects' (CVZ 2010a:2-4).

#### Economic evidence

In case the CFH assessed a new drug as having a therapeutic added or similar value that qualifies for placement on List 1B, the budget-impact and cost-effectiveness are considered. A budget-impact analysis is also required for a drug that is clustered on both Lists, 1A and 2, and whose extended indication is the first to be registered in the GVS (Ministry of Health and CVZ 2011:6).

Additionally, international studies identified via the systematic search algorithm of this thesis will already be presented in case they were available at the time of CFH assessment (applicable only for one study in adalimumab).

## 4.2 Therapeutic value at t=0

### 4.2.1 Dossiers available

As seen in Chapter 3, CVZ advices were issued for imatinib only in second-line use of its main indication CML in the chronic phase of the disease if it is not responding to interferon alpha, and in more advanced phases of the disease (the accelerated and blast crisis phase) (CVZ 2001).

Pegfilgrastim was assessed by the CFH for its sole indication in 2002: reduction of the duration of neutropenia and the risk of febrile neutropenia as induced by chemotherapy, with the exception of chronic myeloid leukaemia and myelodysplastic syndromes (CVZ 2002).

Adalimumab was assessed by the CFH for all six (extended) indications, given that adalimumab is registered on both Lists 1A and 2 of the GVS (CVZ 2003,2006b,2007b,2008c,2009b, CFH 2005).

### 4.2.2 Interchangeability

For imatinib, the interchangeability (i.e., drugs treating the same disease, used in similar patients, administered in a similar way, and showing similar clinical features) with existing medications was rejected given its underlying mechanism, indication, administration and side-effects (CVZ 2001:1).

For pegfilgrastim, the CFH confirmed the interchangeability with filgrastim based on 1.) a similar (main) indication to reduce the duration of neutropenia and the risk of febrile neutropenia; 2.) a similar group of patients as the paediatric use was not examined for any of the haematopoietic growth factors (i.e. filgrastim and lenograstim); 3.) a similar route of administration by means of subcutaneous injections; and 4.) no clinically relevant differences (CVZ 2002:3-4).

For adalimumab, the CFH examined in RA the interchangeability with etanercept and concluded that both 1.) share the same indications, except for Crohn's disease, but the main indication being the same (RA in adults with insufficient response to DMARDs); 2.) can be administered in adults, and children with JIA; 3.) are administered subcutaneously; and 4.) share similar clinical features (CVZ 2003).

### 4.2.3 Therapeutic added value

For imatinib, the CFH assessed the therapeutic value (comprised of efficacy; effectiveness; quality of life; side-effects; applicability; ease of use; and experience) with hydroxycarbamide and bone marrow transplants based on indirect historical comparisons. Since the assessed indication contained previous failure of interferon-alpha, that treatment formed no valid alternative anymore.[11]

For pegfilgrastim, filgrastim was used as comparator.

For adalimumab, either etanercept (RA, PsA, JIA), infliximab (CD), or both (AS, PP) were taken as comparators – depending on the indication and timing. Although the CVZ report for RA mentioned to only compare adalimumab with etanercept and did so with the determination of the interchangeably, the CFH (pharmacotherapeutic) assessment report compared adalimumab to both etanercept and infliximab. The rationale for only using etanercept in the final comparison was given in that infliximab is administered only in hospital settings and was at the time of assessment not included in the GVS (eventual uptake on 1 June 2007). Similarly, infliximab was not considered in the assessment of PsA.

11 CML knows three progressive phases: chronic (4-5 years), accelerated (6-9 months), and the blast crisis (3-6 months).

*Intended effects*

### Efficacy

For imatinib, efficacy was assessed by means of indirect historical comparisons per disease phase. Follow-up periods of clinical trials did not exceed 18, 9 and 12 months for imatinib for the three phases, respectively. Efficacy was measured by two intermediate outcomes, the hematologic and cytogenetic response. These outcomes showed to be a good indicator for respectively physiological and clinical improvements and prolonged survival of more than 6 years for treatment of CML with interferon-alpha (Kantarjian et al. 1995). Both response rates were for imatinib systematically higher than for hydroxycarbamide. The CFH concluded that imatinib seemed to be more efficacious than hydroxycarbamide in the chronic and accelerated phases of CML, and more efficacious than combined chemotherapy in the blast crisis.

For pegfilgrastim, efficacy was not extra assessed as the report looked at the effectiveness of neutropenia prevention and reduction of neutropenia duration between pegfilgrastim and filgrastim based on two clinical studies whose objective was to show that pegfilgrastim is as effective and safe as filgrastim when administered to patients undergoing four cycles of chemotherapy.

For adalimumab, efficacy was always seen as comparable among the competing interventions since no clinical relevant differences could be demonstrated. Indirect comparisons of clinical placebo-controlled randomised trials were carried out in the lack of head-to-head evidence. Also, different efficacy endpoints were used between clinical trials; alongside the different measurement as either primary or secondary outcome (e.g. in RA the three criteria DAS, Paulus and ACR were mentioned, but eventually only the ACR criteria used for comparison across trials given their dominance). Follow-up periods did usually not exceed 24 weeks but were reported in some trials for up to 1 year.

Overall, efficacy as demonstrated by placebo-controlled randomised trials seemed highly favourable for adalimumab. A similar superiority over placebo was also reported for the two competing TNF-antagonists. The use of an indirect comparison disqualifies a conclusive interpretation on the different magnitudes of efficacy documented between TNF-agents.

### Effectiveness

For imatinib, conclusive effectiveness data (assessed by the gain of survival) were missing in all three phases. Again, no direct comparisons between imatinib and standard care were available. In one study for the accelerated phase was the lack of definitive effectiveness data mentioned, seeing that the median survival was not yet reached after a follow-up time of 9 months. For hydroxycarbamide, survival rates were reported of more than 4 years, about 8 months, and 3-6 months for the three phases respectively. Only bone marrow transplant was recognised as being able to cure; however, it forms an option for only a small proportion of patients and is related with high transplant-related mortality (3-years survival prognosis of 57%-67% in chronic; 44% in accelerated; and 19% in blast crisis).

For pegfilgrastim, the two earlier mentioned clinical trials looked at the duration of type 4 neutropenia in the four cycles of chemotherapy and the incidence of febrile neutropenia. Both studies showed no clinical relevant difference in the duration of neutropenia between comparators.

For adalimumab, effectiveness was assessed in RA and PsA by means of radiological progression and generally regarded as being comparable among competing interventions. In AS and JIA, the lack of published (long-term) data was mentioned that hindered an assessment on the effectiveness. The other two reports (CD, PP) excluded detailed comments on this item.

### Quality of Life

Quality of life was not assessed in imatinib and pegfilgrastim. One report stated that the influence of the medication on the quality of life would only be assessed if specific research was conducted and available (CVZ 2001:29), which was not the case for both drugs.

For adalimumab, quality of life was measured – where evidence was available – with disease specific instruments like the HAQ DI (Disability Index of the Health Assessment Questionnaire) in RA, PsA, and the adjusted CHAQ-DI for children in JIA; the 'Inflammatory Bowel Disease Questionnaire' (IBDQ) in CD; and the Dermatology Life Quality Index (DLQI) in PP. Evidence for the quality of life was either showing a similar significant improvement for all comparators in PsA and PP; was lacking in AS; or regarded as insufficient and too limited for an adequate (indirect) comparison in CD and JIA. In RA, quality of life was only investigated for adalimumab compared to placebo, which was clinically meaningful in favour of adalimumab; but no comparative assessment with etanercept and/or infliximab was documented.

## *Unintended effects*

### Side-effects

For imatinib, side-effects were assessed as being mild-to-moderate, not toxic, and similar to those of hydroxycarbamide. Bone marrow transplant is recognised in being able to cure patients, but at the risk of a high transplant-related mortality (within three years between 40-80%).

In pegfilgrastim, the most common adverse event of bone pain appeared with both drugs. Holmes found a difference in the total percentage of febrile neutropenia, with the meaning of this, as the CFH remarked, being unknown. In fact, Holmes used a lower-dosed and higher-dosed pegfilgrastim group versus one filgrastim treatment group. The group with a lower dose received higher percentages of febrile neutropenia, which might explain the variation observed.

For adalimumab, side-effects were in all reports regarded as in general seemingly comparable between TNF-inhibitors; for RA and JIA were additionally the absence of long-term data mentioned.

## *Applicability*

The applicability was in general regarded as comparable or not clinically relevant for the three drugs in all indications. For imatinib, the comparison was merely done to other chemotherapeutics; the applicability of bone marrow transplants is limited to patients younger than 60 years. For pegfilgrastim, the CFH mentioned that this item was assessed by means of an indirect comparison.

## *Ease of use*

The ease of use was seen as similar for imatinib and hydroxycarbamide (oral administration, allowing self-administration at home); different for pegfilgrastim and filgrastim (pegfilgrastim fulfils with a one-off admission during a cycle of chemotherapy while filgrastim needs to be administered daily); and assessed for adalimumab first as higher than that of etanercept (RA, PsA, and AS) or infliximab (PP); then regarded as depending on patient's preferences (CD), and finally judged as not differing to etanercept (in PP and JIA). Ease of use remained unmentioned for infliximab in the assessment of AS.

The varying assessment results over time for adalimumab can be attributed to the different dosage regimen for etanercept, which is recommended to be administered twice weekly and adalimumab

suffices with once every other week. In the report of JIA (CVZ 2009b), a precise distinction was made between 'ease of use' and 'frequency of administration', which resulted in a judgement of similar ease of use for both drugs given the same administration by subcutaneous injection. Retrospectively, that result would have been appropriate for all assessments comparing adalimumab and etanercept (i.e., RA, PsA, AS, and PP), and also for pegfilgrastim.

### *Experience*

Experience was seen as limited for imatinib and all newly assessed indications of adalimumab. For pegfilgrastim, this item was not assessed.

### *Therapeutic value judgement*

For imatinib, the CFH concluded that it seemed to have an added value in the treatment of CML after no response to interferon-alpha, compared to the standard care of chemotherapy, and in case that a bone marrow transplant is no option (CVZ 2001: p. 2/34).

For pegfilgrastim, a similar value was established when assessing the interchangeability with filgrastim.

For adalimumab, the CFH concluded in all six assessments that a similar therapeutic value to the other TNF inhibitors could reasonably be assumed. Only the report for JIA stated a preference of etanercept over adalimumab for patients treated with TNF-blockers owing to the higher amount of available long-term data for etanercept on efficacy and safety with associated higher experience in its use.

**Table 5:** CFH assessment reports

| | | Comparator | Efficacy | Effectiveness | Quality of Life | Side-effects | Applicability | Ease of use | Experience | Therapeutic value |
|---|---|---|---|---|---|---|---|---|---|---|
| *Imatinib* | CML (2001) | HU; BMT | Seemingly higher. | ***(Definitive) data missing*** | ***No data available.*** | Similar to HU; BMT can cure but high related mortality. | No relevant differences. | Similar. | Limited. | Added value. |
| | GIST (2002) | - | - | - | - | - | - | - | - | - |
| | ALL (2006) | - | - | - | - | - | - | - | - | - |
| | DFSP (2006) | - | - | - | - | - | - | - | - | - |
| | HES&CEL (2006) | - | - | - | - | - | - | - | - | - |
| | MDS/MPD (2006) | - | - | - | - | - | - | - | - | - |
| *Pegfilgrastim* | Neutropenia (2002) | Filgrastim | Same. | Same. | ***Not assessed.*** | Same. | No relevant differences. | Difference in frequency of administration | ***Not assessed.*** | Same value. |
| *Adalimumab* | RA (2003) | ETA; (de facto also INFL) † | Clinical relevant differences not demonstrated. | Significantly reduced radiological progression. | Clinical relevant improvement (over placebo, *ETA unmentioned*). | Overall comparable. ***Lacking long-term data.*** | Comparable. | Better. | Limited. | Same value. |
| | PsA (2005) | ETA† | About as efficacious. | About as effective. | Similar improvement. | Comparable. | Comparable. | A bit higher. | Limited. | Same value. |
| | AS (2006) | ETA; INFL‡ | Seems comparable. | ***No published research (yet).*** | ***No published data available.*** | Similar. | Comparable at large. | Slightly higher (vs ETA); *INFL not mentioned*. | Limited. | Same value. |
| | CD (2007) | INFL | Both efficacious, no preference. | ***Not mentioned by CFH.*** | ***Insufficient data available.*** | In general comparable. | Comparable at large. | Dependent on patient's preference (no explicit decision) | Limited. | Same value. |
| | PP (2008) | ETA; INFL | Seems comparable. | ***Not mentioned by CFH.*** | Similar improvement. | Overall comparable. | No big differences. | No differences (vs ETA); better (vs INFL) | Limited. | TNF inhibitors have an added value |
| | JIA (2009) | ETA | Comparable. | ***Long-term data lacking*** | ***No data available.*** | Seems comparable. ***Lacking long-term data.*** | Comparable. | No difference. | Limited. | Same value. (Preferred: etanercept) |

Figures in ***bold and italic*** indicate uncertain factors from lacking evidence data.
BMT: bone marrow transplant; HU: hydroxycarbamide

## 4.3 Economic evidence at t=0

### 4.3.1 Pharmacoeconomic reports

No pharmacoeconomic report was included in any dossier. They could not have been expected to be available for any of the three drugs owing to the fact that the initial applications were submitted 2 to 4 years before such dossiers became mandatory in 2005 (4 imatinib; 3 pegfilgrastim; 2 adalimumab).

Even if such dossiers would have been mandatory, all three marketing authorisation holders would have been (partially) exempted to supply a pharmacoeconomic dossier: imatinib would have been exempted from supplying a pharmacoeconomic dossier in favour of supplying a cost-minimisation analysis due to the fact that orphan drug designations were granted for all its indications; pegfilgrastim and adalimumab would have been exempted based on their successful application to be clustered in List 1A (Ministry of Health and CVZ 2011:6).[12]

### 4.3.2 International economic evaluations

No economic evaluation study could have been considered by the CFH at the time of reimbursement assessment (imatinib - CML:11/2001; pegfilgrastim: 12/2002; adalimumab - RA: 11/2003; PsA:09/2005; AS:07/2006; CD:08/2007; and JIA:01/2009) or successful central registration (imatinib - GIST: 05/2002; ALL, DFSP: both 09/2006; HES&CEL, MDS/MPD: both 11/2006) except for one indication in adalimumab (PP 02/2008). The evaluation of Nelson et al. published in January 2008 (as Epub in November 2007) could have been considered to support the decision making.

**Table 6:** Economic evaluations published at t=0

| | *Imatinib* | | | | | | *Pegfilgrastim* | *Adalimumab* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CML (2001) | GIST (2002) | ALL (2006) | DFSP (2006) | HES&CEL (2006) | MDS/MPD (2006) | Neutropenia (2002) | RA (2003) | PsA (2005) | AS (2006) | CD (2007) | PP (2008) | JIA (2008) |
| **T=0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1** | 0 | 0 |
| T=1 | 12 | 4 | 0 | 0 | 0 | 0 | 9 | 11 | 1 | 1 | 5 | 6 | 1 |

T=1 only displayed for the sake of completeness.

Nelson et al. (2008) conducted in their evaluation two analyses alongside a 12-week clinical trial in the USA; they indirectly compared the cost-effectiveness of biologic interventions in achieving a minimally important difference for the Dermatology Life Quality Index (DLQI MID), and in achieving a PASI-75 response; both versus an inactive dummy treatment (i.e., placebo).

Placebo treatment cannot be considered as standard for patients with plaque psoriasis in the presence of alternative systemic therapies. In addition, Nelson and colleagues considered – like other studies for PP performed outside European jurisdictions – the two agents efalizumab and alefacept as interventions, which are not registered in Europe (anymore).[13] Both medicines were removed from the analysis of this thesis without altering other outcomes since both were never used as comparators.

12 Exemption from pharmacoeconomic evaluations is granted for (a) orphan drugs, (b) if the costs do not exceed five years after market launch €500,000 per year, or (c) if a drug has a similar therapeutic value with another pharmaceutical but cannot be clustered together in List 1A, plus the inclusion is not related with additional costs. Exemption from the pharmacoeconomic analysis does not include an exempt from the budget-impact analysis. Additionally, manufacturers are obliged to supply a cost-minimisation study (Ministry of Health and CVZ 2011:6).

13 Alefacept was never approved for the Dutch (or European) market by the CBG (or EMA). Marketing authorisation for efalizumab was suspended on 17 April 2009 by the European Commission (and subsequently withdrawn on request of the manufacturer in August 2009) due to increased safety concerns that culminated in three confirmed cases (of which two fatal) of progressive multifocal leukoencephalopathy after long-term use (EMA 2009).

Outcomes were most favourable for adalimumab in terms of DLQI improvement (9.5-10.2), and among the highest in the PASI-75 responders (80.0%). ICERs for adalimumab compared to placebo were reaching at baseline about €5,000 per patient achieving DLQI MID, and about €11,000 per PASI-75 responder. Sensitivity analyses were not conducted.

The authors concluded that adalimumab and infliximab would be the most cost-effective biologic agents. However, no uniform decision rule is defined for cost-effectiveness ratios in PP. The inherent limitations of the study design make the evaluation appear less significant as conclusive evidence.

### 4.3.3 Budget-impact analyses

No budget-impact analysis was formally conducted for the two drugs applying for the reference pricing system on List 1A (pegfilgrastim and adalimumab) as those analyses are not considered legitimate according to the law.

For the extended indications of adalimumab, no budget-impact analysis was required (although listed in List 1A and 2) given that adalimumab was for all of the extended indications not the first to request reimbursement (either etanercept and/or infliximab requested reimbursement for these indications before). Nevertheless, the CVZ took the liberty to make small comments on the budgetary impact in the letter to the Minister of four extended indication-reports:

- For AS, the CVZ remarked that the extension would most likely cause no additional costs for the outpatient pharmaceutical budget since the application would exactly be the same for adalimumab and etanercept, and the costs fall within the range estimated for etanercept in this indication.
- For CD, the CVZ expected about 12-20% lower treatment costs per patient with adalimumab than infliximab, based on the yearly acquisition costs (€14,669-16,298 for adalimumab initial dose, compared to €18,311 for infliximab 5mg/kg for a 70kg patient). It would be unclear whether the lower treatment costs of adalimumab generate lower expenditures given infliximab's inclusion in the GVS only two months before adalimumab's CFH assessment in August 2007. In fact, every treatment of CD patients then creates additional costs for the outpatient pharmaceutical budget.
- For PP, the yearly acquisition costs per patient were estimated to be about €17,167 for infliximab; €14,130-17,391 for etanercept depending on the dosage regimen (12 weeks of 2x50mg or 40 weeks of 2x25mg); and €15,211 for adalimumab. The CVZ concluded that the extended indication PP would not lead to rising costs for the health care insurance system.
- For JIA, the extension of treatment options with adalimumab was expected to barely cause higher costs for the health care insurance system because the drugs differ not or only slightly in their costs (€14,125 for adalimumab versus €14,130 for etanercept per patient per year).
- RA had no such comment and PsA was not accompanied by a CVZ report or letter to the Minister.

It remains unclear whether the roughly estimated annual treatment costs per patient were adequately inflated over time for all interventions (e.g. etanercept). Also, the formal uptake of infliximab in June 2007 into the GVS was an advantage for the marketing authorisation holder when requesting reimbursement for CD in July 2007; he was then exempted from conducting a budget-impact analysis (etanercept is not indicated for Crohn's disease given its proven inefficacy; CVZ 2008b).

For imatinib, the CFH conducted a budget-impact analysis based on a compulsory model submitted by the marketing authorisation holder. The total costs of inclusion for the health care budget were estimated to be about € 2.7 million per year (5.9 million Dutch guilders; VAT included), with 118

treated patients impacting the budget by an estimated prevalence of 325 patients per year for this indication (estimate based on period 1989-95 in the Netherlands). The CFH remarked that the financial estimation contains uncertainty due to the limited knowledge on the actual amount of patients in the different phases, and the use of diverse medications in daily practice (CVZ 2001:3).

In retrospective, this economic impact appears widely underestimated with the total costs reaching €36 million in 2010 (for 1,471 users). However, the original analysis of 2001 merely considered the costs of second-line treatment in CML. Patients receiving imatinib as first-line therapy were at that time not captured in the calculations, nor were any for the other extended indications.

## 4.4 Concluding remarks

High uncertainty existed regarding the extended indications for imatinib that were reimbursed without additional assessment. For the other reports, uncertainty was often enough articulated in the reports by adjectives like “about”; “seemingly”; “overall”; and similar phrasings. The wording of the cells in *Table 5* on page 20 was taken from the CFH assessment reports and reflect this fact.

Imatinib and adalimumab were characterised by only indirect comparisons. The absence of appropriate effectiveness and quality of life data was mentioned several times across indications and medications. In the most extreme cases, the absence of data rendered the conduct of an assessment impossible. No generic quality of life instrument was applied in any indication (if applied at all). The lack of long-term data was repeatedly remarked by the CFH. The follow-up durations of no longer than 18 months must be regarded as insufficient to form the evidence basis for lifelong chronic diseases (imatinib and adalimumab). Another source of concern in adalimumab forms the frequently practiced selection of only adalimumab responders in the initial phase for randomisation in a subsequent maintenance phase.

Of all 8 available advices, 5 of them lacked sufficient information on effectiveness data, 5 others lacked sufficient data on quality of life, 2 of them stated lacking long-term information on side-effects, and 1 lacked any statement on the experience (see *Table 7*). Only one advice was without declaration of missing or insufficient information (PsA for adalimumab). The criteria efficacy; applicability; and ease of use were always possible to be assessed across all eight advices.

**Table 7**: Lacking or insufficient data per criterion of available advices from CVZ

| | Efficacy | Effectiveness | Quality of life | Side-effects | Applicability | Ease of use | Experience | *Total missing per advice* |
|---|---|---|---|---|---|---|---|---|
| imatinib (CML) | + | o | o | + | + | + | + | 2 |
| pegfilgrastim (neutropenia) | + | + | o | + | + | + | o | 2 |
| adalimumab (RA) | + | + | + | o | + | + | + | 1 |
| adalimumab (PsA) | + | + | + | + | + | + | + | 0 |
| adalimumab (AS) | + | o | o | + | + | + | + | 2 |
| adalimumab (CD) | + | o | o | + | + | + | + | 2 |
| adalimumab (PP) | + | o | + | + | + | + | + | 1 |
| adalimumab (JIA) | + | o | o | o | + | + | + | 3 |
| *Total missing per criterion* | 0 | 5 | 5 | 2 | 0 | 0 | 1 | - |

+ : criterion with sufficient data, o : criterion with lacking or insufficient data

For all three medicines, economic considerations played no visible role in the decision of whether or not to reimburse the three medications as reflected in the marginal economic evidence available in the advices. The only study obtainable for adalimumab was not of high methodological quality and relevance for the Dutch setting. Therefore, international assistance for assessing the cost-effectiveness was absent at the time of decision making and could not have been considered by the CVZ.

Given that the uncertainty was not trivial at t=0, the next step forms the investigation of the uncertainty at t=1 or better: the evidence available for its reduction.

# Chapter 5

Certainty in cost-effectiveness at present (t=1)

## 5.1 Cost-effectiveness evidence: publication development

### 5.1.1 Introduction

This section provides an overview of economic evaluation studies published over time for all three drugs. First, the findings from the systematic search algorithm are presented that led to the inclusion of eligible studies. Second, the time period between reimbursement decision making and the first published economic evaluation study is presented for an overview on the timeliness for cost-effectiveness research. Third, a cumulative presentation is given for the density of cost-effectiveness evidence. The research question to be answered was:

Q2.1: *(How) did cost-effectiveness evidence develop over time?*

Underlying rationale was whether a re-assessment of the chosen drugs is actually possible based on published economic evaluation studies.

### 5.1.2 Systematic search algorithm

The systematic literature search strategy as described in the *Methodology* section provided in total for all three medications a high amount of potentially relevant articles (*N*=199). After screening all articles, 54 full economic evaluation studies met the inclusion criteria (excluding duplications). Of these, 3 full-text copies were unable to retrieve (2 for imatinib; 1 for adalimumab); two other studies for adalimumab were excluded as they reported only on an aggregated level for the different TNF-inhibitors. Eventually, 49 studies qualified as eligible for analysis (14 for imatinib; 9 for pegfilgrastim; 26 for adalimumab). The inquiries of pharmaceutical companies provided in total one additional article for imatinib not indexed in PubMed (see *Appendix 2*).

### 5.1.3 Timeliness economic evaluation evidence

It could be expected from manufacturers to supply a pharmacoeconomic evaluation with the reimbursement application if they were to request inclusion on List 1B of the GVS from 2005 onwards. Although the three medications chosen were reimbursed before that date, the medicines would need to comply with that regulation if they asked for uptake nowadays. Therefore, the year of reimbursement submission is depicted in all subsequent tables (*Tables 8-10*).

For imatinib, economic evaluation studies were published two years after reimbursement submission (CML); three years after successful registration (GIST); and never for ALL, DFSP, HES&CEL, and MDS/MPD (see *Table 8).*

**Table 8:** Economic evaluations published for imatinib over time (incidental)

| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CML (2001) | **0** | 0 | 2 | 3 | 2 | 1 | 0 | 2 | 1 | 1 | 0 | 12 |
| GIST (2002) | | **0** | 0 | 0 | 1 | 0 | 1 | 2 | 0 | 0 | 0 | 4 |
| ALL (2006) | | | | | | **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| DFSP (2006) | | | | | | **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| HES&CEL (2006) | | | | | | **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| MDS/MPD (2008) | | | | | | **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| *Off-label use* | | | | | | | | | | | | 0 |
| Total | 0 | 0 | 2 | 3 | 3 | 1 | 1 | 4 | 1 | 1 | 0 | 16 |

In **bold** the years of reimbursement application (only CML, all other indications depicted with the registration year in the absence of an formal reimbursement procedure/ decision making)
Displaying also articles excluded from analysis [i.e., Skrepnek et al., 2005 (for CML), Huse et al., 2007 (for GIST)].

For pegfilgrastim, the first full economic evaluation study was published five years after reimbursement application (see *Table 9*).

**Table 9:** Economic evaluations published for pegfilgrastim over time (incidental)

| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Neutropenia (2002) | | **0** | 0 | 0 | 0 | 0 | 1 | 1 | 6 | 1 | 0 | 9 |
| *Off-label use* | | | | | | | | | | | | 0 |
| Total | | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 6 | 1 | 0 | 9 |

In **bold** the year of reimbursement application

For adalimumab, economic evaluation studies were published in the year of reimbursement submission (CD, PP); one year after reimbursement application (RA, AS); and 3 (JIA) to 6 (PsA) years after reimbursement application (see *Table 10*).

**Table 10:** Economic evaluations published for adalimumab over time (incidental)

| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RA (2003) | | | **0** | 1 | 1 | 2 | 1 | 1 | 2 | 1 | 1 | 12 |
| PsA (2005) | | | | | **0** | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| AS (2006) | | | | | | **0** | 1 | 0 | 0 | 0 | 0 | 1 |
| CD (2007) | | | | | | | **1** | 0 | 3 | 0 | 1 | 5 |
| PP (2008) | | | | | | | | **1** | 2 | 2 | 2 | 7 |
| JIA (2008) | | | | | | | | **0** | 0 | 0 | 1 | 1 |
| *Off-label use* | | | | | | | | | 1 | | | 1 |
| Total | | | 0 | 1 | 1 | 2 | 5 | 2 | 8 | 3 | 7 | 29 |

In **bold** the years of reimbursement application
Displaying also articles excluded from analysis [i.e., Brennan et al., 2007, Kielhorn et al., 2008 (both for RA), and Cummins et al., 2011 (for PsA)].

Overall, evidence for the main indications was available 2 years (imatinib), 5 years (pegfilgrastim), and 1 year (adalimumab) after reimbursement applications were filed (see *Table 11*). Extended indications took 3 years up to 'none-published(-yet)' for imatinib, and 0 to 6 years for adalimumab. In total, the mean (median) time for evidence was 2.33 (2) years for the nine indications with economic evidence (excluding indications without any evidence).

**Table 11**: Years between reimbursement decision and first (full) economic evaluation

| *Imatinib* | | | | | | *Pegfilgrastim* | *Adalimumab* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CML (2001) | GIST (2002) | ALL (2006) | DFSP (2006) | HES&CEL (2006) | MDS/MPD (2006) | Neutropenia (2002) | RA (2003) | PsA (2005) | AS (2006) | CD (2007) | PP (2008) | JIA (2008) | Mean [excl. 4*0] | Median [excl. 4*0] |
| 2 | 3 | - | - | - | - | 5 | 1 | 6 | 1 | 0 | 0 | 3 | 1.62 [2.33] | 3 [2] |

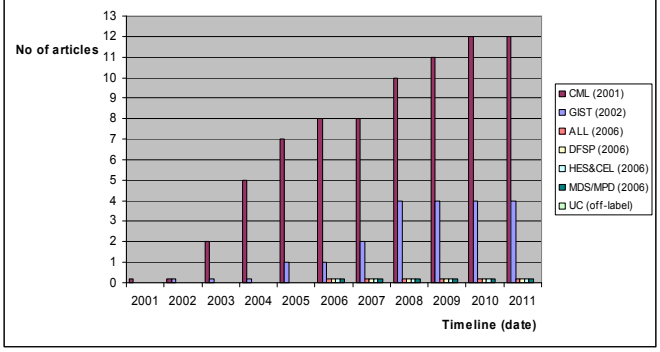
No article published (yet) is indicated with a " - ". Contrary, a " 0 " expresses the coinciding availability of studies and the reimbursement decision making process in the same year.

The non-availability of evidence for four indications of imatinib can partially be accounted to the use as orphan medication, as can the long frame of 6 years for PsA in adalimumab be related to a low total amount of patients.

### 5.1.4 Economic evaluation density

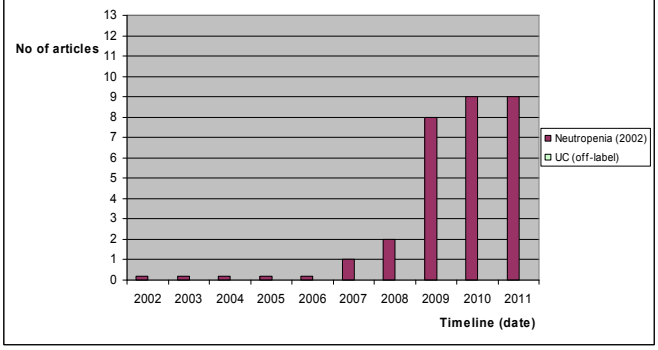
For imatinib, evidence on cost-effectiveness existed merely for CML and GIST at t=1. Three-fourth of articles concerned CML (12/16), one-fourth concerned GIST (4/16). No off-label use was explored (see *Figure 1*).

**Figure 1:** Published economic evaluations for imatinib (cumulative)



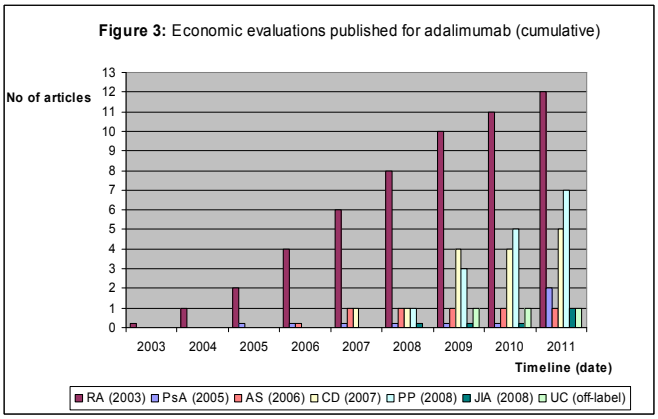

For pegfilgrastim, evidence on cost-effectiveness for neutropenia was reaching a peak in 2009 with six economic evaluation studies being published that year, eventually reaching nine studies in total. Off-label use was not explored (see *Figure 2*).

**Figure 2:** Published economic evaluations for pegfilgrastim (cumulative)




For adalimumab, the highest amount of evidence existed by far for RA; followed by PP and CD; and finished with great distance by PsA, AS, JIA, and one off-label indication (see *Figure 3*). In total 41% of studies focused on rheumatoid arthritis (12/29), 21% on plaque psoriasis (6/29), 17% on Crohn's disease (5/29), 7% on psoriatic arthritis (2/29), and one each for ankylosing spondylitis, juvenile idiopathic arthritis, and ulcerative colitis (off-label).

**Figure 3:** Economic evaluations published for adalimumab (cumulative)




The average (median) amount of studies published per indication was 4.08 (2); excluding the four indications without any evidence, the amount increases to 5.89 (5) studies per indication (*Table 12*).

**Table 12** Amount of (full) economic evaluation studies published

| *Imatinib* | | | | | | *Pegfilgrastim* | *Adalimumab* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CML (2001) | GIST (2002) | ALL (2006) | DFSP (2006) | HES&CEL (2006) | MDS/MPD (2006) | Neutropenia (2002) | RA (2003) | PsA (2005) | AS (2006) | CD (2007) | PP (2008) | JIA (2008) | Mean [excl. 4*0] | Median [excl. 4*0] |
| 12 | 4 | 0 | 0 | 0 | 0 | 9 | 12 | 2 | 1 | 5 | 7 | 1 | 4.08 [5.89] | 2 [5] |

Most studies were conducted for the main indications. In addition, extended indications with more treatment alternatives and uncertainty in the therapy regimen had also more articles (e.g. CD, PP).

### 5.1.5 Concluding remarks

The general conclusion from this section is: a cost-effectiveness review for the selected three expensive outpatient drugs seems possible. Studies were published in a timely manner following reimbursement decision making, although not in the year of reimbursement. Launching a re-assessment of the cost-effectiveness after 4 years appears possible. Also, studies were available for most indications and it remains arguable to assess the (not-assessed) indications with real-life data.

However, the amount of studies can be a misleading factor to draw valid conclusions from. Therefore, the next section will deal with qualitative aspects of the articles and offers a valuation of single studies from the perspective of the Netherlands.

## 5.2 Study quality and relevance for the Netherlands

### 5.2.1 Introduction

In this section, it is first looked at how well the studies complied per cost-effectiveness criterion on an aggregated level; then, the relationship of the NL-TQS to certain article characteristics is explored; lastly, methodological concerns will be described. The research question to be answered reads:

> Q2.2: *How well do economic evaluation studies comply with essential criteria proposed in this thesis as NL-TQS (based on, inter alia, the Dutch guidelines for pharmacoeconomic research and the criteria of Drummond)?*

Rationale was whether a re-assessment of the drugs is actually possible with the material found.

### 5.2.2 Compliance with cost-effectiveness (NL-TQS) criteria

Study compliance with criteria of the Dutch Total Quality Score Instrument (NL-TQS), which was based by large on the Dutch pharmacoeconomic requirements, varied among the drugs. The overall average was calculated and reported for all 49 studies. Otherwise, imatinib and pegfilgrastim would be disadvantaged due to their lower amount of studies (14 and 9 versus 26 for adalimumab).

Published economic evaluations had the highest compliance (i.e., a proportion of studies $\geq 0.80$) for: the study population as registered in the Netherlands (Item 2); the preferred CEA or CUA as analysis technique (Item 5); applying modelling techniques (Items 7); discount rates in line with international guidance (Item 8); total costs and outcomes valuation (Items 12 and 15); conducting an incremental analysis (Item 16); performing a univariate sensitivity analysis and varying both costs and effectiveness parameters (Item 17); making conclusions that followed the data presented (Item 19); and elaborating on inherent shortcomings and potential biases of outcomes and assumptions (Item 22).

The lowest compliance (i.e., proportion of studies $\leq 0.20$) had: considering a societal perspective (Item 4); applying differential discount rates in line with Dutch guidance (Item 8); measuring productivity costs (Item 10); using population-based utilities (Item 14); discussing the transferability of outcomes (Item 20); and discussing ethical and distributional implications of the findings (Item 21).

Several items remain not fully or partially not sufficiently complying. Many concerned (or were a consequence of): the outcomes measurement and elicitation of preferences; uncertainty analyses; the unmet societal perspective; and general characteristics included (see *Table 19* in *Appendix 3*).

### 5.2.3 Valuation of studies (NL-TQS)

Based on the valuation of every single study, an indication on the relevance was able to be obtained. The composition of that value according to the NL-TQS can be found in the *Appendices 5-7*.

Studies (*N*=49) appeared to range in the NL-TQS from a 20 to a 47, with the mean total quality score being 34.9 (SD=6.0). Studies for adalimumab showed a higher variation (36.23, SD=7.0) than those for imatinib (35.07, SD=3.5); articles in pegfilgrastim reached no higher values than a 35, with an average of 30.89 (SD=4.2). The mean number of authors was 5.6 per article (SD=2.8). 15 studies were conducted in the UK, 14 in the USA; only two concerned the Netherlands. The majority of articles was published in a medical journal (31/49). For an overview of the article characteristics see *Appendix 4*.

The relationship of the TQS on several key study characteristics is listed below (*Table 13*).

**Table 13:** Relationship country-specific quality scores (NL-TQS) and study characteristics

| Characteristic (valid observations) | Variable (*n*) | TQS, mean (SD) |
|---|---|---|
| Type of publication (N=49) | Medical (n=31) | 33.97 (6.5) |
| | Health economics (n=18) | 36.56 (4.6) |
| Primary funding source (N=49) | Pharma company (n=33) | 34.48 (5.3) |
| | Nonprofit sponsor (n=13) | 38.23 (5.3) |
| | Unstated (n=3) | 25.33 (4.7) |
| Country setting (N=49) | UK (n=14) | 39.64 (3.9) |
| | USA (n=15) | 33.67 (3.9) |
| | Europe [without UK] (n=15) | 32.47 (7.5) |
| | Others [outside Europe and USA] (n=5) | 32.80 (4.0) |
| Time horizon (N=49) | Sufficiently long (≥20 years) (n=13) | 37.27 (5.2) |
| | Insufficiently long (<20 years) (n=13) | 32.26 (5.7) |
| Analysis type (N=49) | CUA (n=29) | 37.38 (5.7) |
| | CEA (n=8) | 30.13 (4.4) |
| | CEA/CUA (n=10) | 33.60 (3.2) |
| | CBA (n=1) | 23.00 (-.-) |
| | CMA (n=1) | 27.00 (-.-) |
| Comparator (N=49) | Standard/usual care (n=38) | 36.16 (5.7) |
| | Non-standard/usual care (n=11) | 30.64 (5.0) |
| Indication (N=49) | Main-indications [CML/neutropenia/RA] (n=30) | 34.60 (6.1) |
| | Extended indications (n=19) | 35.42 (5.9) |
| Drug (N=49) | Imatinib (n=14) | 35.07 (3.5) |
| | Pegfilgrastim (n=9) | 30.89 (4.2) |
| | Adalimumab (n=26) | 36.23 (7.0) |
| No. of authors (N=49) | 1 to 4 (n=21) | 35.33 (5.0) |
| | 5 to 8 (n=23) | 34.00 (6.5) |
| | ≥9 (n=5) | 37.40 (7.2) |
| Study perspective (N=49) | Societal (n=7) | 39.14 (4.3) |
| | 3P Payer (societal in sensitivity analyses) (n=5) | 41.40 (3.4) |
| | Third-party payer (n=37) | 33.24 (5.5) |
| Modeling source (N=49) | Based on peer-reviewed publications (n=27) | 38.00 (4.8) |
| | Others (n=22) | 31.14 (5.0) |

Indications for a higher value in the relevance and quality can be seen for the following characteristics: studies published in a health economics-related journal; funded by a nonprofit sponsor; conducted in a UK setting; sufficiently long (≥20 years); using a CUA framework; considering standard or usual care; applying a societal perspective; and sourcing peer-reviewed publications for a model.

It can be hypothesised that these factor are influential in determining a higher value of the NL-TQS in at least these three medications. However, the average NL-TQS score showed in most cases a widely overlapping standard deviation for items. Therefore, it can easily be concluded that the NL-TQS instrument is not specific enough to be readily applied in determining studies quality for a Dutch context. Its use as a hard decision criterion to exclude studies has to be dismissed.

### 5.2.4 Methodological concerns

The instrument helped to identify methodological elements that formed reason for concern. These evolved around the following items (for the more detailed analysis, see *Appendix 3*):

- *Comparator*: standard (or usual) care was considered in 76% of all studies;
- *Analysis time period*: sufficient durations in about 63%; especially pegfilgrastim and adalimumab were limited here in that they considered a time frame of ≤1 year for chronic, severe conditions that require a longer time period for sophisticated analyses.
- *Modelling*: applied in 86% of studies, only 64% complied with the Dutch requirement to source peer-reviewed data; especially in imatinib and pegfilgrastim formed expert opinion frequently a major source of information. Markov models usually considered mortality – except when the time horizon was too short. Parameters were often modelled as time-dependent to account for health deteriorations over time and to overcome the lacking 'memory' of Markov models. Strikingly in pegfilgrastim, similar scenario models that incorporate both a decision tree and transition probabilities for a Markov model was applied in two-third of analyses. Most models were logically appealing; transparently described in terms of their assumptions, properties (i.e., transition probabilities), logic and structure; and seemingly tried to represent reality as close as necessary while being as simple as possible.
- *Best available effectiveness source*: A systematic search algorithm as indicator the attempt to identify the best available clinical effectiveness data was reported in only 39% of studies. In imatinib, the availability of one leading multicenter, randomised trial (named 'IRIS') made most studies not report a systematic literature search; the best available evidence was anticipated to be already sourced. It remained often unclear if the best available source was used for the other comparators (especially hydroxycarbamide and best supportive care).
- *Uncertainty on clinical effectiveness data*: Imatinib was characterised by a short follow-up of the IRIS trial in the first studies, which eventually incorporated a 5 years follow-up of the study. Also, the allowed cross-over in the trial is controversial. In pegfilgrastim, clinical trials differed in the allowed chemotherapy regimen, which generated different risk levels for febrile neutropenia. Also, the generalisability of studies with patients aged lower than 65 is debatable as more than half of all cancer patients are older than 65 years. In adalimumab, no head-to-head trials were available for the biologics. Placebo-controlled randomised trials showed differences in study designs, participants, allowed concomitant drug use, and included co-morbidities. Extrapolating data due to the short-term follow up of clinical trials was frequently practised.
- *Cost calculations*: Indirect costs in terms of productivity losses were seldom considered (22%). These costs seem highly relevant for pegfilgrastim given the higher frequency of administration for the standard comparator filgrastim. In adalimumab, indirect costs may also be an influential factor given the conditions adalimumab is indicated for, which generally affect patients several years before reaching the retirement age. Regarding direct medical costs: hospitalisation (often seen as influential cost driver) was (inadequately) excluded in four studies for imatinib and nine studies for adalimumab (PsA, PP, JIA and UC). Cost measurements lacked in half the studies a clear depiction of resource utilisation and/or the base year of cost calculations (41%). Overall, unit costs, probabilities, and validated sources were well documented.
- *Health outcomes*: many studies denoted effects in QALYs as composite health outcome measure (78%). They derived utilities by means of mapping preference weights via regression analysis (32%, solely in adalimumab) or based on expert panels (21%). Regression functions

mapped preferences from disease severity measures to obtain health utilities. Underlying assumption was in all cases that these measures are valid indicators for the quality of life. However, functional and disease-specific questionnaires might not adequately capture all effects on quality of life. Consequently, mapping algorithms might be flawed. Further, hard data obtained from patients in controlled trials should be preferred over soft data obtained from experts (Buxton et al. 1997:225).

Utilities (elicited via either direct or indirect measurement) were more often patient-based (36%) than population-based (11%). Imatinib and pegfilgrastim elicited in addition preferences by questioning clinical experts (neither patient- nor population-based). The remaining articles provided no clear information on the basis of valuation (28%).

In pegfilgrastim, several studies considered additionally survival alone via 'life-years gained'. In imatinib, life-years gained was applied next to other clinical efficacy outcomes (e.g., per surrogate responder). In adalimumab, four cost-effectiveness studies used conventional disease specific efficacy outcomes as primary measure (i.e., percentage of PASI-75 responders for PP; and ACR Pedi 30 responders for JIA). It remains desirable to concentrate on cost-utility research in order to enhance comparability within and across indications (and innovations).

- *Measure of variability*: The application of a measure of variability differs between cost items, health outcomes, and incremental ratios. In total only 31% of studies reported a measure of variability for the total costs; 43% reported such measure for the effectiveness outcomes obtained; and 38% included such measure for the ICER estimates. The other studies omitted any information on the uncertainty regarding the estimates sourced.
- *Uncertainty analysis*: Most studies conducted to a varying extend sensitivity analyses (94%). Deterministic univariate sensitivity analyses were more often applied than probabilistic sensitivity analyses (94% versus 53%). Effectiveness parameters were varied in 88% of all evaluations; cost parameters in 80%. Uncertainty analysis was relatively seldom supported by the depiction of cost-effectiveness planes (29%) or acceptability curves (37%).

### 5.2.5 Concluding remarks

It can be seen that the compliance with key Dutch requirements (i.e., a societal perspective; including productivity costs; and the differential discount rate) is low among economic evaluations. Concurrently, influential factors for the NL-TQS seemed to have an intermediate compliance: using a CUA framework (80%); considering standard or usual care (76%); sufficiently long (64%); sourcing peer-reviewed publications for a model (64%); funded by a nonprofit sponsor (34%); and applying a societal perspective (24%). The high standard deviations showed that the NL-TQS is no appropriate measure to base a judgement on of whether or not to exclude specific studies.

Bearing in mind that less than 40% of studies stated a systematic search algorithm and can be expected to have the best available clinical data sourced, therapeutic uncertainty prevails. This is underpinned by the low amount of included measures of variability for estimates. In conclusion, the study relevance seemed moderately fair enough to base the analysis on; however, it remains the second-best option (with real-life data being the best alternative).

## 5.3 Cost-effectiveness results (at t=1)

### 5.3.1 Introduction

With the preparation of the previous sections, it became clear that a re-assessment based on international economic evaluations is possible (Section 5.1), and that most of these studies can fairly be considered relevant for the Dutch setting (Section 5.2). These auxiliary sections paved the path for assessing the cost-effectiveness at present with the outcomes of the literature (this section).

Next, the cost-effectiveness results from the different analyses are reviewed from the Dutch perspective. Most importantly, a decision rule will need to be applied in order to make legitimate cost-effectiveness conclusions. Generally speaking: the lower the ICER the more likely an intervention is seen to be cost-effective; the higher the ICER the less favourable the cost-effectiveness of technologies. However, since cost-effectiveness is no single reimbursement criterion, other considerations gain in importance the higher the ICER to justify reimbursement.

In the Netherlands, no willingness-to-pay threshold is formally expressed from official side. An unauthorised, thoroughly crafted threshold of €80,000/QALY was proposed by the RVZ that attracted much attention (RVZ 2006). Moreover, the ceiling value of €80,000/QALY was seen as the maximum willingness-to-pay for very severe diseases (RVZ 2006:7). A liberal assumption frequently made in cost-effectiveness analysis is to disregard the severity of diseases and to compare the incremental ratio obtained against the maximum threshold value. The difficulty currently still exists to determine the exact slope of such a willingness-to-pay threshold. Although a continuous, positive, non-linear, S-shaped graph appears most likely, the exact curvature remains unknown.

Another issue is that it can be argued that an intervention cannot be regarded as cost-effective with high certainty in case a reasonable and well-designed sensitivity analysis yields incremental ratios for a non-negligible probability that exceed the decision rule.

Following these considerations, the threshold of €80,000/QALY will be used as maximum decision rule to indicate the likelihood of cost-effectiveness for the Netherlands. ICER point-estimates will be appraised in context with the results from uncertainty analysis. Furthermore, ICERs displayed are converted and inflated to 2010 Euros for reason of comparability.

A note for the reader: economic evaluation studies are abbreviated with numbers in the following part. Corresponding studies are listed separately in the *Bibliography*. Incremental cost-effectiveness outcomes are also depicted in a tabulated format in the *Appendices 8-10*.

### 5.3.2 Case 1: Imatinib

*Chronic myeloid leukemia*

First-line therapy compared to standard therapy (interferon-alpha) resulted in ICER point-estimates likely to be considered cost-effective (€46,000 to €55,000 per QALY,[2-6] with one study from China reaching a converted €8,000/QALY).[7] ICERs ranged in sensitivity analysis between €52,000 to €91,000/QALY (€11,000/QALY for China) and were in all studies reported to be sensitive to the price of imatinib.[1-7] Cost-effectiveness analysis resulted in ICERs of €45,000 to €51,000 per life-year gained for imatinib compared to interferon-alpha.[2,5-7] Concurrent treatment of interferon-alpha with low-doses of the chemotherapeutic agent cytarabine was barely influencing cost-effectiveness ratios.

Imatinib resulted in baseline ICERs of about €150,000/QALY when compared to hydroxycarbamide – the former standard care and still a treatment option especially in patients not tolerating interferon-alpha.[3,4] Outcomes were specifically sensitive to the expected progression and survival for the different treatment options, reaching at the upper bound €250,000/QALY.[4] Noteworthy, outcomes were based on the 18-month data from the IRIS-trial.

Compared to stem cell transplantation, imatinib reached an ICER of €75,000/QALY and was able to dominate stem cell transplants in sensitivity analysis.[8] Again, imatinib's costs were most sensitive.

Compared to a historical group of patient being treated with combination chemotherapy and palliative care in hospital or at home, imatinib reached an ICER of about €55,000/QALY when administered first in the accelerated phase, and €79,000/QALY when administered first in the blast crisis.[9] The ICER estimates were most sensitive to the price of imatinib and the discount rate, reaching about €114,000/QALY in the accelerated phase and €228,000/QALY in the blast crisis.

Second-line therapy with imatinib was compared in one study with hydroxycarbamide after interferon-alpha failure, the originally registered indication of imatinib as assessed by the CFH.[10] Results suggest that imatinib could be considered cost-effective with an ICER point-estimate of €72,000/QALY. Uncertainty analysis revealed imatinib being sensitive to its price and the discount rate, leading to a maximum ICER at the upper bound of €117,000/QALY.

Another study resulted in a high estimate of €126,000/QALY when continuing treating with imatinib 400mg/kg after imatinib 400mg/kg failure, compared to interferon-alpha therapy. Escalating imatinib dose to 800mk/kg resulted in an ICER of €58,000/QALY compared to interferon-alpha.[5] No sensitivity analyses were conducted. Imatinib escalation was not compared to interferon-alpha after imatinib 400mg/kg failure; rather, the comparator arm consisted solely of continuous interferon-alpha.

A third analysis compared dasatinib to imatinib dose-escalation of 800mg/kg with an ICER of €7,000/QALY.[11] In sensitivity analysis, dasatinib was able to dominate the escalation strategy in the best case while it reached an ICER of about €72,000/QALY at the upper limit (all patients imatinib resistant from onset). Dasatinib is likely to be considered cost-effective in imatinib-refractory patients.

#### *Gastrointestinal stromal tumours*

All studies concerned advanced-staged GIST which was metastatic and unresectable with surgery. One study compared imatinib to a historical control group that was treated, if treated at all, with surgery, radiation and chemotherapy and resulted in an ICER point-estimate of €47,000/QALY.[12] Sensitivity analysis resulted in barely higher estimates of €53,000/QALY at the upper limit as a consequence of alterations to survival rates. Two other studies investigated the costs per life-year gained and came to a range of €12,000 to €39,000 per LYG.[13,14] Where clearly documented, uncertainty analysis resulted in a maximum of €38,000 per LYG (price sensitivity for imatinib and estimated survival).[13] Given the disease severity and lacking effective alternatives, reimbursement in GIST seems justified.

### 5.3.3 Case 2: Pegfilgrastim

#### *Febrile neutropenia*

First-line treatment (or more specific for this indication: primary prevention of febrile neutropenia; i.e., administered from the first cycle of chemotherapy onwards) with pegfilgrastim was examined in the majority of studies.[16-20,22-23] Most studies considered filgrastim as comparator (usually 6 days),[17-20,22] while two studies considered 'No G-CSF' as intervention.[15,16] Of those studies

considering No G-CSF as intervention, only one used it as comparator.[15] In that study, primary prophylaxis of pegfilgrastim amounted to about €36,000 per avoided hospitalisation for FN.[15] The second study showed that No G-CSF and filgrastim were both dominated by pegfilgrastim.[16] Sensitivity analysis was able to show an upper value of €10,000/QALY.

Similarly, all cost-utility analyses of pegfilgrastim compared to 6-day filgrastim (17-20,22) showed ICER point-estimates ranging from €430 to €29,000 per QALY. Pegfilgrastim dominated filgrastim when administered for the longer recommended period of 11-days.[18,22] This is mainly because the total medication costs of filgrastim increased due to the daily administration.

Cost-effectiveness analyses were conducted in most studies concurrently to cost-utility. ICER point-estimates of pegfilgrastim ranged from €410-€27,000 per life-year gained compared to 6-day filgrastim;[17-20,22] or dominated No G-CSF or 11-day filgrastim.[15,22] Five studies also looked at the cost per febrile neutropenia event avoided;[18-22] versus 6-day filgrastim the ICER ranged between €1,800-€13,000 per FN avoided; 11-day filgrastim were dominated by pegfilgrastim.[22]

Second-line treatment (secondary prophylaxis; i.e., administered only after an confirmed FN event) was considered in two studies.[15,21] Compared to No G-CSF, secondary prophylaxis of pegfilgrastim was able to result in an ICER of €58,000 per avoided hospitalisation for FN.[15] The other study comparing primary to secondary prophylaxis pegfilgrastim found an ICER point-estimate of €98,000/QALY, which varied in sensitivity analysis from €42,000 to €250,000 per QALY.[21]

A cost-effectiveness analysis reached €93,000/LYG for primary prophylaxis of pegfilgrastim versus secondary prophylaxis pegfilgrastim.[21] Primary versus secondary prophylaxis with pegfilgrastim led to an ICER of about €40,000 per FN event avoided.[21]

Remarkably, many analyses were conducted without sensitivity analysis. This is more often observed for cost-effectiveness outcomes than cost-utility results. Overall, the costs per outcome were much higher with secondary prophylaxis than primary prophylaxis. Restricting reimbursement to the administration after the event of FN (equaling secondary prevention) could be a more cost-effective therapy option given the ICER estimates of <€80,000/QALY.

### 5.3.4 Case 3: Adalimumab

*Rheumatoid arthritis*

First-line therapy with adalimumab combined with methotrexate is unlikely to be considered cost-effective compared to traditional DMARDs (point-estimates of above €160,000 per QALY).[24,25] Contrary, adalimumab monotherapy seemed inconclusive in its results when compared to traditional DMARDs (point-estimates of about €85,000 and €55,000 per QALY). Considering that one study was primarily focussing on women; concealed the total QALYs gained; and explored the uncertainty for adalimumab in only one single univariate analysis of one parameter,[25] adalimumab monotherapy can be seen to exceed the threshold in the methodologically more sound analysis.[24]

Second-line therapy of adalimumab combined with MTX is likely to result in a robust cost-effectiveness ratio within the Dutch ceiling when compared to non-biologic standard care (point-estimates of about €41,000 to €52,000 per QALY).[24,26-27] Adalimumab alone is also likely to be considered cost-effective (point-estimates from about €48,000 to €76,000 per QALY).[24,26] The administration in patients with late RA led to no cost-effective result for any therapy (point-estimate of above €100,000/QALY).[24] The comparison with other biologics showed inconclusive results that indicated adalimumab not being cost-effective but dominated by etanercept,[29] or adalimumab dominating infliximab while etanercept yielded more QALYs at a ratio of about €80,000/QALY.[28]

Third-line adalimumab therapy after traditional DMARDs plus one TNF-antagonist failed resulted in an unfavourable high ICERs for adalimumab when compared with returning to DMARDs (point-estimates above €220,000/QALY); yet, the authors regarded their analysis as exploratory (no uncertainty analysis was conducted).[24] Another more sophisticated analysis conducted in 2011 showed adalimumab being cost-effective at baseline and in sensitivity analyses when compared with a return to non-biologic treatment (point-estimate: €44,000/QALY; upper limit from sensitivity analysis: €79,000/QALY.[30] Compared to a biologic agent (infliximab after infliximab-failure), adalimumab was reported to be able to dominate the comparator (no values transparently displayed). [27,31].

Fourth-line use of adalimumab after previous DMARDs and two other TNF-inhibitors failed was examined in another analysis; the comparator was comprised of returning to traditional DMARDs. Adalimumab yielded baseline incremental ratios always above €700,000/QALY that cannot be seen as cost-effective anymore.[24] Sensitivity analyses were not applied and outcomes not robust.

### *Psoriatic arthritis*

Adalimumab in third-line use after traditional DMARDs failure seemed cost-effective compared to no active therapy for mild-to-moderate disease (point-estimate: €23,000/QALY).[34] Estimates appeared robust in sensitivity analysis and varied the most with alterations to effectiveness parameters (yet between €12,000/QALY to €22,000/QALY).

Rejecting adalimumab as cost-effective treatment based on the slight difference in effectiveness (etanercept: +0.42 more QALYs) that led to adalimumab being extendedly dominated by etanercept seems inadequate given the underlying indirect comparison of treatments and the inherent risk of biased outcomes. Etanercept was also less robust in sensitivity analysis and yielded ICERs at the upper limit of €44,000/QALY. It remains unanswered how the cost-effectiveness would be when compared to continuing DMARD therapy (or surgery, both of which are usually only applied in severe forms).

### *Ankylosing spondylitis*

Adalimumab appeared cost-effective as third-line therapy in patients with AS that were intolerant or had an insufficient response to ≥2 NSAIDs if compared to traditional DMARDs or NSAIDs (point-estimate: €37,000/QALY).[35] Results suggested that treatment should be restricted to responders after 2 to 3 months as the treatment of patients with adalimumab despite the level of response was associated with the highest ICER of €100,000/QALY compared to NSAIDs or DMARDs therapy. As the authors correctly noted, the restriction practice would be in line with guidance of the British Society of Rheumatology as well as the Netherlands (CVZ 2006b:6).

### *Crohn's disease*

Second-line adalimumab use for severe CD was very likely to be cost-effective compared to non-biologic pharmacotherapy plus surgery (point-estimates: €12,000-€25,000/QALY).[37,38] Moderate-to-severe disease is likely to be cost-effective in case the treatment period is limited and dependent on therapeutic response (point-estimates: €16,000 to €52,000/QALY).[36,37] Outcomes were sensitive to the treatment duration, time horizon, and hospitalisation rate (estimates ranged from €33,000 to €280,000/QALY). Use in patients with moderate CD alone is likely to be considered cost-ineffective (point-estimate: €250,000/QALY).[38] No sensitivity analysis was explored. Adalimumab dominated a biologic comparator at baseline and under varying parameter assumptions.[39]

Moreover, the outcomes of four analyses suggest the more cost-effective application of episodic biologic therapy instead of continuous maintenance – regardless of the comparator.[38] However, the authors mention that the maintenance analysis is exploratory due to short follow-ups of clinical trials.

The resulting ICER for third-line infliximab of over €260,000/QALY compared to adalimumab cannot be regarded as cost-effective in favour of the dose escalation strategy. The study indicated that adalimumab might be a cost-effective alternative for infliximab-refractory patients.[40]

### *Plaque psoriasis*

One study yielded an ICER likely to be considered cost-effective when compared to a non-biologic intervention (point-estimate €47,000/QALY).[42] Another study of only one-year duration resulted in a favourable ICER of €48,000/QALY at baseline.[41] Uncertainty analysis reached values for adalimumab up to €57,000/QALY for the 10 years analysis,[42] and €125,000/QALY for the other.[41] Differences in outcome can be attributed to the time horizons; modeling techniques; perspectives; and included cost factors. Compared to a biologic, adalimumab was highly cost-effective (point-estimate: €400/QALY).[45] In sensitivity analysis, the ICER ranged up to €17,000/QALY.

Cost-effectiveness analyses revealed incremental ratios of €10,000-€20,000 per PASI-75 responder against non-biologic comparators,[43,44] and €16,000 per PASI-75 responder against biologics.[46] Sensitivity analyses resulted in ICERs of up to €25,000 per PASI-75 responder compared to non-biologics and €76,000 per PASI-75 responder when compared to biologics.

Although one study reported a decision rule with cut-off values, the underlying argumentation was flawed and based on a misinterpretation. Therefore, no definite conclusions can be drawn from these analyses in the absence of a valid reference as decision rule. It could be questioned why mapping techniques of PASI to QALYs where not more widespread used.

### *Juvenile idiopathic arthritis*

Only one cost-effectiveness analysis was conducted for JIA, comparing adalimumab with conventional DMARDs. It can be seen that adalimumab yielded the highest and least robust ICER of all interventions (point-estimate of €31,000 per ACR Pedi 30 responder; sensitive to the assumed efficacy of biologic and DMARD treatment and reaching up to €50,000 per ACR Pedi 30 responder). However, the ACR Pedi 30 response rate was also the highest among all interventions.[48]

The documented threshold value of CA$30,000/QALY remained unexplained and seems arbitrarily chosen in alignment with the NICE threshold for cost-utility analyses (not cost-effectiveness). Conclusive evidence for adalimumab being cost-effective in JIA must be seen as lacking.

### *Off-label use (ulcerative colitis)*

One cost-utility analysis was conducted for a non-licensed indication, namely: ulcerative colitis refractory to non-biologic treatment.[49] Positive effects achieved with adalimumab after infliximab-failure in other registered indications were anticipated. Adalimumab was therefore added to treatment after normal dose infliximab failed, or when patients were non-responsive to 10mg/kg dose escalation. Adalimumab is likely cost-ineffective when compared to usual care after infliximab 5mg/kg-failure (ICER point-estimates above €230,000/QALY).[49] Estimates did not range in sensitivity analysis below €178,000/QALY (but up to €580,000/QALY). Long-term research beyond 5 years is lacking.

### 5.3.5 Concluding remarks

In first-line treatment for CML, imatinib seemed cost-effective when compared to interferon-alpha, stem cell transplant, and a combination of chemotherapy and palliative care. When compared to hydroxycarbamide, imatinib is less likely to be considered cost-effective (ICERs of about €150,000/QALY). Interestingly, in the two studies considering hydroxycarbamide as intervention, the QALYs gained between hydroxycarbamide and interferon-alpha varied only slightly and the authors mentioned that the use of interferon-alpha as comparator in many studies would be questionable. The use of interferon-alpha is able to influence cost-effectiveness results in the advantage of imatinib as the less expensive hydroxycarbamide would lead to higher ICER values. Therefore, cost-effectiveness of imatinib in first-line seems still not fully demonstrated for all relevant comparators.

In second-line therapy of CML, imatinib seemed cost-effective compared to hydroxycarbamide after interferon-alpha failure, the indication officially registered in the Netherlands and assessed by the CFH, with a cost-effectiveness ratio of <€80,000/QALY. Unfortunately, imatinib dose escalation was not compared with a switch to interferon-alpha after interferon-alpha failure for both arms. A comparison after initial imatinib failure may also be of interest. Lastly, dasatinib seemed more cost-effective than imatinib 800mg/kg escalation after imatinib <600mg/kg failure.

In therapy of advanced GIST, imatinib seemed also cost-effective. However, resectable GIST was not explored, as were less severe cases not explored and should form a future research opportunity.

Primary prevention with pegfilgrastim of febrile neutropenia was likely to result in outcomes mainly considered cost-effective. Secondary prevention resulted in ICERs that indicate a possible more cost-effective administration after an FN event occurred.

Uncertainty remains around the actual duration of therapy in daily practice. As a means of cost containment, several articles mention the practice of administering only 6 instead of 11 days of filgrastim. This practice is seen to be associated with a higher risk of FN and, accordingly, should be discouraged. Pegfilgrastim seems to less expensive and still provides a safe prophylaxis against FN while being administered only once per cycle of chemotherapy.

**Table 14**: Cost-effectiveness results per indication

| Indication | Specification | C/E result |
|---|---|---|
| *Imatinib* | | |
| CML (2001) | First-line | ~ (+) |
| | Second-line | + |
| GIST (2002) | Second-line (unresectable) | + |
| | Second-line (resectable) | ? |
| ALL (2006) | - | ? |
| DFSP (2006) | - | ? |
| HES&CEL (2006) | - | ? |
| MDS/MPD (2006) | - | ? |
| *Pegfilgrastim* | | |
| Neutropenia (2002) | First-line | ~ (+) |
| | Second-line | + |
| *Adalimumab* | | |
| RA (2003) | First-line (alone) | ~ (+) |
| | First-line (+MTX) | - |
| | Second-line (alone) | + |
| | Second-line (+MTX) | + |
| | Second-line (late RA) | - |
| | Third-line | + |
| | Fourth-line | - |
| PsA (2005) | Third-line | + |
| AS (2006) | Third-line | + |
| CD (2007) | Second-line (severe) | + |
| | Second-line (moderate) | - |
| | Second-line (mod-to-sev) | + |
| | Second-line (episodic) | + |
| | Third-line | (+) |
| PP (2008) | | (+) |
| JIA (2008) | | (~) |
| Off-label (UC) | Third-line | - |

+: likely cost-effective; -: unlikely cost-effective; ~: unknown cost-effectiveness

Adalimumab seems likely to be cost-effective in rheumatoid arthritis as second-line therapy when combined with methotrexate; in first-line therapy only when administered alone. Third-line therapy after TNF-failure seems also cost-effective regardless of the comparator. Fourth-line therapy seems inefficient. In Crohn's disease, adalimumab is most likely cost-effective when applied as episodic treatment; more uncertainty surrounds the maintenance therapy and treating only moderate forms of disease. In PP, adalimumab might be cost-effective but the need for additional criteria seems given in the light of the lower severity of the disease. For PsA, the application seems cost-effective; for AS, cost-effectiveness is only given with treatment cessation for patients not responding to adalimumab after 2 to 3 months; for JIA, the cost-effectiveness analysis is difficult to interpret but a factor to be considered is the target group of children and adolescents; and for UC, adalimumab after infliximab-failure is highly unlikely to be considered cost-effective. Results were more often reaching the threshold with the baseline value only.

## 5.4 Concluding remarks (for t=1)

Uncertainty surrounding reimbursement decisions revolved around the published studies. Enough economic evaluations seemed to be published for all three drugs in most indications (except for ALL, DFSP, HES&CEL, and MDS/MPD in imatinib), with a fair relevance for the Netherlands.

Outcomes showed in general a favourable picture of cost-effectiveness for second-line CML, second-line (unresectable) GIST; febrile neutropenia; first-line RA (administered alone); second-line RA (alone or with MTX); third-line RA; in PsA, AS, and PP; and moderate-to-severe CD. Unfavourable outcomes were obtained for first-line RA (with MTX); second-line RA in patients with late disease; fourth-line RA; moderate CD; ulcerative colitis; with JIA being also relatively uncertain.

Given that these studies are characterised by differences in methodology, design, and included characteristics, concerns on the accuracy of outcomes prevail. In particular three potential factors for biases shall be highlighted here: publication, funding, and drug price deflation.

### *Publication bias*

Most studies showed a favourable cost-effectiveness ratio within commonly cited thresholds (if applicable). Even in cost-effectiveness studies without broadly agreed ceiling value, the reference to the cost-utility decision rule was frequently made. In total, 61% of studies referred to a willingness-to-pay threshold. These attempts point to the lack of a consensus on acceptable cost-effectiveness ratios and the disadvantages of that study design in the absence of a clear decision rule. It can also be seen that the 'easier' interpretation of cost-utility ratios led to an increased amount of cost-utility analyses (80%). Overall, it cannot be excluded that a certain bias exists regarding the publication of cost-ineffective results and the withdrawal of such studies (as suggested in Bell et al. 2006).

Another observation forms the publication in rather medical than health economics-related journals. It could be expected that the requirements for acceptance are lower in medical than economical journals. Therefore, the general quality may be lower for those studies.

### *Funding bias*

The sponsorship by the pharmaceutical industry for economic studies may be a confounding factor. Three-fourth of studies provided a disclosure on the primary funding source (77%), with little variation among the drugs (85% imatinib, 78% pegfilgrastim, 73% adalimumab). Where providing a funding disclosure, about two-third declared sponsorship by a pharmaceutical company (65%) with most industry sponsoring being done for pegfilgrastim (86%), then imatinib (64%) and adalimumab (58%). It remains desirable that studies are commissioned by independent, non-profit sponsors to reduce any direct or indirect (conscious or unconscious) influence (Freemantle and Maynard 1994).

Another concern regards the observation of a researcher group co-authoring several studies in pegfilgrastim. All co-authors were employed by the same consulting company and the articles show striking similarities in the structure and scenario applied.

Thirdly, a relation between funding and journal type seems to be observable in that 73% of the pharmaceutical company sponsored articles were published in medical journals, and 69% of nonprofit sponsored in health economics-related journals. To test this association on significance, a 2x2 contingency table was constructed and Fisher's exact test run to test for statistical significance. A chi-squared test was rejected given that the expected values in the table include numbers below 5.

**Table 15**: Fisher's exact test on funding and journal

| | | Pharmaceutical industry-funded | | |
|---|---|---|---|---|
| | | No | Yes | Grand Total |
| Medical journal publication | Yes | 4 | 24 | 28 |
| | No | 9 | 9 | 18 |
| | Grand Total | 13 | 33 | 46 |

Fisher's exact test calculates the probability that if 28 medical journal publications were to be chosen at random, what is the probability that 24 would be among the 33 pharmaceutical industry funded articles, and 4 among the 13 nonprofit sponsors. The directional hypothesis is: economic evaluations being funded by pharmaceutical companies tend to be published in medical journals while those funded by nonprofit sponsors tend to be published in health economics-related journals.

The exact probability of finding this positive association is P=0.0113. The null hypothesis (equal to no association between funding and journal publication) can be rejected at a significance level of $\alpha$=0.05. Even when investigating the undirectional hypothesis, the probability of finding any association between funding and journal publication becomes P=0.0170 and the null hypothesis remains rejected. It can be concluded that industry funding and medical journal publication tend to be associated for this subset of economic evaluation studies at a statistically significant level.

### *Drug price deflation*

It can be argued that the cost-effectiveness ratios are likely to increase over time (i.e., a decreasing ICER) given that the price of the drug is usually mentioned as an influential factor in sensitivity analysis, plus the existing empirical evidence of price deflation for pharmaceutical products over time (Hoyle 2011). When looking back for the three drugs in time, the price development of all three drugs remains at about 0% as seen when subtracting the quantity change from the total expenditure change (see *Table 16*). Therefore, price developments were relatively stable and fluctuated around 0%.

**Table 16**: Expenditure, reimbursement costs, utilisation, and price developments (GIP database)

| | | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 |
|---|---|---|---|---|---|---|---|---|---|---|
| Development expenditures (costs, TC) | Imatinib | - | 130% | 35% | 30% | 28% | 6% | 10% | 4% | 0% |
| | Pegfilgrastim | | - | 219% | 60% | 48% | 12% | 22% | 11% | 5% |
| | Adalimumab | | | - | 66% | 43% | 34% | 57% | 25% | 15% |
| Development utilisation (DDDs, U) | Imatinib | - | 130% | 35% | 30% | 30% | 3% | 11% | 5% | -8% |
| | Pegfilgrastim | | - | 219% | 60% | 48% | 10% | 23% | 10% | -6% |
| | Adalimumab | | | - | 66% | 44% | 32% | 58% | 24% | 4% |
| Development drug prices (TC - U) | Imatinib | - | 0% | 0% | 0% | -3% | 2% | -2% | -1% | 8% |
| | Pegfilgrastim | | - | 0% | 0% | -1% | 2% | -1% | 1% | 11% |
| | Adalimumab | | | - | 0% | -1% | 2% | -1% | 1% | 11% |

In total, a certain amount of uncertainty prevails that limits the study. More details on the limitations will be addressed in the discussion part.

# Chapter 6

## Consequence from evidence at t=1 for reimbursement decisions

This chapter aims to answer whether the positive decisions made at t=0 were justified and the evidence of t=1 has effect on continuous reimbursement. The research question to be answered is:

Q3: *Is the positive reimbursement decision in light of the new evidence still legitimate?*

The answer to this question flows from the synthesis of the outcomes obtained at t=0 (*Chapter 4*) and the results on cost-effectiveness (*Chapter 7*). Considering that an unofficial threshold ratio was chosen, only trends of cost-effectiveness should be traced. Also, possible consequences following a review procedure shall be addressed. The consequences for reviewed pharmaceuticals will subsequently be discussed and the following question tried to be answered:

Q4: *How would a review tend to change the decision?*

The second question is mainly of explorative nature. After all, only cost-effectiveness considerations were in the focus here (and not legal, ethical, or other societal aspects).

### 6.1 Legitimacy of reimbursement decisions

#### Case 1: Imatinib

In imatinib, the registered indications were not assessed by the CVZ – except for CML in second-line use. For that indication, long-term effectiveness and quality of life data in support of the therapeutic value were absent at t=0 (although the survival was high in a subsequent 5 years follow-up of the IRIS-trial). At the same time, only the budget-impact was considered (no pharmacoeconomic dossiers were available, nor were international evaluations published at that time). At present, the result of one study pointed towards a use of imatinib likely to be considered cost-effective at a threshold of <€80,000/QALY (for a tabulated overview on the outcomes of t=0 and t=1, see *Table 17*).

For no other indication was a formal reimbursement assessment made. The cost-effectiveness evidence was ambiguous for the extended first-line administration in CML, while results were likely to be considered cost-effective in unresectable GIST. For resectable GIST and the four other indications ALL, DFSP, HES&CEL, and MDS/MPD, no formal assessment was done by the CVZ nor were full economic evaluations published. It remains unclear whether reimbursement of these indications would be considered cost-effective. However, a fact in favour of imatinib is the registration as orphan medication for all six indications. Therefore, it would be unethical to conclude from the (absent) evidence that reimbursement was not justified at the moment of decision making. Moreover, an investigation into these indications seems reasonable to help gain information about these relatively uncertain indications (from an economical perspective).

### Case 2: Pegfilgrastim

Febrile neutropenia, the single indication registered for pegfilgrastim, was assessed by the CFH and lacked data on the quality of life and experience. Concurrently, no economic data was available (neither budget-impact, nor pharmacoeconomic evidence or international studies). From the present viewpoint, primary prevention with pegfilgrastim is very likely to be considered cost-effective when compared to filgrastim, less likely when compared to secondary prevention with pegfilgrastim. Uncertainty existed about the real-life frequency of administration for filgrastim (which directly influences the cost-effectiveness ratio). The original reimbursement decision seems justified.

### Case 3: Adalimumab

Adalimumab was assessed on all six of its indications. However, the indications were restricted to moderate-to-severe disease and patients not adequately responding (or contra-indicated) to alternative forms of therapy. Few published cost-effectiveness analyses did not match these registered indications.

Second-line adalimumab in moderate to severe active RA was assessed by the CFH and lacked data on the side-effects, while also no economic data was available. International economic evaluations at t=1 showed that the indication is likely to be considered cost-effective. First-line treatment with adalimumab was not assessed by the CFH after reimbursement was extended to it two years later in 2005. Present cost-effectiveness outcomes for first-line therapy indicated ambiguous results that pointed into a more positive trend if administered alone, and results considered likely to be cost-inefficient if administered with methotrexate. Reimbursement in second-line RA seems justified while the first-line administration is more uncertain and dependent on the concurrent therapy regimen.

For active and progressive PsA, the CFH assessment showed no major uncertainty on any assessment criterion. However, economic analyses were again absent. At t=1, one study published in the *Health Technology Assessment* series formed a perfect match for the indication and showed a high likelihood to be considered cost-effective. Consequently, reimbursement seems justified.

Severe active AS was characterised by uncertainty in the assessment of the therapeutic value on the items effectiveness and quality of life; economic analyses were absent. At t=1, one study closely matching the Dutch registered indication resulted in a cost-effectiveness ratio likely to be considered cost-effective. Hence, the reimbursement decision seems appropriate and justified.

Moderate to severe CD was lacking data on the effectiveness and quality of life at t=0; economic analyses were also not available. At present, results of economic evaluations indicated that the administration of adalimumab can be considered as cost-effective. Reimbursement seems justified.

Moderate to severe chronic PP was not assessed on its effectiveness at the time of reimbursement decision making; also, a budget-impact and pharmacoeconomic report were missing. However, at the time of decision making, one cost-effectiveness analysis was available. Outcomes were difficult to interpret and the comparator consisting of an inactive dummy treatment (placebo). At t=1, studies showed several methodological limitations that increased the uncertainty and reliability of outcomes. Overall, a trend towards cost-effectiveness ratios likely to be considered efficient were observed, but no conclusive judgement on the appropriateness of reimbursement seems possible.

Active JIA expressed uncertainty in the therapeutic value for three items: effectiveness, quality of life, and side-effects. Economic analyses were absent. At t=1, one cost-effectiveness analysis was available but difficult to interpret qua outcomes per surrogate endpoint. Uncertainty remains about the appropriateness of reimbursement. Remarkably, this indication formed the only one in which the CFH clearly favoured the comparator over adalimumab given its long-term data and experience.

## Additional analyses

Next to the official indications, several other administrations were assessed in published economic evaluation studies for pegfilgrastim and adalimumab. Imatinib was without any extensive restrictions and therefore all analyses considered before.

In pegfilgrastim, the secondary prophylaxis for febrile neutropenia after the event of FN was considered in few articles and compared to primary prophylaxis. Results give reason to review the recommendation of primary prophylaxis as the secondary use might be more cost-effective. Further investigation would be needed in support of this indicative signs.

In adalimumab, the concurrent sequential use of more than two classical biologic agents seemed inefficient in RA, regardless of the order of administration. In CD, treatment of moderate disease only was also not likely to be considered cost-effective. However, episodic treatment (i.e., re-treatment of patients with relapse after initial response) of CD might be a more cost-effective treatment than continuous maintenance therapy. And the off-label indication ulcerative colitis refractory to infliximab treatment was pointing to adalimumab being highly unlikely to be considered cost-effective.

All these analyses point to treatment options where reimbursement should be (re-)considered.

**Table 17**: Synthesis of results from T=0 and T=1

| | | | T=0 | | T=1 |
|---|---|---|---|---|---|
| Medication | Indication | Treatment line | Clinical uncertainty | Economical certainty | Cost-effectiveness (<€80,000/QALY) |
| *Imatinib* | CML (2002) | First-line | ? | ? | ~ (+) |
| | CML (2001) | Second-line | Effectiveness<br>QoL | **BI +**<br>PE -<br>Int. EE - | **+** |
| | GIST (2002) | Second-line (unresectable) | ? | ? | **+** |
| | GIST (2009) | Second-line (resectable) | ? | ? | ? |
| | ALL (2006) | First-line | ? | ? | ? |
| | | Second-line | ? | ? | ? |
| | DFSP (2006) | First-line | ? | ? | ? |
| | | Second-line | ? | ? | ? |
| | HES&CEL (2006) | First-line | ? | ? | ? |
| | MDS/MPD (2006) | First-line | ? | ? | ? |
| *Pegfilgrastim* | FN (2002) | First-line | QoL<br>experience | BI -<br>PE -<br>Int. EE - | ~ (+) |
| *Adalimumab* | RA (2005) | First-line (alone) | ? | ? | ~ (+) |
| | | First-line (+MTX) | ? | ? | - |
| | RA (2003) | Second-line (alone) | Side-effects | BI - | **+** |
| | | Second-line (+MTX) | | PE -<br>Int. EE - | **+** |
| | PsA (2005) | Third-line | No major uncertainty | BI -<br>PE -<br>Int. EE - | **+** |
| | AS (2006) | Third-line | Effectiveness<br>QoL | BI -<br>PE -<br>Int. EE - | **+** |
| | CD (2007) | Second-line (mod-to-sev) | Effectiveness<br>QoL | BI -<br>PE -<br>Int. EE - | **+** |
| | PP (2008) | Third-line | Effectiveness | BI -<br>PE -<br>**Int. EE +** | ~(+) |
| | JIA (2008) | Third-line | Effectiveness<br>QoL<br>Side-effects | BI -<br>PE -<br>Int. EE - | ~ (?) |
| | Off-label (uveitis) | Third-line | Rational | ? | ? |
| **Additional analyses** | | | | | |
| *Pegfilgrastim* | FN (2002) | Second-line | ? | ? | + |
| *Adalimumab* | RA (2003) | Second-line (late RA) | ? | ? | - |
| | | Third-line | ? | ? | + |
| | | Fourth-line | ? | ? | - |
| | CD (2007) | Second-line (severe) | ? | ? | + |
| | | Second-line (moderate) | ? | ? | - |
| | | Second-line (episodic) | ? | ? | + |
| | | Third-line | ? | ? | ~ (+) |
| | Off-label (UC) | Third-line | ? | ? | - |

*Clinical uncertainty* – Items mentioned were lacking or not assessed in the original reports; ? : no assessment
*Economical certainty* – BI: budget-impact analysis; PE: pharmaco-economic dossier; Int. EE: international economic evaluations; + : available; - : not available; ? : no assessment
*Cost-effectiveness* – + : likely cost-effective (i.e., <€80,000/QALY); - : unlikely cost-effective (i.e., >€80,000/QALY); ? : no analysis; ~ ( ) : ambiguous results with the trend in round brackets

## 6.2 Modifications to reimbursement status

First of all, it needs to be noted that the evidence found was incomplete and qualitatively not always appropriate. It seems desirable to investigate the real-world cost-effectiveness in the Netherlands, taking factors into account like the real-life adherence (e.g. adalimumab is usually administered by patients themselves); any kind of dosage intensification (either escalating the dosage, reducing the dosing interval, or a combination of both); the compilation of patient characteristics in the study (e.g. the history of disease or the severity); and price developments (possible in- and deflation), which are elements likely to affect the cost-effectiveness ratio. A reimbursement agency like the CVZ would be able to require manufacturers to supply studies sourcing real-world patient data (e.g. via registries).

Following that restrictive note, it seems inappropriate to conclude any consequences for the reimbursement status of the three investigated drugs. Rather, general consequences from a re-assessment shall be addressed. Decisions include (dependent on the additional evidence generated) to further reimburse the technology without any changes; or to revise additional conditions of List 2; and/or to lower the drug price; or to terminate reimbursement.

*Continuous reimbursement*

In analogy to coverage with evidence development schemes: if the degree of uncertainty surrounding the initial reimbursement decision can be reduced to an acceptable minimum, continuous reimbursement might be appropriate (Hutton et al. 2007:430). However, if the uncertainty was not overcome, or certainty gathered on the inefficient use, consequences for reimbursement seem logical.

*Conditional reimbursement*

In case it could be demonstrated that drugs show an increased unauthorised or inappropriate use (with the former being the off-label use for conditions not registered and the latter being the use opposing current professional guidelines), additional restrictions might be necessary to impose (in agreement with professional groups). Conversely, if the re-assessment shows the inappropriateness of current reimbursement restrictions, a relaxation or suspension of conditions might be appropriate.

*Drug price alteration*

In cases of uncertain cost-effectiveness or technologies being considered cost-ineffective, manufacturers could lower the price of an intervention to decrease the cost-effectiveness ratio below acceptable thresholds (e.g. the €80,000 per QALY of the RVZ). This would require them to reduce the price within a profit margin as otherwise no incentive exists to still market the product.

*Termination of reimbursement*

As a means of last resort, the factual delisting of medications from reimbursement is a threat that should be enabled to follow a re-assessment. It is possible to see variations of reimbursement policies in different jurisdictions as demonstrated with the cases efalizumab, refocoxib, and benfluorex in the past. In addition, the strengthened negotiation position of the decision maker – imposed by the threat of delisting – may have direct consequences to other possible consequences (like price decreases). Lastly, in cases where alternative treatments are clearly more cost-effective with high certainty than the intervention of interest, termination of reimbursement must be the logical consequence.

# Chapter 7

## Conditions for conducting a re-assessment procedure

This chapter provides insights into practical considerations of conducting a re-assessment procedure in the Netherlands for outpatient medications. Information gathered in previous chapters will be used and synthesised to answer the following question:

Q5: *Under which conditions is it feasible and desirable to conduct a review?*

The conditions mentioned in this chapter are not meant to be exhaustive.

### 7.1 Medication selection

A re-assessment procedure needs to be worth its conduct. It is pointless to invest in research that generates certainty in areas of pharmaceutical products when the opportunity costs of that investment prevent the assessment of other drugs (more likely to be profiting from a review). After all, the resources for the reimbursement authority CVZ are limited.

For non-expensive medicines, it seems reasonable to accept a higher uncertainty regarding the real-life cost-effectiveness as the research investments would not justify any expected budgetary consequences (e.g. an even lower price). However, when the actual expenditures of a drug amount to a level considered expensive under the Dutch definition, it becomes debatable whether society still obtains a good value for money. In those cases, it seems justified to schedule an investigation into the real-life cost-effectiveness. Considering the limited number (a total of 25 within 22 years), which amount to about 22% of the total medical expenditure, it seems practical to concentrate on these medicines.

It could be considered to restrict the re-assessment to certain indications only, if it can reasonably be demonstrated that those are the main cost-drivers. A simple example taken from the list of expensive drugs forms the immunosuppressant tacrolimus: if used to reduce transplant rejections (ATC-code L04AA05), the medication is considered expensive since 2008 (costs/DDD: €13.36, total costs: €23 million); if used in moderate-to-severe eczema after corticosteroids (ATC-code D11AX14), it is not considered expensive (costs/DDD: €1.14, total costs: €2.7 million; all 2010 values).

In other cases, an examination of all indications may be more appealing: e.g. in imatinib, it remains debatable which indication is the major cost driver as all were considered for an orphan designation.

### 7.2 Re-assessment time period

The time period for the re-assessment needs to be sufficiently long enough to give the manufacturers the additional time needed to perform the required analyses. A look on the experience with the re-assessment of expensive inpatient medications may be able to help identify a suitable period.

Currently, inpatient expensive drugs are obliged to be reviewed after 4 years. The CVZ is mandated with the task to nominate medications for the NZa policy guidelines according to the definition of expensive (CVZ 2010b:6). In a similar fashion, expensive outpatient medicines could be identified.

In the past, most outpatient drugs could not be considered expensive right at the onset of reimbursement. A retrospective analysis of all outpatient medicines ever considered expensive in the Netherlands for the period of 1989 through 2010 according to the earlier outlined definition for inpatient drugs (*N*=25) resulted in a mean years of 4.92 after initial reimbursement that both criteria were met (i.e., ten times higher daily costs than the average daily drug costs; and total costs of at least 0.5% of the total drug costs). The median was 3.0 years and the maximum 16 years (for leuproreline).

Given that the drugs were on average already for 5 years on the market, it seems reasonable to expect the presence of certain patient data (e.g. in patient registries). In addition, a previous analysis on the evidence development of international cost-effectiveness studies showed that for the three selected medicines of this study, full economic evaluations were being published between on average 2 to 3 years after positive reimbursement decision (see *Chapter 5*).

It can be concluded that a time period of 4 years after the identification of outpatient medications to comply with the definition of being expensive would be sufficient to conduct the additional outcomes research. Special treatment for indications of rare conditions could be considered (e.g. prolonging the time with 1-2 year(s); facilitating access to real-life registry data; reducing technical and methodological requirements; or the a-priori least-preferable solution of suspending the requirement).

## 7.3 Exploring additional considerations

Information gathered in a re-assessment procedure needs to follow basically the same features of information gathered additionally in coverage-with-evidence-development schemes: it needs to be able to reduce previously identified uncertainty; to be relevant to the decision making; timely available; and the benefit of the process needs to outweigh its costs (Hutton et al. 2007:429).

It was learned from previous policy measures in the Netherlands on conditional reimbursement (i.e., List 2 of the GVS) that transparency, legitimacy, and feasibility were three main factors for achieving the aimed policy objectives in practice (Niezen et al. 2007). The same seems applicable for a re-assessment procedure. It seems practicable to build on these experiences with the considerations of Daniels and Sabin in their framework of 'accountability for reasonableness' (Daniels and Sabin 1998). The four conditions mentioned for reimbursement systems are: transparency on the process and decision making; relevance and reasonableness of the criteria that lead to a decision; revision and appeal of decisions; and regulatory enforcement (Daniels 2008).

Adapted to the re-assessment procedure, criteria for a re-assessment must be clearly stated – on the procedure, eligibility definition, and possible consequences. Similar to the publicly available pharmacoeconomic guidelines and the Outcomes Research format for expensive inpatient drugs, it must be transparent which criteria form the basis of the judgement for the real-life cost-effectiveness. In addition, the criteria for eligibility of a re-assessment must be openly communicated, as must the results of the outcomes research (e.g. in the *Staatscourant* as part of the explanations on the change in the Rzv, as proposed already in ZFR 1997:36). 'Expensive' as defined for inpatient medications would be such a clearly defined criterion, which would be needed to be officially defined for outpatient drugs. The criteria need to be relevant and reasonable to support the outcome of demonstrating the cost-effective application of drugs in clinical practice. Also, stakeholders should be involved in the entire process of re-assessment and given the chance to comment on the procedure. It needs clarification under which conditions a stakeholder could appeal the outcome of a re-assessment. Any decision made on the basis of a re-assessment needs to be revisable, as well as the initial reimbursement decision in the light of new evidence. Lastly, the enforcement of regulations requires the structures, resources, and political willingness to back decisions based on the re-assessment.

Especially the political will forms a reason for concern and depends on the consequences of a review-procedure. Indeed, the current Minister of Health is a longstanding proponent of temporary including new pharmaceutical innovations. However, the potential consequence of delisting a medication could be perceived as a serious public health threat that may lead to societal unrest, as anticipated in 1999. It remains open whether a politician elected for a limited time period would be willing to take the risks of jeopardising the chances to be re-elected and his/her public popularity.

Regarding the stakeholder involvement: pharmaceutical companies should be actively involved in funding re-assessment analyses (as remarked by the ZFR in 1997: the burden of proof on the effectiveness should lie at the marketing authorisation holder, not the Minister of Health or CVZ; ZFR 1997:29); research organisations and medical centres in the conduct of them; research funders like the NWO or ZonMw could be involved in providing additional funds for research that could be intended for journal publication (ZonMw is already involved in partially funding outcomes research in expensive inpatient drugs; CVZ 2009a:15); and patient organisations should be enquired to contribute in factors outside the scope of economic evaluations but within health technology assessments.

Concerning the research funding, it remains desirable to commission research independent from the conscious or unconscious influence of the pharmaceutical industry or for-profit organisations. This flows as logical consequence from section 5.4 and in line with other empirical evidence (e.g. Friedberg et al. 1999; Miners et al. 2005; Bell et al. 2006). It could be considered to let marketing authorisation holders contribute into a new fund that is specifically designed for the conduct of such research. The CVZ also suggested to reallocate a share of the public money received by academic institutes in the range of about €630 million (2009 values) for innovation research to a newly created fund (CVZ 2009a:30). Another option could be to pay the CVZ (or NWO), which then commissions the work to scientific centres (similar to NICE in the UK). The CVZ preferred the last (CVZ 2009a:19-20).

The CVZ also pointed to the possibility of provisionally funding interventions through subsidies based on articles 68 Zvw and 44 AWBZ that can be interpreted as “no, unless” rule, meaning that the care would need to be intended for inclusion in the benefit package (CVZ 2009a:27). Alternatively, the Minister could allocate subsidies herself from her budget (CVZ 2009a:28).

The CVZ favours subsidies over temporary reimbursement given its inherent disadvantages (potential sunk costs of investments; cross-border claims of this insured care without the necessary evidence generation; the possible removal from the benefit package; and the absence of a ceiling for the costs) (CVZ 2009a:27,36-37,39). Contrary, subsidies have the advantage of being limited for a certain time period. This forces a decision on whether or not to reimburse the care at a fixed time and facilitates the structured in- and exclusion of temporary included innovations, while underlining the provisional character of the care and counteracting the fear that once an intervention reached the basic benefit package it would be hard to remove again (CVZ 2009a:36-37,39). However, an open information policy on the temporary character of the care and the potential risk of exclusion from the benefit package still needs to be communicated clearly (ZFR 1997:29).

## 7.4 Concluding remarks

It is feasible to conduct a review of outpatient pharmaceuticals if the research justifies the costs, for which the re-assessment should be restricted to expensive drugs. Also, a re-assessment within 4 years seems highly achievable. Lastly, other considerations like a transparent process; clear set criteria and definitions; the involvement of main stakeholders; and the political support for the consequences of a re-assessment procedure need to be taken into account. Manufacturers should directly be kept involved in the funding of outcomes research and indirectly in the conduct.

# Chapter 8

## Discussion

This thesis sees itself in the conceptual line of the academic and political awareness for temporary inclusion and reimbursement of promising pharmaceutical innovations since more than one decade in the Netherlands. However, where the latest policy proposal directed the attention to new expensive pharmaceuticals, the focus of this exploratory study were the already reimbursed – yet expensive – outpatient medications and the advances of re-assessing their cost-effectiveness.

The main research question was whether a re-assessment of expensive outpatient medicines on their cost-effectiveness is feasible and desirable in the Netherlands; thereby enabling a more cyclic decision making procedure to address the increased uncertainty at the time of decision making.

Three pharmaceutical products were chosen as case studies: imatinib, pegfilgrastim, and adalimumab. All of them fulfilled the (inpatient) definition of expensive, have been reimbursed since the early 2000s, and are among the top 6 of most expensive outpatient drugs for the year 2010. Yet, only 8 reimbursement dossiers existed for the 13 registered and reimbursed indications of the three drugs.

### 8.1 Background remarks

At the moment of decision making, uncertainty surrounded to a large extent the clinical evidence of the chosen medications as presented in the public reimbursement dossiers of the CVZ. Several CFH assessments based the judgement for the criterion 'intended effects' on an indirect comparison of merely randomised controlled efficacy trials. The criteria (long-term) effectiveness and quality of life were often not able to be answered at the time of decision making (in 5 of the 8 dossiers). Side-effects lacked in two reports long-term data. In total, clinical uncertainty was not trivial for at least two drugs.

Although efficacy outcomes are essential to demonstrate whether an intervention can work, they are insufficient to demonstrate adequately the impact on patients' mortality and morbidity. Or as formulated by the reimbursement authority in common parlance: "*het geneesmiddel moet niet alleen werken, maar ook helpen*" [the medication needs not only to work, but also to help] (ZFR 1997:28).

Furthermore, economic considerations played no visible role for all three cases at the time of reimbursement decisions. Merely one budget-impact analysis was available (for CML in imatinib) and no pharmacoeconomic dossiers (given primarily the timings of initial application: all before 2005). In addition, only one international cost-effectiveness study of moderate quality and relevance could have been available to the knowledge of the reimbursement authority (for PP in adalimumab).

It can plausibly be assumed that cost-effectiveness should play a role in the drugs decided upon before 2005. The CVZ communicated in a recent report that the exemption from a pharmacoeconomic analysis "does not mean that cost-effectiveness plays no role in the final assessment and decision-making" (CVZ 2010c:7). Medicines with equivalent therapeutic value and no added costs need to be accompanied by a cost-minimisation analysis when requesting exemption (CVZ 2010c:6-7). Today, adalimumab and pegfilgrastim would need to submit a CMA if they asked for reimbursement again.

Overall, it can be observed that the uncertainty surrounding the 3 medications was relatively high to be accepted for a conclusive reimbursement decision. Other considerations – like the possible denial of reimbursement for a treatment with a high (maybe unmet) medical need – must have been decisive.

Two of the drugs seem to embody what the Minister of Health addressed in her letter in May 2011, that sufficient information is frequently lacking at the time of reimbursement application.

The systematic review conducted in this thesis looked retrospectively on the economic evidence available in 2011. It was seen that, ceteris paribus, the efficient use of medications in officially assessed indications seemed reasonable given the underlying data and evidence of full cost-effectiveness studies published; less so for the use in non-assessed applications of adalimumab. First-line therapy with these expensive drugs appeared ambiguous (especially in pegfilgrastim and adalimumab). In addition, episodic treatment may in some cases be a more efficient alternative than continuous maintenance therapy (at least for adalimumab in CD). Investigating the use of adalimumab in PP remains a future research priority as the outcomes were less convincing and, although in a favourable range, cost-effectiveness remained controversial. For JIA, the evaluation available obtained no composite outcome (i.e., QALYs) and results remain difficult to interpret.

Albeit the cost-effectiveness evidence available in 2011 was not without methodological flaws, the relevance and quality for the Dutch setting can be judged as overall being moderately fair. It remains remarkable that several studies were still based on indirect comparisons in adalimumab. The appropriateness of the often sourced efficacy trials (of limited duration) to reflect real-world conditions can be questioned (e.g. in light of real-world adherence). Others remarked the influence of the chosen study population on the incremental ratios (Chen et al. 2006); and several studies remarked the likelihood of more favourable outcomes if including indirect costs due to less absenteeism from work (e.g. Chen et al. 2006:76; Malottki et al. 2011:118; Rodgers et al. 2011).

In addition, the evidence sourced may not be free of certain biases. Concerns for flawed cost-effectiveness outcomes surrounded mainly the potential for publication and funding bias. Also, concerns were raised in pegfilgrastim given the eye-catching similar structure and design in five different studies. All studies in common was the affiliation of at least one author to the same consulting company. It remains for pegfilgrastim highly desirable to commission further research for the relevant comparator less in the focus of published evaluations (i.e., administration as secondary prevention). In total, economic quasi-certainty was obtainable at t=1. However, the inherent limitations of using second-best data need to be acknowledged (see 8.3: *Strengths and limitations*).

## 8.2 General comments

The tension on access to care, patient protection, and cost containment is reflected in the case studies. In adalimumab, the CVZ could have communicated beforehand to conduct head-to-head trials between the different biologics instead of making an indirect comparison. The tension arose at the time of decision making as to not deny important care while basing the assessment merely on efficacy trials.

National licensing agencies (like the CBG) and the international EMA should be held responsible in controlling efficacy as best described by the question “can it work?”; national reimbursement authorities should be held accountable of answering the questions “does it work?” and “is it worth it?”, which translate directly into effectiveness and cost-effectiveness. In light of the findings of this thesis, the question arises whether the CVZ satisfactorily fulfilled its task.

One could get the impression that the national reimbursement authority acts very lenient in its decisions and accommodates to its clients: the pharmaceutical companies. It is also interesting to observe the change in labels for the assessment criteria ‘efficacy, effectiveness, and quality of life’ to one criterion of ‘intended effects’ in 2010 (CVZ 2010a). Does the CVZ issue advices that can, in analogy to a common legal maxim, best be described with ‘in dubio pro medicamento’?

This allegation appears to be incorrect when looking back at the stringent assessments of the past six years. On average 15.2% of all reimbursement applications were advised by the CVZ to be denied during the 5 years before 2010. In 2010, the year that the assessment criteria were changed, the CVZ issued negative advices to the Minister in 26% of all submissions (6 out of 23 assessed applications) (Franken et al. 2011). All 6 negative assessments reported a negative outcome on methodological aspects of the effectiveness that were the main reason for denial as no convincing therapeutic (added) value could be determined. Either the CVZ became stricter while applying seemingly less restrictive criteria; or the quality of evidence was (somewhat arbitrarily) at a low level in 2010. Whatever the reason: allegations on 'laissez faire' reimbursement decisions can reasonably be dismissed.

The exemption of a budget-impact analysis for drugs clustered on List 1A (like pegfilgrastim and adalimumab) remains debatable. In the past, generic drugs were seen to increase in price and approximate the cluster's average level (Brouwer and Rutten 2002). That counteracted the anticipated higher price competition from generics since manufacturers have little incentive in setting prices below the average reimbursement ceiling value (Koopmanschap and Rutten 2003:S49). A recent review of experience gained from reference pricing systems in Germany, the Netherlands, Sweden, and the United Kingdom confirmed that the system is effective in lowering prices to the reference level, but not beyond (Drummond et al. 2011:269-270).

Other concerns regard the absence of pharmacoeconomic evaluations for these medicines. The issue associated with exempting drugs from demonstrating their cost-effectiveness if applying for inclusion in the reference pricing system is best illustrated with adalimumab. The CVZ assumed for all its indications an overall comparable budget-impact of about €15,000 per annum and patient compared to the other two TNF-inhibitors in the same cluster (i.e., etanercept and infliximab). However, the cost-effectiveness of neither infliximab nor etanercept were ever assessed. This illustrates a loophole of the current legislation (not necessarily applicable for the TNF-antagonists!): if the earlier reimbursed medication has an unproven cost-effectiveness, other medicines being clustered with that drug can free-ride on the accepted economic evidence. Inefficient drugs might be concealed and benefit from reimbursement in a cluster while bypassing the obligation to demonstrate their cost-effectiveness.

## 8.3 Strengths and limitations

The strength of this thesis is the structural approach to investigate whether a re-assessment would be feasible based on published economic evaluation studies, and under which conditions it would be desirable. It adds to the existing knowledge that a review based on published evaluations would indeed be possible for most indications; that those studies were overall timely available after on average 2.33 years following initial reimbursement decision; and that the studies can be considered as fairly relevant for the Dutch setting (mean NL-TQS=34.9; SD=6.0).

The systematic literature search strategy used in this thesis provided in total for all three medications a high amount of possibly relevant articles ($N \approx 200$); many of which were duplications. That can be taken as sign for a comprehensive indexing and sufficient search. Eventually, about 50 full economic evaluations qualified for inclusion. This is in line with empirical results from Sweden of a higher amount of economic evaluations available for expensive medicines (Lundkvist et al. 2005).

Assuming that the marketing authorisation holder could be expected to submit a pharmaco-economic dossier in the year of reimbursement application was favouring manufacturers when calculating the duration till the first evaluations were available. Calculating with the year of reimbursement decision (often made in the next calendar year), the time between first publication and reimbursement would be shorter and suggest that manufacturers could submit a re-assessment dossier even in less than 4 years.

The findings on the relevance and quality of the evaluations for the Netherlands confirmed that "reviews of economic evaluations have demonstrated that the quality of these studies is highly variable and their reporting often inadequate" (Centre for Reviews and Dissemination 2007:1). International economic evaluations follow different guidelines and recommendations. It is apparent that transferring outcomes across jurisdictions requires considerable efforts (Drummond and Pang 2001).

Indications for biased outcomes pointed to a statistically significant association of evaluations funded by the pharmaceutical industry and being published in medical journals (one-sided Fisher's exact test: $P=0.0113$; $\alpha=0.05$). Other concerns regarded publication bias due to the majority of favourable cost-effectiveness ratios; while a potential drug price deflation can be rejected for the three case studies.

The inflation and conversion of cost-effectiveness outcomes was done in analogy to several other reviews to enhance comparability of outcomes (e.g. Doan et al. 2006; Smart et al. 2010; Uyl-de Groot and Giaccone 2005). These and other reviews inspired the design and reporting of this thesis (also: Foster et al. 2010; Peterson et al. 2009; and Lighthart et al. 2007).

The cost-effectiveness threshold of €80,000 per QALY was suggested by the RVZ. No decision rule is officially stated in the Netherlands (yet). Apparently, the conclusions reached in this thesis depend on the chosen ceiling value (which was – as is common praxis with existing thresholds – not inflated; see Eichler et al. 2004). For that reason, and due to the inherent second-best quality of the data, no recommendations were given for the reimbursement status of the three cases.

However, some argue for an even lower ceiling value of only €40,000 per QALY as cut-off point where a reasonable cost-effectiveness stops (Busschbach 2010:23). This reasoning is supported empirically as many cost-effective interventions in the GVS are below €40,000/QALY (Meerding et al. 2007). Regardless of the maximum: it is apparent that additional arguments (like disease severity) rise in importance the closer interventions approach the chosen ceiling (Busschbach 2010:22).

The compiled NL-TQS is a unique instrument that helped to guide the analysis of this thesis. It proved that the appealing approach of assigning numerical values to different economic studies is no easy task. The generalisability of the checklist can be questioned. It is not intended to replace existing instruments. Moreover, it needs to be remembered that the remarks of the CVZ, on which the checklist was based, are again 5 years old by now; and made back-then for the guidance of the year 1999.

The author did not have the resources to conduct (or access to material of) real-life cost-effectiveness research. Instead, published economic evaluations were systematically reviewed but must be regarded as second-best data. Hence, in the absence of real-world data, this thesis can only suggest improvements but cannot be used for optimisation of healthcare resource allocation in the Netherlands.

## 8.4 Recommendation and call for reform

Up to now, the challenging conclusion reached by Koopmanschap and Steenhoek in 2007 has not yet been dismantled, namely that policy makers are implicitly willing to accept up to 12 times higher than expected costs of outpatient medicines based on the experience and price development of imatinib (Koopmanschap and Steenhoek 2007:21). The current Ministerial proposal (which does not consider already reimbursed medicines) further fuels that suggestion.

It seems advisable for Dutch policy makers to expand the proposal of re-assessing new innovative medications with those already reimbursed but characterised by uncertainty at the moment of decision making and/or high budget-impact. Also, high uncertainty in the appropriateness of drug use should lead to more critical scrutiny of the real-world cost-effectiveness (Busschbach 2010:44).

Similar periodic re-assessments as conducted in Belgium, France or Sweden could be taken into account as reference (Polain et al. 2010:36). Even if the real-world findings support what the results of this thesis suggest – favourable cost-effectiveness outcomes for the assessed indications but less certainty in other use – the re-assessment would enhance the legitimacy of continuous reimbursement; ensure the most advantageous allocation of resources; and justify ongoing investment in costly care.

This thesis showed that Dutch economic evaluations were underrepresented for the three investigated drugs. It can be asked whether more Dutch pharmacoeconomic research should be conducted (preferably commissioned by the reimbursement authority). An alternative forms the development of more sophisticated techniques to transfer international studies to the Dutch setting (e.g. based on the model of Welte et al. 2004). Successful examples are rare but existent (e.g. Knies et al. 2009).

Furthermore, the thesis confirmed the need for reform of the two-tiered reimbursement process. Currently, final decisions need to be made at the time of application with the evidence available. In the absence of a structured re-assessment procedure, the moment of decision making becomes the bottleneck in the entire process of market launch and during the life-cycle of outpatient drugs. The importance of efficiency evidence cannot be underestimated – especially for expensive medicines.

The information gathered in this thesis for t=1 appears to be at least widely ignored by the CVZ (and CFH) – if not unknown. Reimbursement decisions were made with due diligence but in the restricted frame provided by the dichotomous system. In the absence of an effective remedy to require extra information, combined with the lack and time-consuming conduct of that research, the authority was left with no choice than to give recommendations with the existing evidence. It seems serendipitous that none of the three cases appeared to have benefitted by large from cost-ineffective reimbursement.

A more cyclic reimbursement system seems promising in being able to safeguard access to new forms of care while ensuring a reasonable management of the benefit package. High costs are acceptable as long as the drugs are ‘good’ enough, i.e. they are worth the costs (Jönsson 2011:98). Indeed, new innovations affect cost factors like medical services, hospitalisations, and productivity losses due to decreased work inability; however, an “unrestricted reimbursement policy is not an option” anymore (Uyl-de Groot et al. 2010:287-91). Temporarily including new innovations must be seen as next step into the right direction to raise attention to the efficiency of expensive medications.

## 8.5 Conclusion

A re-assessment procedure is no joy in itself but a unique, exceptional remit. It institutes a process of research on the value for money of costly medicines whose appropriate, value-based pricing is in the doubt. Such procedure needs to be meaningful, feasible, and supporting the available evidence for a higher degree of certainty. Expected benefits need to outweigh the resources invested.

The advantage of a review (in line with the ideas of coverage with evidence developments) forms the possibility to gather information at a later point in time while enabling temporary reimbursement and postponing the final decision. The current obligation of conducting outcomes research for expensive inpatient medicines in the Netherlands should be transferred to existing expensive outpatient drugs. Re-assessing the cost-effectiveness based on international economic evaluations is often enough unable to provide conclusive evidence to justify the reimbursement under real-world conditions.

The system change proposed in this thesis complements the new plans of the Dutch Minister of Health. The two-tiered, one-time reimbursement decision making system is about to become history. It can be concluded that a formalised re-assessment is the right way to steer outcomes research in a meaningful way for decision making.

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# Appendices

**Appendix 1:** Instrument for data extraction from economic evaluations
**Appendix 2:** Flow diagrams of systematic literature searches (adopted from Cheng et al. 2005)
**Appendix 3**: Analysis of compliance with cost-effectiveness criteria
**Appendix 4**: NL-TQS article characteristics
**Appendix 5:** NL-TQS for imatinib
**Appendix 6:** NL-TQS for pegfilgrastim
**Appendix 7**: NL-TQS for adalimumab
**Appendix 8**: Cost-effectiveness results for imatinib
**Appendix 9**: Cost-effectiveness results for pegfilgrastim
**Appendix 10**: Cost-effectiveness results for adalimumab

## **Appendix 1:** Instrument for data extraction from economic evaluations

A self-constructed checklist was developed to assess economic evaluation studies on their quality from the perspective of the Netherlands. Given the Dutch perspective, the instrument was strongly based on the 'Pharmacoeconomic Guidelines' of the CVZ from 1999 and 2006. A wording was chosen that the CVZ would be able to find itself in.

Since the CVZ confirmed the applicability for the 1999 Guidelines only and the updated 2006 guidance would lack important procedural aspects if considered alone (those that were shifted to other parts), the 1999 Guidelines will be used as main reference frame for the analysis here. However, where updates were given in 2006, those will be complemented to the 1999 Guidance (e.g. the 2006 Guidelines allowed and included CMA studies as legitimate analysis type in the Guideline of the analysis technique).

Next to the 2006 update, it seems reasonable to search for alternative checklists and instruments that might enrich the Dutch guidance. This also in light of the fact that not industry submissions of drugs will be reviewed, but (inter-)national cost-effectiveness studies with different methodologies and techniques (one obvious example form cost-benefit analyses, which are not considered the best choice according to the Dutch guidelines). In addition, (the Dutch) reimbursement authorities are not expected to be the main audience of all articles

**Table 18:** Instrument comparison and checklist compilation

| Item | 1999 Guidelines | 2006 Guidelines | CHEC-List | QHES-instrument | Drummond 2005 | *Derived checklist (NL-TQS)* |
|---|---|---|---|---|---|---|
| 1 | 1. Audience | | 3. Well-defined research question? | 1. Study objective | 1. Well-defined question | *Criterion (1)* |
| 2 | 2. Perspective | 1. Perspective | 6. Perspective | 2. Perspective | (1. Viewpoint stated) | *Criterion (4)* |
| 3 | 3. Timing of studies | | | 3. Best available source | 3. Effectiveness established | *Criterion (9)* |
| 4 | 4. Performer of study | | 18. Conflict of interest between researcher - funder | 16. Disclosure on source of funding | | *Criterion (24)* |
| 5 | 5. Analysis technique | 3. Analysis technique | 4. Economic study design | 13. Choice of economic model | | *Criterion (5)* |
| 6 | 6. Indications | | 1. Study population | 4. Subgroup analysis | | *Criterion (2)* |
| 7 | 7. Comparator | 2. Comparator | 2. Alternatives | | 2. Competing alternatives | *Criterion (3)* |
| 8 | 8. Incremental/ total analysis | 8. Incremental analysis | 13. Incremental analysis | 6. Incremental analysis | 8. Incremental analysis | *Criterion (16)* |
| 9 | 9. Analysis period | 4. Analysis period | 5. Time horizon | 8. Analytical horizon | | *Criterion (6)* |
| 10 | 10. Efficacy versus effectiveness | | 10. Outcomes identified | 10. Primary outcomes measures | 4. Consequences identified | *Criterion (13)* |
| 11 | 11. Quality of Life and utilities | 6. Valuation of QoL and QALY's | 11. Outcomes measured | 11. Outcome measures/scales | 5. Consequences measured | *Criterion (14)* |
| 12 | 12. Outcomes of cost-utility analysis | 6. Valuation of QoL and QALY's | 12. Outcomes valued | 11. Outcome measures/scales | 6. Consequences valued | *Criterion (15)* |
| 13 | 13. Cost identification | 5. Cost ident., meas., and valu. | 7. Costs identified | | 4. Costs identified | *Criterion (10)* |
| 14 | 14. Cost measurement | 5. Cost ident., meas., and valu. | 8. Costs measured | 9. Measurement of costs | 5. Costs measured | *Criterion (11)* |
| 15 | 15. Cost valuation | 5. Cost ident., meas., and valu. | 9. Costs valued | 7. Data abstraction | 6. Costs valued | *Criterion (12)* |
| 16 | 16. Discounting | 9. Discounting | 14. Discounting | 8. Discounting | 7. Differential timing | *Criterion (8)* |
| 17 | 17. Reliability and validity (sensitivity analysis) | 10. Uncertainty analysis | 15. Sensitivity analysis | 5. Sensitivity/ statistical analysis | 9. Uncertainty | *Criterion (17)* |
| 18 | 18. Reporting of analysis | | | 12. Transparently displayed | 10. results include all issues of concern | *Criterion (18)* |
| 19 | 19. Modeling | 7. Modeling | | | | *Criterion (7)* |
| 20 | | 11. Use of expert panel | | | | *Included in 'best available evidence' (9)* |
| 21 | | | 16. Conclusions follow from data? | 15. Conclusions based on study results? | | *Criterion (19)* |
| 22 | | | 17. Generalizability discussed to other settings/patients? | | 10.3 Generalizability | *Criterion (20)* |
| 23 | | | 19. Are ethical/distributional issues discussed? | | 10.4 distribution/ethical issues | *Criterion (21)* |
| 24 | | | | 14. Explicit discussion of potential bias? | | *Criterion (22)* |
| 25 | | | | | 10.2 Results compared to other studies? | *Criterion (23)* |
| **Total** | **19** | **11** | **19** | **16** | **13** | **24** |

In orange items not addressed in the respective checklist.

These criteria sum up to 24 items in total. They will count onefold for the final composition of the NL-TQS. Up to 26 additional context-specific bonus points can be acquired that are designed to meet specific requirements of the CVZ. Thereby, the studies are weighted according to preferences stated by the Secretary of the CFH as well as specific requirements formulated in the Pharmacoeconomic Guidelines (both 1999 and 2006).

First of all, one general bonus point [+1] can be gathered for each of eight criteria that meets the special requirements (and expectations) formulated in both CVZ Guidelines. Eligible criteria are: a sufficiently long time horizon to be able to capture all important and relevant costs and effects (criterion 6); a discount rate applied of 4% for costs and 1,5% for effects (criterion 8); considering direct costs inside and outside the healthcare sector plus indirect costs outside the healthcare sector (criterion 10), clearly state unit quantities and unit costs (criterion 11); validating costs from a reliable source (criterion 12); using a generic, disease-specific, or domain-specific questionnaire (criterion 14); applying 'QALYs' as outcome measure (criterion 15); and clearly disclose a funding source and conflict of interest (criterion 24).

In addition, a higher weighting is given to specific preferences communicated by the CFH in 2005 (Appendix 1, p.18). Seven guidelines among the 19 in total were explicitly emphasised by the CFH Secretary as important: the perspective (criterion 4), analysis technique (criterion 5), indication (criterion 2), comparator (criterion 3), the identified outcome (efficacy versus effectiveness; here criterion 13), the uncertainty analysis (reliability and validity; here criterion 17), and the modelling of results (criterion 7). Of these seven, the Secretariat considered the guideline over the comparative treatment (criterion 3) as the most important, directly followed by the guidelines on the perspective and efficacy versus effectiveness (criteria 4 and 13 respectively).

Consequently, additional [+2], [+3], or [+4] bonus points are awarded according to these stated preferences. That means, a study is eligible for these bonus points in case it meets the following criteria:

- Study population (criterion 2): The study population corresponds to the indication officially registered in the Netherlands. (2 points)
- Analysis technique (criterion 5): CUA or CEA are applied, with a general preference given to CUA [CMA is NOT awarded bonus points given that costs are very likely to differ between different country settings.]. (2 points)
- Modelling (criterion 7): Model based on peer-reviewed publications and constructed as simple as possible; yet as inclusive as necessary. (2 points)
- Uncertainty analysis (criterion 17): Univariate sensitivity analysis for deterministic variables, probabilistic sensitivity analysis for stochastic variables; including costs, effects, and cost-effectiveness with corresponding confidence intervals. Also, the methods, parameter choices and the range of parameters are clearly mentioned. (2 points)
- Perspective (criterion 4): include societal perspective (3 points)
- Outcomes identified (criterion 13): Effectiveness in terms of morbidity and mortality (i.e. life expectancy/ life years gained and quality of life) is preferred over efficacy outcomes – if applicable and available. (3 points)
- Comparator (criterion 3): standard care needs to be used; standard care is defined as first choice therapy in the Netherlands in daily practice with proven effectiveness. (4 points)

In total, adding up all points allows for a maximum of 50 points:

$$((24*1)+(8*1)+(4*2)+(2*3)+(1*4))=50$$

By not excluding a point when e.g. a perspective other than societal is stated, the studies are not penalised and still get a point when stating at least any perspective.

The final 24 items used to guide the analysis and derive a numerical score are:

*Item 1: Audience* – Were addressees clearly mentioned in the article? Were articles aiming to inform decision-makers? If articles mentioned no addresses clearly, can an audience reasonably be assumed from the journal the study is published in (e.g. clinicians if published in medical journals, decision makers if published in health economics-related journals)?

*Item 2: Study population* – Coincides the used study population with the Dutch registered indication?

*Item 3: Comparator* – Were comparators used considered as standard or usual care in the Netherlands?

*Item 4: Perspective* – Was a perspective stated? Was a societal viewpoint adopted?

*Item 5: Analysis technique* – Was a cost-effectiveness or cost-utility analysis conducted?

*Item 6: Analysis time period* – How long was the analysis time frame? Was the time period sufficiently long enough to capture all major events of the disease?

*Item 7: Modelling* – Were modelling techniques applied? If applied: were input data sourced from peer-reviewed publications? Was a Markov model or decision tree used? Overall, was modelling appropriate?

*Item 8: Discounting* – Was discounting applied? If yes, at which rate and in line with Dutch guidance?

Item 9: Best available effectiveness source – Was a systematic literature review conducted and the search algorithm stated?

*Item 10: Costs identified* – Which cost factors were identified? Were indirect costs (productivity costs) considered?

*Item 11: Costs measured* – What is the base year of calculations, in which currency? Were valid references sourced? Were resource utilisation and unit costs clearly depicted?

*Item 12: Costs valued* – Were total costs displayed? Was a measure of variability shown for the point-estimate?

*Item 13: Outcomes identified* – Which outcomes were identified as main effect measure? Were QALYs used?

*Item 14: Outcomes measured* – How were outcomes measured? If utilities were used, how were they obtained? Directly or indirectly measured? Measured in patients or the general public? Maybe unclear basis?

*Item 15: Outcomes valued* – Were the total outcomes displayed? Was a measure of variability included?

*Item 16: Incremental analysis* – Were incremental cost-effectiveness ratio's computed for two different interventions? Was a measure of variability depicted?

*Item 17: Uncertainty analysis* – Was an uncertainty analysis applied? Was a univariate and/or probabilistic sensitivity analysis conducted? Were effect and cost parameters varied? Was a cost-effectiveness plane and cost-effectiveness acceptability curve included?

*Item 18: Transparent reporting* – Were the main structure of the article coherent and the line of argumentation clear? Were input data and the underlying strategy to obtain those data clearly presented? Were diagrams, tables, figures, or other visual techniques applied to facilitate understanding of models or results?

*Item 19: Conclusions follow data* – Were the conclusions drawn valid and based on the data presented?

*Item 20: Transferability* – Was the transferability of outcomes obtained discussed?

*Item 21: Discussion of ethical and distributional issues* – Were ethical and/or distributional factors (e.g. by using budget-impact analyses) addressed?

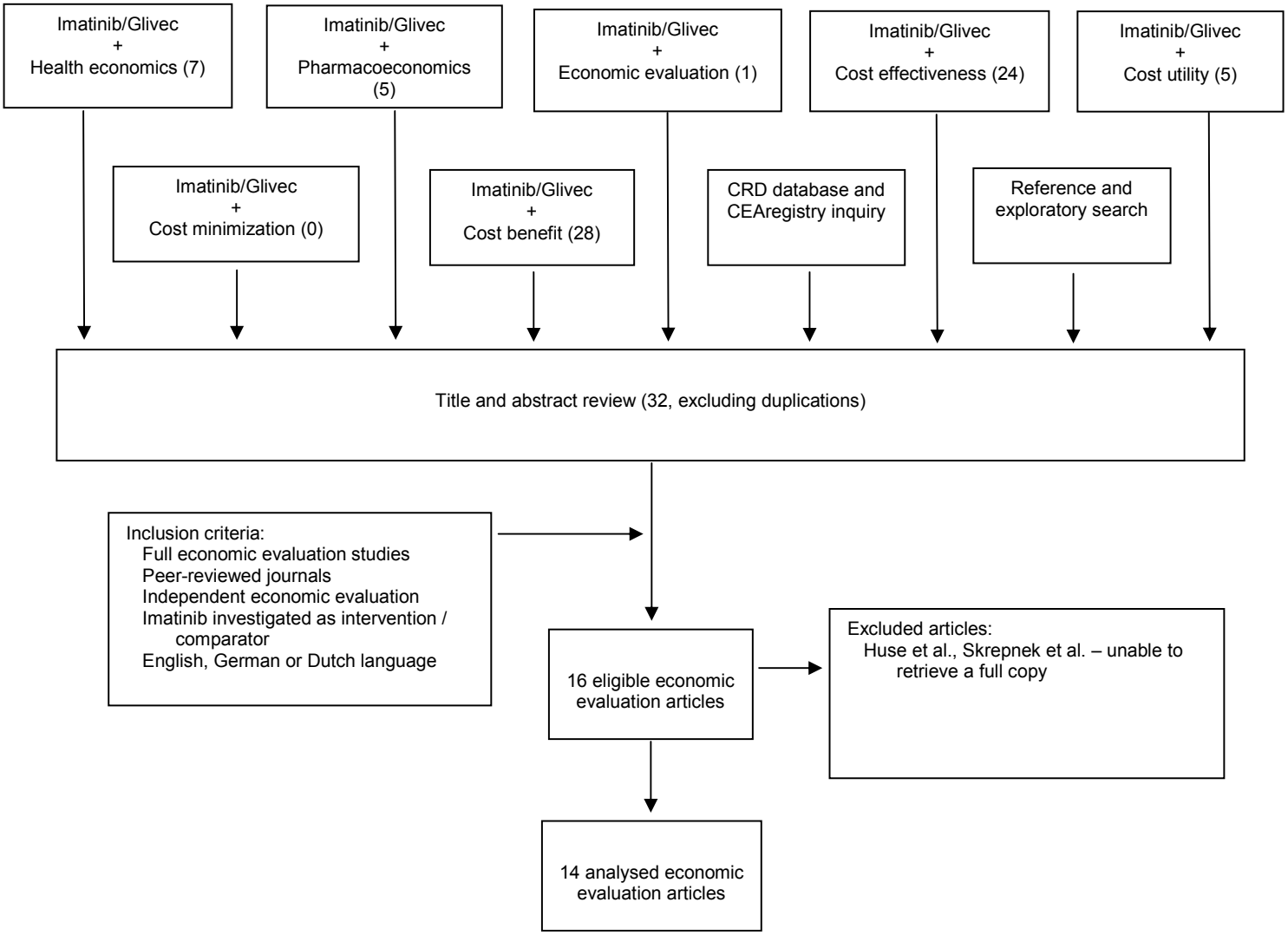
*Item 22: Explicit discussion of bias* – Were limitations and potential sources for bias explicitly named?

*Item 23: Context placement* – Were articles referring to other economic evaluations and an ICER threshold?

*Item 24: Funding source* – Was a disclosure of the primary funding source provided? Was the funder affiliated to the pharmaceutical industry or a nonprofit sponsor?

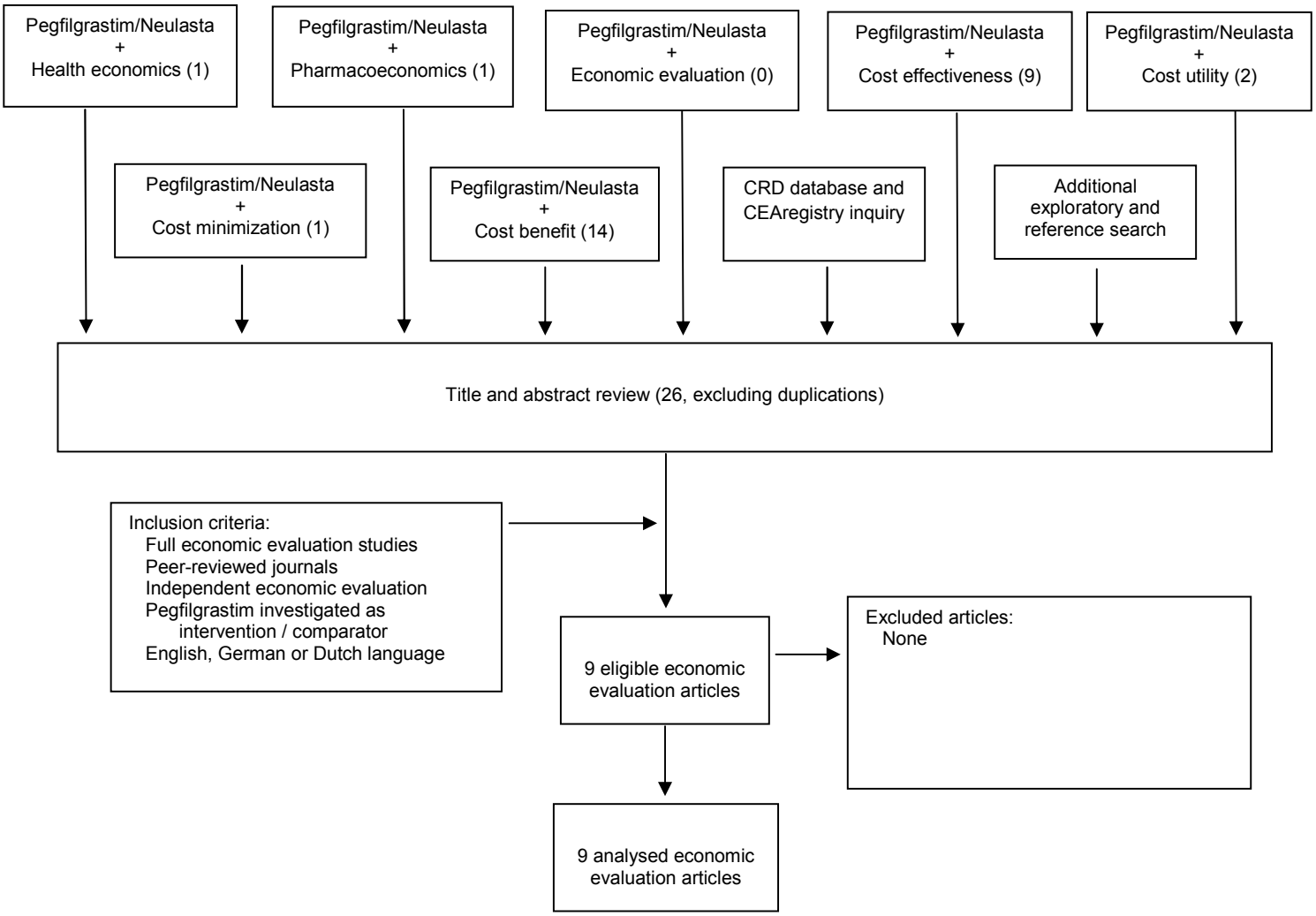
**Appendix 2**: Flow diagrams of systematic literature searches (adopted from Cheng et al. 2005)

**Figure 4**: Flow diagram of systematic literature search for imatinib



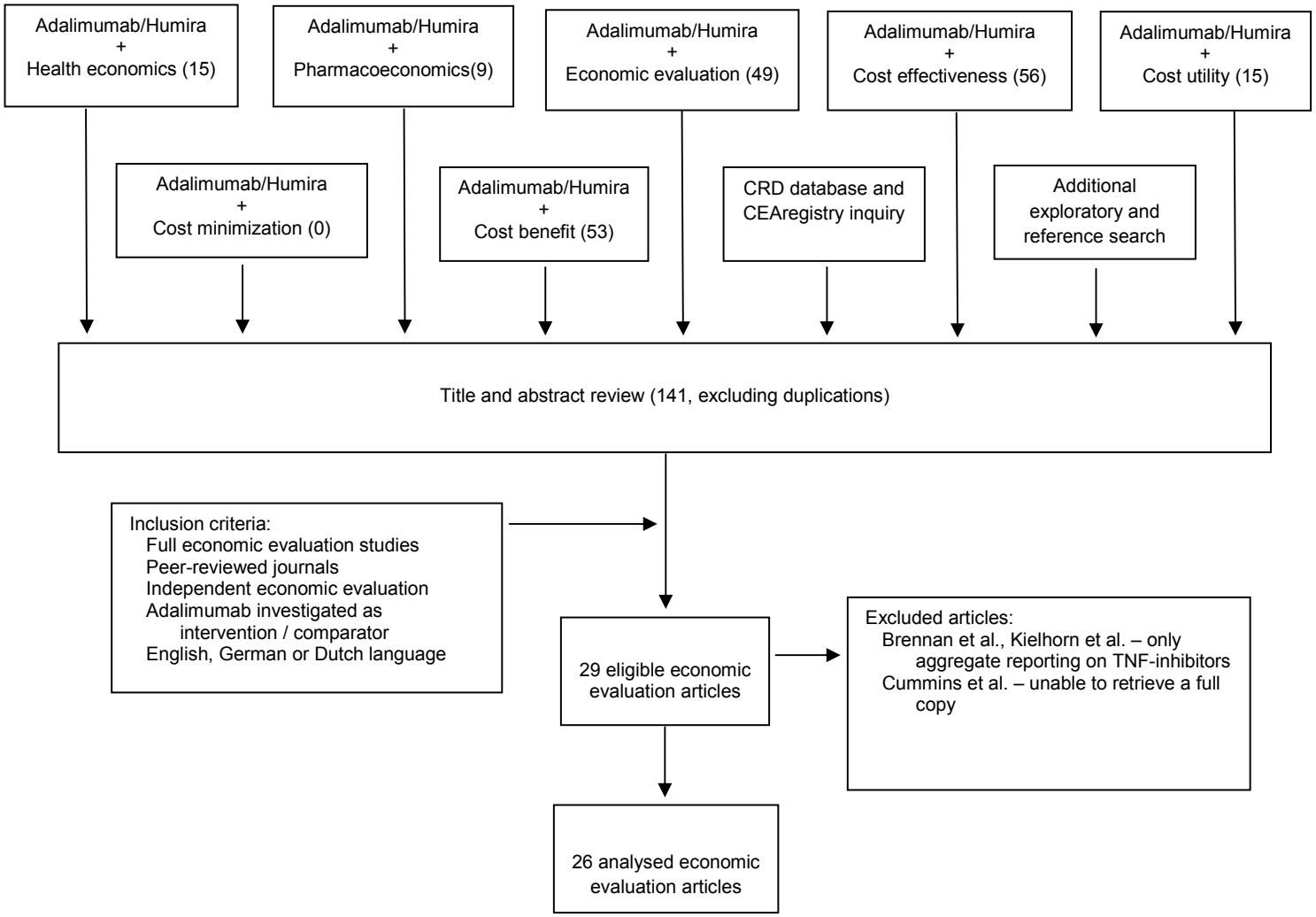

The systematic search strategy as described in the *Methodology* section identified 32 articles for imatinib. After a thorough screen of the potentially relevant articles, 16 full economic evaluation studies were eligible for analysis (see *Figure 4*). Two studies were unable to retrieve in full-text (Skrepnek et al. for CML, Huse et al. for GIST).

**Figure 5:** Flow diagram of systematic literature search for pegfilgrastim




For pegfilgrastim, 26 articles were identified as potentially relevant, of which eventually 9 qualified for inclusion (see *Figure 5*).

**Figure 6:** Flow diagram of systematic literature search for adalimumab




141 articles were identified for adalimumab by the systematic search algorithm. 29 full economic evaluations met the inclusion criteria of this study. One article for PsA was not possible to retrieve in full (Cummins et al., 2011), two other studies reported only on an aggregated level for the different TNF-inhibitors. Eventually, 26 articles were eligible for analysis (see *Figure 6*).

## **Appendix 3**: Analysis of compliance with cost-effectiveness criteria

### Item 1: *Audience*

About half the studies can reasonably be expected to address decision-makers as audience (49%). Imatinib and adalimumab were slightly above that value (50% and 54%, respectively), pegfilgrastim below (33%). It seems that studies for pegfilgrastim were more often directed at clinicians. It could be hypothesised whether this reflects the repeatedly made remark in the articles that the clinical practice of filgrastim administration deviates from the recommended regimen as also applied in clinical trials (5-6 days instead of recommended 10-11 days).

### Item 2: *Study population*

The study population was in almost all cases coinciding with the population registered in the Netherlands (96%), regardless of the medicine (100% imatinib and pegfilgrastim, 92% adalimumab). Adalimumab was the only medicine with an off-label investigation of cost-effectiveness (in refractory ulcerative colitis).

### Item 3: *Comparator*

A comparator equivalent to Dutch standard (or usual) care was considered in three-fourth of cases (76%); variation from this mean percentage was higher for imatinib (93%) and pegfilgrastim (56%) than for adalimumab (73%). In imatinib, the absence of many treatment alternatives made it easy to chose an comparator considered equivalent. In pegfilgrastim, the use of no G-CSF or pegfilgrastim itself as standard/usual comparator was debatable; as was the use of a placebo for comparison with adalimumab (since pegfilgrastim is no 'breakthrough' medication). In addition, some studies in plaque psoriasis considered as alternative interventions the two agents efalizumab and alefacept, which are not registered in Europe (anymore).

### Item 4: *Perspective*

A societal analysis was conducted in one-fourth of studies (24%). For imatinib, all except one study did not consider the societal perspective (7%), often due to the severity of disease and no anticipated productivity losses from that patient groups. Caregiver costs were also mostly not included, although relevant. In pegfilgrastim, one study considered the societal perspective (11%) while most others referred in the discussion section to the expected better cost-effectiveness results if indirect costs would be included, given that travel costs born by patients are decreasing when they need only once an inpatient administration of pegfilgrastim, compared to daily with the other G-CSF. In adalimumab, several studies applied a societal perspective (38%), of which half was only explored in sensitivity analysis after a payer perspective at baseline.

### Item 5: *Analysis technique*

Most studies used the preferred technique of the CVZ of cost-effectiveness or cost-utility analysis (96%), regardless of medication (100% imatinib, 89% pegfilgrastim, 96% adalimumab). For pegfilgrastim, one cost-benefit analysis was conducted and for adalimumab one cost-minimisation analysis.

### Item 6: *Analysis time period*

Time horizons of sufficient duration were applied in about two-thirds of studies (63%). In imatinib (86%), the duration was often sufficient enough given the overall survival of patients that did not exceed around 13-14 years in CML (5-6 years in GIST) for patients treated with imatinib. Study durations of $\geq$ 15 (10) years seem appropriate for CML (GIST). In pegfilgrastim (67%), several studies were limited to the cycles of chemotherapy administration and often to only the first four. Effects from the prevention of (febrile) neutropenia, which might be fatal, could therefore not adequately be valued. In adalimumab (50%), the time horizon of eleven economic analyses was $\leq$1 year, mostly explained by the short follow up of underlying clinical trials. However, all registered indications of adalimumab comprise chronic, severe conditions.

Item 7: *Modelling*

Many studies applied some sort of modelling technique (86%) in all three medications (93% imatinib, 89% pegfilgrastim, 81% adalimumab). In most studies exceeding 1 year, extrapolation was applied to forecast key input data (like survival, costs, and resource utilisation). Of those studies modelling, only two-thirds complied with the Dutch requirement to source peer-reviewed data for the model (64%). In imatinib (46%) and pegfilgrastim (25%), expert opinion formed often a major source for input data. Contrary, models for adalimumab were usually populated with peer-reviewed data (90%).

A transition-probability based Markov model was most often applied (60%), but to a varying extend in the different drugs (69% imatinib, 75% pegfilgrastim, 48% adalimumab). Strikingly in pegfilgrastim, the use of similar scenario models that incorporate both a decision tree and transition probabilities for a Markov model was applied in two-third of analyses. Accordingly, decision trees were applied on average in 33% of all modelling studies, but 0% in imatinib, 100% in pegfilgrastim, and 29% of adalimumab. In most cases, models were transparently described in terms of their assumptions, properties (i.e., transition probabilities), and structure. Markov models usually considered mortality except when the time horizon was too short. Parameters were often modelled as time-dependent to account for health deteriorations over time and to overcome the lacking 'memory' of Markov models.

Discussions on the appropriateness of models arose only for CD in adalimumab, where the use of the framework proposed by Silverstein et al.[14] was dismissed by some on the basis of validity concerns: the Markov states were derived from treatment patterns during 1970 to 1996 in a US population sample, while definitions of disease states changed over time (Loftus et al. 2009:1307). Also, the population-based sample would be likely to include many patients with mild forms of CD, not reflecting the current indication for TNF-inhibitors (Loftus et al. 2009:1308). Proponents argued that the framework of Silverstein allows for standard care to be modelled as being resistant to standard therapy before the advent of biologic drugs (Dretzke et al. 2011:124), and Silverstein modelled health states as to approach the production in health (e.g. mild or active disease), not CDAI scores (though seen as disadvantage by others again; Loftus et al. 2009:1308).

All models seemed logically appealing; were transparently presented in their structure and logic; and seemingly tried to represent reality as close as necessary while being as simple as possible.

Item 8: *Discounting*

Discounting followed in most cases requirements set by national authorities and international guidance (82%) but more often in imatinib (93%) and adalimumab (88%) than pegfilgrastim (44%). Discount rates ranged from a constant 3% for costs and benefits for studies conducted in Germany, the USA, Sweden, and Finland, 4% for the Netherlands, and 5% for Canada and Mexico. In the UK, a differential rate of 6% for costs and 1.5% for effects was applied before NICE guidance 2004, and a constant rate of 3.5% after NICE guidance 2004. Articles with a limited time horizon of ≤1 year did not discount. Although appropriate, that might still be desirable to state.

Two studies in adalimumab for the UK from 2006 and 2007 did not comply with most actual NICE guidance from 2004 but with the former of 2001. The researchers overlooked the new guidance on uniform discounting when agreeing on the research protocol in January 2005 and finalising the protocol in March 2005, and also did not detect this error during the editorial review in March 2006 (Chen et al. 2006:6). Resulting influence on outcomes remains unexplored as the discount rate was not subject to sensitivity analyses [in another, excluded analysis from Brennen et al. was the NICE research protocol of Chen and colleagues from 2005 cited when justifying the chosen differential discount rate (Brennen et al. 2007:1346) and sensitivity analyses performed with 3.5%; it was found to be the most influential factor of the costs and ICERs (not QALYs) of both, TNF-antagonists and DMARDs]. Three studies in imatinib published in 2005 for the UK were also complying with 2001 NICE guidance due to the lengthy process of editorial review before acceptance for publication.

In pegfilgrastim, five studies did not discount costs due to the limited nature of administration and associated costs for ≤1 year; effects were nevertheless discounted at 3% per annum. Discount rates in line with Dutch guidance were applied in only two studies for imatinib (14%); the average drops to 4% in total.

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14 Silverstein MD, Loftus EV, Sandborn WJ, Tremaine WJ, Feagan BG, Nietert PJ, *et al.* Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology* 1999;117:49–57.

Item 9: *Best available effectiveness source*

A systematic search algorithm as indicator the attempt to identify the best available clinical effectiveness data was reported in 39% of studies (29% imatinib, 44% pegfilgrastim, 42% adalimumab). In imatinib, the availability of one leading multicenter, randomised trial made most studies not report on another literature search; the best available evidence was anticipated to be already sourced. It remained unclear if the best available source was often enough sourced for the other comparators (especially hydroxycarbamide and best supportive care). In pegfilgrastim and adalimumab, a search algorithm was frequently lacking without further explanation. All of which leaves a considerable amount of uncertainty in whether the best available material was sourced for the majority of studies.

Item 10: *Costs identified*

Cost identification was highly influenced by the chosen perspective and overall indirect non-medical costs seldom considered (22%). Imatinib (7%) excluded productivity costs (except in one study), reflecting the chosen payer perspective among most studies. Also, costs borne to informal care-givers were mostly not included. In pegfilgrastim (11%), only one study considered productivity and travel costs for patients, which seems highly relevant when choosing filgrastim as comparator given the high difference for the frequency of administration in the advantage of pegfilgrastim. In adalimumab (35%), productivity costs were considered in the analyses from a societal perspective. In all remaining cases, indirect costs were not included owing to a lack of sufficient data.

Regarding direct medical costs: all cases were at least considering study medications, monitoring costs, and administration. Hospitalisation costs (often regarded as influential cost driver) were excluded in four studies for imatinib and nine studies for adalimumab (PsA, PP, JIA and UC).

Item 11: *Costs measured*

Cost measurements lacked in half the studies a clear depiction of resource utilisation and/or the base year of cost calculations (41%). Next to these: in imatinib (50%) it was impossible to verify for one study whether validated references had been sourced as the estimates came from an unpublished industry model that was adjusted for the purposes of the analysis; two other articles considered cost estimates from three different years. In pegfilgrastim (11%), assumptions on cost factors made by the authors were frequently obtained. In adalimumab (46%), no other deviation than those listed above were found. Overall, unit costs, probabilities, and validated sources were better documented than resource utilisation and the base year of calculations.

Item 12: *Costs valued*

Total costs per patient for all interventions were displayed in most studies (94%) and all for imatinib and pegfilgrastim (both 100%); in adalimumab (88%), one study did not calculate total costs while another study made miscalculations for one treatment alternative (ustekinumab), which lead to it being the only therapy investigated that achieved less total costs when administered with twice the dose as normal; therefore, results and conclusions regarding ustekinumab are likely to be flawed.

Only 31% reported a measure of variability for total costs (43% imatinib, 0% pegfilgrastim, 35% adalimumab).

Item 13: *Outcomes identified*

Many studies denoted effects in QALYs as composite health outcome measure (78%), with small variation among pharmaceutical products (76% imatinib, 78% pegfilgrastim, 81% adalimumab). In pegfilgrastim, several studies considered additionally survival alone via ‘life-years gained’. In imatinib, life-years gained was applied next to other clinical efficacy outcomes (e.g., per surrogate responder). In adalimumab, four cost-effectiveness studies used conventional disease specific efficacy outcomes as primary measure (i.e., percentage of PASI-75 responders for PP; and ACR Pedi 30 responders for JIA). It remains desirable to concentrate on cost-utility research in order to enhance comparability within and across indications (and innovations).

### Item 14: *Outcomes measured*

Of studies identifying QALYs as outcome measure, utilities were often derived by means of mapping preference states via regression analysis (32%) or elicited from expert panels (21%).

Regression functions were solely applied for adalimumab (71%), where preferences were mapped from disease severity measures (HAQ-DI in RA, HAQ and PASI in PsA, BASDAI and BASFI in AS, CDAI in CD, and PASI or DLQI in PP) to obtain health utilities in 11 studies. Underlying assumption was in all cases that these measures are valid indicators for the quality of life in the lack of elicited health utility values and the need for preference weights in cost-utility analyses. Contrary, expert opinion was used in all three drugs to varying degrees (32% imatinib, 43% pegfilgrastim, 5% adalimumab). Direct utility measurement was applied in 23% of cases (11% imatinib, 43% pegfilgrastim, 29% adalimumab), indirect measurement in the others (mostly EQ-5D).

Utilities (elicited via either direct or indirect measurement) were most often patient-based (36%), and more often so in adalimumab (57%) than imatinib (21%) or pegfilgrastim (14%). Population-based utilities, applied on average in 11% of studies, were common for a small share in imatinib (16%) and adalimumab (10%), not pegfilgrastim (0%). Imatinib and pegfilgrastim elicited in addition preferences by questioning clinical experts (neither patient- nor population-based). The rest of articles provided no clear information on the basis of valuation (28%), more often in pegfilgrastim (43%) and adalimumab (33%) than imatinib (16%).

### Item 15: *Outcomes valued*

Total outcomes per patient and per treatment were documented in almost all studies (96%) except for two in adalimumab (92%); they did not report the total QALYs gained due to the underlying indirect nature of comparison (Spalding et al. 2006) or insignificant differences found (Walsh et al. 2007). Several articles reported a measure of variability for the effectiveness outcomes obtained (43%), with the highest share accounting for adalimumab (62%), less for imatinib (36%) and none for pegfilgrastim (0%).

### Item 16: *Incremental analysis*

Most studies conducted an incremental analysis of costs and benefits between competing programmes (94%); one study for each drug lacked to report calculated incremental cost-effectiveness ratios: in imatinib (93%), the chosen comparator (interferon-alpha) would not have been interchangeable with imatinib at the time of analysis (Groot et al. 2006:95); in pegfilgrastim (89%), one study was a cost-benefit analysis that applied a contingent valuation approach; and one study in adalimumab (96%) calculated no incremental ratios between competing interventions but the respective cost-effectiveness ratio per single programme only.

A measure of variability was included in 38% of reported ICER estimates (36% imatinib, 13% pegfilgrastim, 46% adalimumab). The others omitted any information on the uncertainty regarding the point estimate.

### Item 17: *Uncertainty analysis*

Most studies conducted to a varying extend sensitivity analyses (94%), except for two studies in adalimumab (Walsh et al. 2007 and Benucci et al. 2009). Deterministic univariate sensitivity analyses were applied more often than probabilistic sensitivity analyses (94% versus 53%); variation among drugs was lower for the deterministic analyses (93% imatinib, 100% pegfilgrastim, 92% adalimumab) than the probabilistic analyses (36% imatinib, 44% pegfilgrastim, 65% adalimumab).

Effectiveness parameters were varied in 88% of all evaluations (86% imatinib, 78% pegfilgrastim, 92% adalimumab), cost parameters in 80% of all studies (86% imatinib, 78% pegfilgrastim, 77% adalimumab).

Cost-effectiveness planes were present in 29% (36% imatinib, 11% pegfilgrastim, 31% adalimumab); cost-effectiveness acceptability curves (the curve or probabilities expressed numerically against different thresholds) in 37% (21% imatinib, 44% pegfilgrastim, 42% adalimumab).

### Item 18: *Transparent reporting*

Transparent reporting was fulfilled in all parts of the study design and conduct for only 43% of analyses (29% imatinib, 11% pegfilgrastim, 62% adalimumab). Many studies missed to report transparently at some point of the articles, be it unit costs, resource utilisation and base year of analysis, the search strategy for clinical parameters, utilities applied and the measures to obtain them, or the outcomes of (and ratio for) sensitivity analysis.

In one study for imatinib, the rationale for the chosen comparator (i.e., sunitinib) was not clearly enough presented. In adalimumab, one study lacked transparency among the reported data as it did not present any utilities and QALYs obtained, making it impossible to check the outcomes; another study seemed to have mixed up references among clinical effectiveness data (i.e., stating a phase II adalimumab trial for infliximab values) with unknown consequences; a different study investigated infliximab versus adalimumab without making it clear that in fact switching to adalimumab was used in the infliximab arm after infliximab-failure.

Many studies displayed diagrams, tables, or figures to clarify models, results, and additional information (like parameters, search strategies, or trial participants' characteristics).

### Item 19: *Conclusions follow data*

Overall, conclusions followed the data presented in most studies (94%) except three for adalimumab (88%). For the study not reporting transparently on QALYs, one of the crucial items for economic evaluations, conclusions drawn were not verifiable. Another study likely conducted errors in calculating total costs. A third misinterpreted an article from the USA on cost-effectiveness thresholds applied in plaque psoriasis and consequently made flawed assumptions with unknown consequences for the whole analysis.

### Item 20: *Transferability*

The transferability to other country settings was discussed by few studies (24%). Mostly studies for adalimumab addressed the transferability (38%), to a far lesser extent studies for pegfilgrastim (11%) and imatinib (7%).

Some mention the difficulty for transferring results to different settings due to variance in costs, utilisation, and treatment protocols; others emphasised the similarity between different settings (e.g. Canada to the USA) and that results can provide an indication on cost-effectiveness. One study concerned the transferability of study results to be adopted in developing countries.

### Item 21: *Ethical and distributional issues*

Ethical and distributional issues were addressed in only a minority of studies (10% and 24% respectively). Ethical issues were addressed at an equally low level for imatinib (14%), pegfilgrastim (11%), and adalimumab (8%). Distributional issues were addressed with budget-impact analyses in about one-third for imatinib (29%) and adalimumab (31%), but none in pegfilgrastim (0%).

Some studies mentioned in a subordinate clause restricted budgets and the need for decision makers to allocate resources in the most efficient way. Such general comments can hardly be classified as *discussing* distributional (or ethical) issues and studies were consequently classified as 'not discussing'.

### Item 22: *Discussion of bias*

Most articles elaborated on inherent shortcomings and potential biases to their outcomes, study designs, underlying sources, and assumptions made (98%). One study in adalimumab (96%) only compared the outcomes of their pragmatic trial with other published results.

#### Imatinib

In imatinib, the short follow-up of the underlying effectiveness trial was discussed; many studies with a longer duration or lifetime horizon called for attention to the extrapolation of data. The allowed cross-over in the trial was discussed and statistically corrected for in few studies.

The comparator was addressed in some studies in that the superiority of interferon-alpha over hydroxyurea in terms of cost-effectiveness might not be fully established with the evidence available and would need updated

research (Dalziel 2005). Along the same line, most studies would not compare imatinib with dasatinib, nilotinib or increased doses of imatinib, because these alternatives are reserved primarily for patients who have not responded to or who developed resistance to first-line imatinib. Others do incorporate some dose intensification in their models by increasing imatinib to 600mg/day in the accelerated phase and 800mg/day in the blast crisis. The accuracy of these modifications were not tested in sensitivity analysis.

Most studies for CML were conducted among patients newly diagnosed with chronic-phase disease; the advanced stages alone were only examined in one single study. For GIST, study populations comprised advanced disease that was unresectable and/or metastatic. The adjuvant use was not explored.

#### Pegfilgrastim

Clinical trials estimates differed in the allowed chemotherapy regimen, which generated different risk levels for febrile neutropenia among studies. Also, chemotherapy costs were frequently excluded from analysis as it was anticipated that the same costs would incur for all patients, regardless of therapy form.

Another assumption is that febrile neutropenia is of such severity that hospitalisation is required. Consequently, most studies considered inpatient treatment. However, their tariffs might differ across settings. Also, there is a huge difference in terms of effectiveness and cost-effectiveness when applying filgrastim only 5-6 days or 10-11 days. The lower rate might more adequately reflect real-life administration.

The age distribution of patients was addressed in few articles. As more than half of all cancer patients are older than 65 years, the generalisability of models with much lower age categories is questionable.

#### Adalimumab

In most cases, the lack of head-to-head effectiveness data between different biologics was mentioned and the external validity of trial data questioned. Placebo-controlled randomised trials with differences in trial designs, study participants, allowed concomitant drug use, and included co-morbidities resulted in increased uncertainty of the indirect comparison. Extrapolating data due to the short-term follow up of clinical trials was frequently criticised. In addition, randomised controlled trials were sometimes regarded as not reflecting adequately real-world conditions. In this line, some studies that used infliximab as comparator addressed real-world adherence which might be greater with a regular visit by a specialist than with self-administered medication.

Different therapy regimens (i.e., dose escalation, episodic treatment, re-treatment, subsequent treatment) were in a few studies considered for CD, PP, and UC. Excluding indirect costs was often seen as influential.

The chosen study population was also remarked by some as being highly influential on the obtained outcomes (e.g. in Chen *et al*., who demonstrated that ICERs for adalimumab were able to range from £35,000 to £140,000 per QALY dependent of whether patients with early RA or late RA were examined).

And the assumption that mortality, costs, and utilities can be mapped as a function of disease severity measures was addressed. Functional and disease-specific questionnaires might not be able to adequately capture all effects on quality of life. Consequently, mapping algorithms might be flawed.

### Item 23: *Contextual embedding*

Most studies embedded their findings into a context of other economic evaluations (80%), although all studies in pegfilgrastim (100%) and about three-fourth in imatinib (79%) and adalimumab (73%). Less studies referred to a willingness-to-pay decision point (i.e., an ICER threshold) (61%), with few variation between the pharmaceuticals (57% imatinib, 56% pegfilgrastim, 65% adalimumab). The remaining studies discussed neither topic but presented their findings in isolation and without a willingness-to-pay threshold.

### Item 24: *Funding source*

About three-fourth of studies provided a disclosure on the primary funding source (78%), with few variation among drugs (86% imatinib, 78% pegfilgrastim, 73% adalimumab). Of those studies providing a funding disclosure, more than two-third declared sponsorship by a pharmaceutical company (66%) with most industry sponsoring being done for pegfilgrastim (86%) than imatinib (67%) and adalimumab (58%).

## **Table 19**: Compliance with NL-TQS (aggregated reporting)

**Table 19**: Proportion of studies satisfying NL-TQS criteria

| | Imatinib | Pegfilgrastim | Adalimumab | Weighted average | Overall average |
|---|---|---|---|---|---|
| Item 1 Audience (DM?) | 50% | 33% | 54% | 46% | 49% |
| Item 2 Study population (as registered in NL?) | 100% | 100% | 92% | 97% | 96% |
| Item 3 Comparator (standard/usual care?) | 93% | 56% | 73% | 74% | 76% |
| Item 4 Perspective (societal?) | 7% | 11% | 38% | 19% | 24% |
| Item 5 Analysis technique (CEA or CUA?) | 100% | 89% | 96% | 95% | 96% |
| Item 6 Analysis time period (sufficiently long?) | 86% | 67% | 50% | 68% | 63% |
| Item 7a Modelling (applied modelling technique?) | 93% | 89% | 81% | 88% | 86% |
| Item 7b Modelling (if applicable: model from peer-reviewed sources?) | 46% | 25% | 90% | 54% | 64% |
| Item 7c Modelling (Markov model?) | 69% | 75% | 48% | 64% | 60% |
| Item 7d Modelling (decision tree?) | 0% | 100% | 29% | 43% | 33% |
| Item 8a Discounting (in line with international Guidance?) | 93% | 44% | 88% | 75% | 82% |
| Item 8b Discounting (following Dutch recommendation?) | 14% | 0% | 0% | 5% | 4% |
| Item 9 Best available effectiveness source (systematic search algorithm stated?) | 29% | 44% | 42% | 38% | 39% |
| Item 10 Costs identified (indirect non-medical [=productivity] costs?) | 7% | 11% | 35% | 18% | 22% |
| Item 11 Costs measured (resource utilisation and/or base year clearly?) | 50% | 11% | 46% | 36% | 41% |
| Item 12a Costs valued (total costs displayed?) | 100% | 100% | 88% | 96% | 94% |
| Item 12b Costs valued (measure of variability included?) | 43% | 0% | 35% | 26% | 31% |
| Item 13 Outcomes identified (QALYs used?) | 76% | 78% | 81% | 78% | 78% |
| Item 14a Outcomes measured (if applicable: utilities elicited directly?) | 11% | 43% | 29% | 28% | 23% |
| Item 14b Outcomes measured (if applicable: utilities (indirectly) mapped by regression analysis?) | 0% | 0% | 71% | 24% | 32% |
| Item 14c Outcomes measured (if applicable: utilities (indirectly) received from expert panels?) | 32% | 43% | 5% | 27% | 21% |
| Item 14d Outcomes measured (if applicable: utilities patient-based?) | 21% | 14% | 57% | 31% | 36% |
| Item 14e Outcomes measured (if applicable: utilities population-based?) | 16% | 0% | 10% | 9% | 11% |
| Item 14f Outcomes measured (if applicable: utilities basis unclear?) | 16% | 43% | 33% | 31% | 28% |
| Item 15a Outcomes valued (total benefits reported) | 100% | 100% | 92% | 97% | 96% |
| Item 15b Outcomes valued (measure of variability included?) | 36% | 0% | 62% | 33% | 43% |
| Item 16a Incremental analysis (incremental analysis displayed?) | 93% | 89% | 96% | 93% | 94% |
| Item 16b Incremental analysis (measure of variability included?) | 36% | 13% | 46% | 32% | 38% |
| Item 17a Uncertainty analysis (univariate sensitivity analysis?) | 93% | 100% | 92% | 95% | 94% |
| Item 17b Uncertainty analysis (probabilistic sensitivity analysis?) | 36% | 44% | 65% | 48% | 53% |
| Item 17c Uncertainty analysis (varying costs parameters?) | 86% | 78% | 77% | 80% | 80% |
| Item 17d Uncertainty analysis (varying effectiveness parameters?) | 86% | 78% | 92% | 85% | 88% |
| Item 17e Uncertainty analysis (cost-effectiveness plane included?) | 36% | 11% | 31% | 26% | 29% |
| Item 17f Uncertainty analysis (cost-effectiveness acceptability curve included?) | 21% | 44% | 42% | 36% | 37% |
| Item 18 Transparent reporting? | 29% | 11% | 62% | 34% | 43% |
| Item 19 Conclusions follow data? | 100% | 100% | 88% | 96% | 94% |
| Item 20 Transferability discussed? | 7% | 11% | 38% | 19% | 24% |
| Item 21a Ethical issues discussed? | 14% | 11% | 8% | 11% | 10% |
| Item 21b Distributional issues discussed? | 29% | 0% | 31% | 20% | 24% |
| Item 22 Discussion of bias? | 100% | 100% | 96% | 99% | 98% |
| Item 23a Contextual embedding (referring to other economic evaluations?) | 79% | 100% | 73% | 84% | 80% |
| Item 23b Contextual embedding (referring to an ICER threshold value?) | 57% | 56% | 65% | 59% | 61% |
| Item 24a Funding source (providing a disclosure of primary funding source?) | 86% | 78% | 73% | 79% | 78% |
| Item 24b Funding source (of those providing a disclosure: funded by pharmaceutical companies?) | 67% | 86% | 58% | 70% | 66% |

DM: decision maker; in red: proportions ≤ 0.20; in blue: proportions ≥0.80

# **Appendix 4**: NL-TQS article characteristics

**Table 20**: Article characteristics (rank-ordered by NL-TQS)

| Medication | Indication | Article | year | type | No. of authors | Country | Funding | Journal | NL-TQS |
|---|---|---|---|---|---|---|---|---|---|
| Adalimumab | AS | Botteman | 2007 | CUA | 6 | UK | Pharma | MED | 47 |
| Adalimumab | RA | Hallinen | 2010 | CUA | 4 | Finland | Pharma | MED | 45 |
| Adalimumab | RA | Bansback | 2005 | CUA | 3 | Sweden | Pharma | MED | 44 |
| Adalimumab | PsA | Rodgers | 2011 | CUA | 17 | UK | Nonprof | HE | 43 |
| Adalimumab | RA | Malottki | 2011 | CUA | 11 | UK | Nonprof | HE | 43 |
| Adalimumab | CD | Dretzke | 2011 | CUA | 9 | UK | Nonprof | HE | 42 |
| Imatinib | CML | Dalziel | 2004 | CUA | 5 | UK | Nonprof | HE | 42 |
| Adalimumab | CD | Loftus | 2009 | CUA | 6 | UK | Pharma | MED | 41 |
| Adalimumab | RA | Chen | 2006 | CUA | 8 | UK | Nonprof | HE | 41 |
| Adalimumab | RA | Davies | 2009 | CUA | 4 | USA | Pharma | MED | 41 |
| Adalimumab | PP | Sizto | 2009 | CUA | 5 | UK | Pharma | MED | 40 |
| Imatinib | CML | Ghatnekar | 2010 | CUA/CEA | 3 | Sweden | Pharma | MED | 40 |
| Adalimumab | CD | Bodger | 2009 | CUA | 3 | UK | Nonprof | MED | 39 |
| Adalimumab | JIA | Ungar | 2011 | CEA | 5 | Canada | Nonprof | MED | 39 |
| Imatinib | CML | Dalziel | 2005 | CUA | 4 | UK | Nonprof | HE | 39 |
| Adalimumab | PP | Knight | 2011 | CUA | 6 | Sweden | Pharma | HE | 38 |
| Adalimumab | RA | Spalding | 2006 | CUA | 2 | USA | Nonprof | HE | 38 |
| Adalimumab | CD | Yu | 2009 | CUA | 8 | USA | Pharma | HE | 37 |
| Adalimumab | RA | Wailoo | 2008 | CUA | 6 | USA | Nonprof | MED | 37 |
| Imatinib | CML | Breitscheidel | 2008 | CUA | 1 | GER | Nonprof | HE | 36 |
| Imatinib | CML | Groot | 2003 | CUA | 6 | NL | Pharma | MED | 35 |
| Imatinib | CML | Warren | 2004 | CUA | 4 | UK | Pharma | MED | 35 |
| Imatinib | CML | Reed | 2004 | CUA/CEA | 5 | USA | Pharma | MED | 35 |
| Imatinib | GIST | Wilson | 2005 | CUA | 7 | UK | Nonprof | HE | 35 |
| Pegfilgrastim | FN | Lyman 1 | 2009 | CUA/CEA | 4 | USA | Pharma | MED | 35 |
| Pegfilgrastim | FN | Lyman 2 | 2009 | CUA/CEA | 4 | USA | Pharma | MED | 35 |
| Adalimumab | PP | Anis | 2011 | CUA | 6 | USA | Pharma | MED | 34 |
| Imatinib | CML | Gordois | 2003 | CUA | 4 | UK | Pharma | MED | 34 |
| Imatinib | CML | Groot | 2006 | CUA | 5 | NL | Pharma | MED | 34 |
| Imatinib | CML | Chen | 2009 | CUA/CEA | 4 | China | Pharma# | HE | 34 |
| Pegfilgrastim | FN | Eldar-Lissai | 2008 | CUA | 4 | USA | Pharma | HE | 34 |
| Pegfilgrastim | FN | Liu | 2009 | CUA/CEA | 4 | UK | Pharma# | HE | 34 |
| Imatinib | CML | Reed | 2008 | CUA/CEA | 4 | USA | Pharma | HE | 33 |
| Adalimumab | PP | Greiner | 2009 | CEA | 2 | Switzerland | Pharma | MED | 32 |
| Adalimumab | UC | Xie | 2009 | CUA | 6 | Canada | Pharma | HE | 32 |
| Pegfilgrastim | FN | Danova | 2009 | CUA/CEA | 4 | Italy | Pharma# | MED | 32 |
| Adalimumab | CD | Kaplan | 2007 | CUA | 4 | USA | Pharma | MED | 31 |
| Adalimumab | PP | Nelson | 2008 | CEA | 5 | USA | Pharma | MED | 31 |
| Imatinib | GIST | Contreras-Hernandez | 2008 | CEA | 9 | Mexico | Pharma# | MED | 30 |
| Pegfilgrastim | FN | Ramsey | 2009 | CUA/CEA | 8 | USA | Pharma | HE | 30 |
| Adalimumab | PP | De Portu | 2010 | CEA | 12 | Italy | Pharma | MED | 29 |
| Imatinib | GIST | Mabasa | 2008 | CEA | 7 | Canada | Unstated | MED | 29 |
| Pegfilgrastim | FN | Sehouli | 2010 | CUA/CEA | 7 | GER | Pharma | MED | 28 |
| Adalimumab | RA | Chiou | 2004 | CUA | 3 | USA | Pharma | HE | 27 |
| Adalimumab | RA | Walsh | 2007 | CMA | 8 | Ireland | Pharma | MED | 27 |
| Pegfilgrastim | FN | Numnum | 2007 | CEA | 5 | USA | Unstated | MED | 27 |
| Adalimumab | PP | Schmitt-Rau | 2010 | CEA | 4 | GER | Pharma | MED | 24 |
| Pegfilgrastim | FN | Tan Sean | 2009 | CBA | 6 | France | Nonprof | MED | 23 |
| Adalimumab | RA | Benucci | 2009 | CUA | 6 | Italy | Unstated | MED | 20 |

#: No declared funding from pharmaceutical companies but co-authored by an employee.
Adalimumab presented in light turquoise; imatinib in light blue; pegfilgrastim in light yellow.

# **Appendix 5:** NL-TQS for imatinib

**Table 21:** Checklist for EEs in CML (imatinib)

| | *2003 Groot* | *2003 Gordois* | *2004 Dalziel* | *2004 Reed* | *2004 Warren* | *2005 Dalziel* | *2006 Groot* | *2008 Reed* | *2008 Breitscheidel* | *2009 Chen* | *2010 Ghatnekar* | **Total items** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (1) Audience | N | N | Y | N | N | N | N | N | N | N | N | 1 |
| (2) Study population **[reg.indication+2]** | Y [1st and 2nd line +2] | Y [1st and 2nd line +2] | Y [1st and 2nd line +2] | Y [1st line +2] | Y [2nd line +2] | Y [2nd line +2] | Y [1st and 2nd line +2] | Y [1st line +2] | Y [1st line +2] | Y [1st line +2] | Y [2nd line +2] | 11 [11] |
| (3) Comparator **[STAND/USUAL+4]** | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | 11 [11] |
| (4) Perspective **[SOC+3]** | Unstated [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | SOC [+3] | 10 [1] |
| (5) Analysis technique **[CUA/CEA +2]** | CUA [+2] | CUA [+2] | CUA [+2] | CUA & CEA [+2] | CUA [+2] | CUA [+2] | CUA & CEA [+2] | CUA & CEA [+2] | CUA [+2] | CEA & CUA [+2] | CEA & CUA [+2] | 11 [11] |
| (6) Analysis time period (allowing time for all relevant and important outcomes) [sufficiently long +1] | 25 years [+1] | 5 years [0] | 20 years [+1] | lifetime [+1] | lifetime [+1] | 20 years [+1] | lifetime [+1] | lifetime [+1] | 5 years [0] | lifetime [+1] | lifetime [+1] | 11 [10] |
| (7) Modelling **[based on peer-reviewed publ+2]** | Y [0] | Y [0] | Y [+2] | Y [+2] | Y [0] | Y [+2] | Y [0] | Y [+2] | Y [+2] | Y [+2] | Y [+2] | 11 [7] |
| (8) Discounting [C 4%, E 1,5% +1] | C/E 4% [+1] | C 6%, E1.5% [0] | C 6%, E1.5% [0] | C/E 3% [0] | C 6%, E1.5% [0] | C 6%, E1.5% [0] | C/E 4% [+1] | C/E 3% [0] | C/E: 3% [0] | C/E 3.5% [0] | C/E: 3% [0] | 11 [2] |
| (9) Best available effectiveness source [systematic search alg.] | U | U | Y | U | U | Y | U | U | U | U | U | 2 |
| (10) Costs identified (which cost type) [dir costs inside/outside care; indir costs outside care +1] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [+1] | 11 [1] |
| (11) Costs measured (cost year and units, and their reference) [units and unit costs +1] | Y [+1] | Y [+1] | Y [+1] | U (no clear utilisation) [0] | Y [+1] | Y [+1] | Y [+1] | U (no clear utilisation) [0] | U (no clear quantities) [0] | U (no clear utilisation) [0] | U (experts estimate utilisation) [0] | 6 [6] |
| (12) Costs valued (concrete total costs) [validated source+1] | Y (+CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (no CI) [+1] | 11 [11] |
| (13) Outcomes identified (e.g QALY, LYG, efficacy endpoints) **[+3]** | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | 11 [11] |
| (14) Outcomes measured (how and state e.g. utilities) [generic, disease-specif, domain-specif questionnaire+1] | Y [0, VAS from expert panel] | Y [0, EQ-5D from expert panel] | Y [0 EQ-5D from IRIS, expert panel for HU] | Y [+1 EQ-5D from IRIS, every 3 months, community-weighted] | Y [0, EQ-5D from expert panel] | Y [+1 EQ-5D from IRIS, every 3 months, community-weighted] | U [0 unclear how utility weights derived] | U [unspecified, though probably from 2004 study 0] | Y [0, SG for SCT from expert panel] | U [0, unstated and referring to Reed 2008] | Y [+1 EQ-5D from general public] | 8 [3] |
| (15) Outcomes valued (concrete QALYs gain etc) [QALY+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (no CI) [+1] | 11 [11] |
| (16) Incremental analysis (with confidence intervals) | N (no CI) | Y (no CI) | Y (no CI) | Y (+CI) | Y (no CI) | Y (+CI) | Y (+CI) | Y (+CI) | Y (no CI) | Y (+CI) | Y (no CI) | 10 |
| (17) Uncertainty analysis (CE plane and ACC curve included?) **[univ./PSA, C&E +2]** | Y (no CE/ACC) [+2] | Y (no CE/ACC) [not PSA 0] | Y (CE/ACC) [+2] | Y (CE, but no ACC) [no PSA 0] | Y (no CE/ACC) [not PSA 0] | Y (no CE, but ACC) [not costs 0] | Y (CE, but no ACC) [no PSA 0, not for scenario-analyse] | Y (no CE/ACC) [not PSA 0] | Y (no CE/ACC) [not PSA 0] | Y (no CE/ACC) [not benefits, no PSA 0] | Y (CE, but no ACC) [not costs 0] | 11 [2] |
| (18) Transparent reporting | Y | Y | P | P | P | Y | P | P | Y | P | P | 4 |
| (19) Conclusions follow data | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 11 |
| (20) Transferability addressed | N | N | N | N | N | N | N | N | Y | N | N | 1 |
| (21) Discussion of ethical and distributional issues | N | P (no ethical) | Y | N | Y | P (no ethical) | N | N | N | N | N | 2 |
| (22) Explicit discussion of bias (includes limitations and assumptions) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 11 |
| (23) Contextual embedding (other studies, threshold) | P (no threshold) | N | Y | P (no other study) | N | P (no threshold) | P (no threshold) | P (no threshold) | Y | Y | Y | 4 |
| (24) Funding source and conflict of interest disclosure [if stated +1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | 11 [11] |
| **Total items reported on** (general = 24; specific = [15]) | **16**/24 [11/15] | **19**/24 [8/15] | **22**/24 [11/15] | **17**/24 [10/15] | **19**/24 [9/15] | **20**/24 [11/15] | **17**/24 [10/15] | **16**/24 [9/15] | **20**/24 [8/15] | **17**/24 [9/15] | **18**/24 [12/15] | |
| **Country specific total quality score** | **35**/50 | **34**/50 | **42**/50 | **35**/50 | **35**/50 | **39**/50 | **34**/50 | **33**/50 | **36**/50 | **34**/50 | **40**/50 | |

Y= yes/clearly reported, N= no/not reported, P=partially reported, U=unclearly reported, NA= not applicable, n/a= not available, 1 year (for discounting).
No, NA, n/a, unclear and partially are regarded negatively and disqualify for yielding one point.

**6,8,10,11,12,14,15,24 give one additional point; 2,5,7,17 give 2 points; 4,13 give 3 points; 3 gives 4 points.**

**Table 22:** Checklist for EEs in GIST (imatinib)

| | *2005 Wilson* | *2008 Mabasa* | *2008 Contreras-Hernández* | **Total items** |
|---|---|---|---|---|
| (1) Audience | Y | N | Y | 2 |
| (2) Study population **[reg.indication+2]** | Y [2nd line +2] | Y [2nd line +2] | Y [2nd line +2] | 3 [3] |
| (3) Comparator **[STAND/USUAL+4]** | Y [+4] | Y [+4] | Y [0 sunitinib unclear] | 3 [2] |
| (4) Perspective **[SOC+3]** | 3PP [0] | 3PP [0] | 3PP [0] | 3 [0] |
| (5) Analysis technique **[CUA/CEA +2]** | CUA [+2] | CEA [+2] | CEA [+2] | 3 [3] |
| (6) Analysis time period (allowing time for all relevant and important outcomes) [sufficiently long +1] | 10 years [+1] | Retrospective [unspecified, 0] | 5 years [+1] | 2 [2] |
| (7) Modelling **[based on peer-reviewed publ+2]** | Y [unknown 0] | N [0] | Y [0] | 2 [0] |
| (8) Discounting [C 4%, E 1,5% +1] | C 6%, E1.5% [0] | C 3%, E 0% [0] | C/E 5% [0] | 3 [0] |
| (9) Best available effectiveness source [systematic search alg.] | Y | Y | U | 2 |
| (10) Costs identified (which cost type) [dir costs inside/outside care; indir costs outside care +1] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | 3 [0] |
| (11) Costs measured (cost year and units, and their reference) [units and unit costs +1] | U (unclear resources) [0] | U (unclear utilisation) [0] | Y [+1] | 1 [1] |
| (12) Costs valued (concrete total costs) [validated source+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (+CI) [+1] | 3 [3] |
| (13) Outcomes identified (e.g QALY, LYG, efficacy endpoints) **[+3]** | Y [+3] | Y [+3] | Y [+3] | 3 [3] |
| (14) Outcomes measured (how and state e.g. utilities) [generic, disease-specif, domain-specif questionnaire+1] | Y [0, EQ-5D mapping from 3 experts] | Y [0] | Y [0] | 3 [0] |
| (15) Outcomes valued (concrete QALYs gain etc) [QALY+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (+CI) [+1] | 3 [3] |
| (16) Incremental analysis (with confidence intervals) | Y (no CI) | Y (no CI) | Y (no CI) | 3 |
| (17) Uncertainty analysis (CE plane and ACC curve included?) **[univ./PSA, C&E +2]** | Y (no CE/ACC) [not PSA 0] | Y (no CE/ACC) [not PSA 0] | Y (CE/ACC) [not DSA and benefits 0] | 3 [0] |
| (18) Transparent reporting | P | P | P | 0 |
| (19) Conclusions follow data | Y | Y | Y | 3 |
| (20) Transferability addressed | N | N | N | 0 |
| (21) Discussion of ethical and distributional issues | N | N | N | 0 |
| (22) Explicit discussion of bias (includes limitations and assumptions) | Y | Y | Y | 3 |
| (23) Contextual embedding (other studies, threshold) | Y | Y | Y | 3 |
| (24) Funding source and conflict of interest disclosure [if stated +1] | Y [+1] | N [0] | N [0] | 1 [1] |
| **Total items reported on** (general = 24; specific = [15]) | **20**/24 [8/15] | **16**/24 [6/15] | **19**/24 [7/15] | |
| **Country specific total quality score** | **35**/50 | **29**/50 | **30**/50 | |

# **Appendix 6:** NL-TQS for pegfilgrastim

**Table 23:** Checklist for EEs in neutropenia (pegfilgrastim)

| | *2007 Numnum* | *2008 Eldar-Lissai* | *2009 Danova* | *2009 Liu* | *2009a Lyman* | *2009b Lyman* | *2009 Ramsey* | *2009 Tan Sean* | *2010 Sehouli* | **Total items** |
|---|---|---|---|---|---|---|---|---|---|---|
| (1) Audience | N | N | N | N | N | N | N | N | N | 0 |
| (2) Study population **[reg.indication+2]** | Y [PP, SP +2] | Y [PP +2] | Y [PP +2] | Y [PP +2] | Y [PP +2] | Y [PP +2] | Y [PP +2] | Y [PP +2] | Y [PP +2] | 9 [9] |
| (3) Comparator **[STAND/USUAL+4]** | Y [0 filgrastim usual] | Y [0 filgrastim usual] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [0] | Y [+4] | Y [0] | 9 [5] |
| (4) Perspective **[SOC+3]** | 3PP [0] | SOC [+3] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 3PP [0] | 9 [1] |
| (5) Analysis technique **[CUA/CEA +2]** | CEA [+2] | CUA [+2] | CUA & CEA [+2] | CUA & CEA [+2] | CUA & CEA [+2] | CUA & CEA [+2] | CUA & CEA [+2] | CBA [0] | CUA & CEA [+2] | 9 [8] |
| (6) Analysis time period (allowing time for all relevant and important outcomes) [sufficiently long +1] | 6 cycles [0] | 1st cycle of 21 days [0] | lifetime [+1] | lifetime [+1] | lifetime [+1] | lifetime [+1] | lifetime [+1] | 2 years [retrospective 0] | lifetime [+1] | 9 [6] |
| (7) Modelling **[based on peer-reviewed publ+2]** | Y [+2] | Y [+2] | Y [0 only partially] | Y [0 only partially] | Y [0 only partially] | Y [0 only partially] | Y [0 only partially] | N [0] | Y [0 unclear] | 8 [2] |
| (8) Discounting [C 4%, E 1,5% +1] | n/a | n/a | C 0%, E3% [0] | C 0%, E3% [0] | C 0%, E3% [0] | C 0%, E3% [0] | C 0%, E3% [0] | n/a | C/E 5% [0] | 6 [0] |
| (9) Best available effectiveness source [systematic search alg.] | U | U | Y | Y | U | Y | U | U | Y | 4 |
| (10) Costs identified (which cost type) [dir costs inside/outside care; indir costs outside care +1] | Y [0, no indir] | Y [+1] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | Y [0, no indir] | 9 [1] |
| (11) Costs measured (cost year and units, and their reference) [units and unit costs +1] | U (unclear base year/ utilisation) [0] | Y [+1] | U (unclear base year/ utilisation) [0] | U (unclear utilisation) [0] | U (unclear utilisation) [0] | U (unclear utilisation) [0] | U (unclear utilisation) [0] | U (unclear utilisation) [0] | U (unclear base year/ utilisation) [0] | 1 [1] |
| (12) Costs valued (concrete total costs) [validated source+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | 9 [9] |
| (13) Outcomes identified (e.g QALY, LYG, efficacy endpoints) **[+3]** | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [0] | Y [+3] | 9 [8] |
| (14) Outcomes measured (how and state e.g. utilities) [generic, disease-specif, domain-specif questionnaire+1] | Y [+1 published literature and phase II / III trials] | Y [0, SG from 180 nurses] | Y [0, SG and VAS from multiple studies asking clinical experts] | Y [0, SG and VAS from multiple studies asking clinical experts] | Y [0, average from multiple studies] | U [0 mix of sources cited] | U [0 mix of sources cited] | Y [+1 directly in general population with VAS] | U [0 unstated] | 6 [2] |
| (15) Outcomes valued (concrete QALYs gain etc) [QALY+1] | Y (no CI) [0] | Y (no CI) [0 QALD not QALY] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [0] | Y (no CI) [+1] | 9 [6] |
| (16) Incremental analysis (with confidence intervals) | Y (no CI) | Y (no CI) | Y (no CI) | Y (no CI) | Y (no CI) | Y (no CI) | Y (+CI) | N | Y (no CI) | 8 |
| (17) Uncertainty analysis (CE plane and ACC curve included?) **[univ./PSA, C&E +2]** | Y (no CE/ACC) [not PSA, not costs, intransparent 0] | Y (CE, but no ACC) [age <65 to include productivity costs; not varied 0) | Y (no CE/ACC) [not PSA 0] | Y (no CE, but ACC) [PSA only for 6-day filgrastim 0] | Y (no CE, but ACC) [+2] | Y (no CE, but ACC) [+2] | Y (no CE, but ACC) [+2] | Y (no CE/ACC) [not PSA, not effects 0] | Y (no CE/ACC) [not PSA 0] | 9 [3] |
| (18) Transparent reporting | P | Y | P | P | P | P | P | P | P | 1 |
| (19) Conclusions follow data | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| (20) Transferability addressed | Y | N | P (11 or 6 days) | N | N | N | N | N | N | 1 |
| (21) Discussion of ethical and distributional issues | N | N | N | N | N | N | N | P (no distributional) | N | 0 |
| (22) Explicit discussion of bias (includes limitations and assumptions) | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| (23) Contextual embedding (other studies, threshold) | P (no threshold) | P (no threshold) | Y | Y | Y | Y | Y | P (no threshold) | P (no threshold) | 5 |
| (24) Funding source and conflict of interest disclosure [if stated +1] | N [0] | Y [+1] | N [0] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | 7 [7] |
| **Total items reported on** (general = 24; specific = [15]) | **16**/24 [6/15] | **18**/24 [9/15] | **18**/24 [7/15] | **19**/24 [8/15] | **18**/24 [9/15] | **18**/24 [9/15] | **17**/24 [8/15] | **14**/24 [5/15] | **17**/24 [7/15] | |
| **Country specific total quality score** | **27**/50 | **34**/50 | **32**/50 | **34**/50 | **35**/50 | **35**/50 | **30**/50 | **23**/50 | **28**/50 | |

PP: primary prevention, SP: secondary prevention

Y= yes/clearly reported, N= no/not reported, P=partially reported, U=unclearly reported, NA= not applicable, n/a= not available, 1 year (for discounting).
No, NA, n/a, unclear and partially are regarded negatively and disqualify for yielding one point.

6,8,10,11,12,14,15,24 give one additional point; 2,5,7,17 give 2 points; 4,13 give 3 points; 3 gives 4 points.

# **Appendix 7**: NL-TQS for adalimumab

**Table 24:** Checklist for EEs in RA

| | *2004 Chiou* | *2005 Bansback* | *2006 Chen* | *2006 Spalding* | *2007 Walsh* | *2008 Wailoo* | *2009 Benucci* | *2009 Davies* | *2010 Hallinen* | *2011 Malottki* | **Total items** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (1) Audience | Y | Y | Y | N | U | Y | N | N | N | Y | 5 |
| (2) Study population **[reg.indication+2]** | Y [2nd line +2] | Y [2nd line +2] | Y [1st, 2nd, 3rd line +2] | Y [1st line +2] | Y [switch INFL to ADA, +2] | Y [2nd line +2] | Y [2nd line +2] | Y [2nd line +2] | Y [2nd, 3rd line +2] | Y [3rd line +2] | 10 [10] |
| (3) Comparator **[STAND/USUAL+4]** | N [0] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | N [0] | Y [+4] | Y [Y,+4, FK.CVZ] | Y [+4] | 8 [8] |
| (4) Perspective **[SOC+3]** | 3PP [0] | SOC [+3] | 3PP [0] | 3PP [SOC in sens. anal. +3] | 3PP [0] | 3PP [0] | unstated (3PP reasonable) | 3PP [SOC in sens. anal. +3] | SOC [+3] | 3PP [0] | 9 [4] |
| (5) Analysis technique **[CUA/CEA +2]** | CUA [+2] | CUA [+2] | CUA [+2] | CUA [+2] | CMA [0] | CUA [+2] | CUA [+2] | CUA [+2] | CUA [+2] | CUA [+2] | 10 [9] |
| (6) Analysis time period (allowing time for all relevant and important outcomes) [sufficiently long +1] | 1year [0] | lifetime [+1] | lifetime [+1] | lifetime [+1] | 1year [0] | lifetime [+1] | 2 years [0] | lifetime [+1] | lifetime [+1] | lifetime [+1] | 10 [7] |
| (7) Modelling **[based on peer-reviewed publ+2]** | Y [0] | Y [+2] | Y [+2] | Y [+2] | N [0] | Y [+2] | N [0] | Y [+2] | Y [+2] | Y [+2] | 8 [7] |
| (8) Discounting [C 4%, E 1,5% +1] | n/a [0] | C/E 3% [0] | C 6%, E1.5% [0] | C/E 3% [0] | n/a [0] | C/E 3% [0] | N [0] | C/E 3% [0] | C/E 3% [0] | C/E 3.5% [0] | 7 [0] |
| (9) Best available effectiveness source [systematic search alg.] | N | Y | Y | Y | Y | Y | Y | U | U | Y | 7 |
| (10) Costs identified (which cost type) [dir costs inside/outside care; indir costs outside care +1] | Y [0, no indir] | Y [0, no indir outside] | Y [0, no indir] | Y [+1] | Y [+1] | Y [0, no indir] | Y [0, no indir] | Y [+1] | Y [0, prod excluded] | Y [0, no indir] | 10 [3] |
| (11) Costs measured (cost year and units, and their reference) [units and unit costs +1] | Y [+1] | U [0] | Y [+1] | U (no clear quantities) [0] | U (no clear quantities) [0] | U (no clear quantities) [0] | U (no clear quantities, base year) [0] | U (no clear quantities) [0] | Y [+1] | Y [+1] | 4 [4] |
| (12) Costs valued (concrete total costs) [validated source+1] | Y (no CI) [+1] | Y (no CI) [0, use of experts] | Y (+CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [0, use of experts] | Y (no CI) [+1] | Y (+CI) [+1] | 10 [8] |
| (13) Outcomes identified (e.g QALY, LYG, efficacy endpoints) **[+3]** | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | 10 [10] |
| (14) Outcomes measured (how and state e.g. utilities) [generic, disease-specif, domain-specif questionnaire+1] | Y [0, VAS] | Y [1 HAQ DI; but transformation] | Y [1 HAQ DI; but transformation to QALY] | Y [1 HAQ DI; but transformation] | Y [1 DAS, HAQ, RAQoL] | Y [1 HAQ DI; but mapping] | P (1 HAQ not stated, but used for mapping] | Y [1 HAQ DI; but mapping] | Y [1 HAQ DI; but transformation] | Y [1 HAQ DI; but mapping] | 9 [9] |
| (15) Outcomes valued (concrete QALYs gain etc) [QALY+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | N (no CI) [0] | P (+CI) [0] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | 8 [8] |
| (16) Incremental analysis (with confidence intervals) | Y (no CI) | Y (no CI) | Y (+CI) | Y (no CI) | Y (no CI) | Y (no CI) | N (only QALY/cost to baseline; assumes QALY gain = 0) (no CI) | Y (no CI) | Y (no CI) | Y (+CI) | 9 |
| (17) Uncertainty analysis (CE plane and ACC curve included?) **[univ./PSA, C&E +2]** | Y (no CE/ACC) [0, no PSA] | Y [+2] | Y (no CE/ACC) [no PSA 0] | P (no CE/ACC) [no PSA; not for ADA 0] | N [0] | Y [not costs 0] | N [0] | Y [+2] | Y (no ACC) [+2] | Y [+2] | 7 [4] |
| (18) Transparent reporting | Y | Y | Y | P | P | P | P | P | Y | Y | 5 |
| (19) Conclusions follow data | Y | Y | Y | U | Y | Y | Y | Y | Y | Y | 9 |
| (20) Generalisability addressed | N | Y | N | Y | N | N | N | N | Y | N | 3 |
| (21) Discussion of ethical and distributional issues | P (no ethical) | N | P | N | N | N | N | N | N | P (no ethical) | 0 |
| (22) Explicit discussion of bias (incl. limitations and assumptions) | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | 9 |
| (23) Context placement (other studies, threshold) | P (no threshold) | Y | Y | Y | P (no threshold) | N | Y | Y | Y | Y | 7 |
| (24) Funding source and conflict of interest disclosure [if stated +1] | N [but Cerner enterprise = for-profit 0] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | N [0] | Y [+1] | Y [+1] | Y [+1] | 8 [8] |
| **Total items reported on** (general = 24; specific = [15]) | **17**/24 [6/15] | **22**/24 [11/15] | **22**/24 [11/15] | **17**/24 [11/15] | **14**/24 [7/15] | **19**/24 [10/15] | **10**/24 [6/15] | **18**/24 [12/15] | **21**/24 [13/15] | **22**/24 [12/15] | **1**/24* [0/15]* |
| **Country specific total quality score** | **27**/50 | **44**/50 | **41**/50 | **38**/50 | **27**/50 | **37**/50 | **20**/50 | **41**/50 | **45**/50 | **43**/50 | **3**/50* |

Y= yes/clearly reported, N= no/not reported, P=partially reported, U=unclearly reported, NA= not applicable, n/a= not available, 1 year (for discounting).
No, NA, n/a, unclear and partially are regarded negatively and disqualify for yielding one point.

Items 6,8,10,11,12,14,15,24 give one additional point; 2,5,7,17 give 2 points; 4,13 give 3 points; 3 gives 4 points.

* Average total score

**Table 25:** Checklist for EEs in CD

| | *2007 Kaplan* | *2009 Bodger* | *2009 Loftus* | *2009 Yu* | *2011 Dretzke* | **Total items** |
|---|---|---|---|---|---|---|
| (1) Audience | N | N | N | N | Y | 1 |
| (2) Study population **[reg.indication+2]** | Y [3rd line 0] | Y [1st, 2nd line +2] | Y [2nd line +2] | Y [2nd line +2] | Y [1st, 2nd line +2] | 5 [4] |
| (3) Comparator **[STAND/USUAL+4]** | Y [0] | Y [+4] | Y [+4] | Y [+4] | Y [+4] | 5 [4] |
| (4) Perspective **[SOC+3]** | 3PP [0] | 3PP [0] | 3PP [SOC in sens. anal. +3] | 3PP [0] | 3PP [0] | 5 [1] |
| (5) Analysis technique **[CUA/CEA +2]** | CUA [+2] | CUA [+2] | CUA [+2] | CUA [+2] | CUA [+2] | 5 [5] |
| (6) Analysis time period (allowing time for all relevant and important outcomes) [sufficiently long +1] | 1 year [0] | lifetime [+1] | 1 year [lifetime in sens. anal. +1] | 1 year [0] | 1year [up to 20 years +1] | 5 [3] |
| (7) Modelling **[based on peer-reviewed publ+2]** | Y [+2] | Y [+2] | N | N | Y [+2] | 3 [3] |
| (8) Discounting [C 4%, E 1,5% +1] | n/a [0] | C/E 3.5% [0] | ≤1 year [C/E 3.5% in sens. anal. 0] | ≤1 year [0] | n/a [0] | 3 [0] |
| (9) Best available effectiveness source [systematic search alg.] | U | Y | U | U (no weights displayed) | Y | 2 |
| (10) Costs identified (which cost type) [dir costs inside/outside care; indir costs outside care +1] | Y [0, no indir] | Y [0, no indir] | Y [+1] | Y [0, no indir] | Y [0, no indir] | 5 [1] |
| (11) Costs measured (cost year and units, and their reference) [units and unit costs +1] | Y [+1] | U (no clear quantities) [0] | Y [+1] | Y [+1] | Y [+1] | 4 [4] |
| (12) Costs valued (concrete total costs) [validated source+1] | Y (+CI) [+1] | Y (+CI) [+1] | Y (no CI) [+1] | Y (+CI) [+1] | Y (+CI) [costs from registry, 1] | 5 [5] |
| (13) Outcomes identified (e.g QALY, LYG, efficacy endpoints) **[+3]** | Y [+3] | Y [+3] | Y [+3] | Y [+3] | Y [+3] | 5 [5] |
| (14) Outcomes measured (how and state e.g. utilities) [generic, disease-specif, domain-specif questionnaire+1] | Y [from RCT publ. +1] | Y [EQ-5D; but mapping from CDAI +1] | Y [unpublished SG data from Canadian patients 0] | Y [unpublished SG data from Canadian patients 0] | Y [from RCT publ. +1] | 5 [3] |
| (15) Outcomes valued (concrete QALYs gain etc) [QALY+1] | Y (+CI) [+1] | Y (+CI) [+1] | Y (+CI) [+1] | Y (+CI) [+1] | Y (+CI) [+1] | 5 [5] |
| (16) Incremental analysis (with confidence intervals) | Y (not CI) | Y (not CI) | Y (not CI) | Y (+CI) | Y (+CI) | 5 |
| (17) Uncertainty analysis (CE plane and ACC curve included?) **[univariate/PSA, C and E +2]** | Y (no CE/ACC) [+2] | Y (no CE/ACC) [no PSA 0] | Y (no CE, but ACC) [+2] | Y (no CE, but ACC) [+2] | Y (no CE, but ACC) [+2] | 5 [4] |
| (18) Transparent reporting | Y | P | Y | Y | Y | 4 |
| (19) Conclusions follow data | Y | Y | Y | Y | Y | 5 |
| (20) Transferability addressed | Y | Y | N | Y | N | 3 |
| (21) Discussion of ethical and distributional issues | N | Y | N | N | P (Budget Impact analysis) | 1 |
| (22) Explicit discussion of bias (includes limitations and assumptions) | P (not addressed impact of adding ada to infl arm) | Y | Y | Y | Y | 4 |
| (23) Contextual embedding (other studies, threshold) | Y | Y | Y | Y | Y | 5 |
| (24) Funding source and conflict of interest disclosure [if stated +1] | P [unclear funding but CoI 0] | Y [+1] | Y [+1] | Y [+1] | Y [+1] | 4 [4] |
| **Total items reported on** (general = 24; specific = [15]) | **18**/24 [**8**/15] | **21**/24 [**10**/15] | **19**/24 [**12**/15] | **20**/24 [**9**/15] | **21**/24 [**12**/15] | **19.8**/24 [**10.2**/15] * |
| **Country specific total quality score** | **31/50** | **39/50** | **41/50** | **37/50** | **42/50** | **38/50** |

Y= yes, N= no, NA= not applicable, n/a= not available, U=unclear, P=partial, 1 year (for discounting).
No, NA, n/a, unclear and partially are regarded negatively and do not give one point.

* Average total score

**Table 26:** Checklist for EEs in PP

| | *2009 Sizto* | *2009 Greiner* | *2010 de Portu* | *2010 Schmitt-Rau* | *2011 Anis* | *2011 Knight* | **Total items** |
|---|---|---|---|---|---|---|---|
| (1) Audience | Y | N | N | N | Y | P | 2 |
| (2) Study population **[reg.indication+2]** | Y [3rd line +2] | Y [2nd line +2] | Y [2nd line +2] | Y [2nd line +2] | Y [1st, 2nd line +2] | Y [2nd line +2] | 6 [6] |
| (3) Comparator **[STAND/USUAL+4]** | Y [0] | Y [0] | Y [+4] | Y [+4] | Y [0] | Y [+4] | 6 [3] |
| (4) Perspective **[SOC+3]** | 3PP [SOC in sens. anal. +3] | 3PP [0] | 3PP [0] | 3PP [0] | U [SOC assumed +3] | U [SOC assumed +3] | 4 [3] |
| (5) Analysis technique **[CUA/CEA +2]** | CUA [+2] | CEA [+2] | CEA [+2] | CEA [+2] | CUA [+2] | CUA [+2] | 6 [6] |
| (6) Analysis time period (allowing time for all relevant and important outcomes) [sufficiently long +1] | U [0] | 9 months [+1] | 1 year [+1] | 12 wks [0] | U [0] | 10 years [+1] | 4 [3] |
| (7) Modelling **[based on peer-reviewed publ+2]** | Y [+2] | Y [+2] | U | N | Y [+2] | Y [+2] | 4 [4] |
| (8) Discounting [C 4%, E 1,5% +1] | n/a [0] | ≤1 year [0] | n/a [0] | n/a [0] | n/a [0] | P [only for sens. anal 0] | 1 [0] |
| (9) Best available effectiveness source [systematic search alg.] | Y | U | U | U | U | U | 1 |
| (10) Costs identified (which cost type) [dir costs inside/outside care; indir costs outside care +1] | Y [+1] | Y [0, no indir] | P [0, no indir and excl hosp] | Y [0, no indir] | Y [+1] | Y [+1] | 5 [3] |
| (11) Costs measured (cost year and units, and their reference) [units and unit costs +1] | Y [+1] | Y [+1] | Y [+1] | U (no clear quantities) [0] | Y [+1] | Y [+1] | 5 [5] |
| (12) Costs valued (concrete total costs) [validated source+1] | Y (no CI) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | P (no CI, miscalculation for ustekinumab) [+1] | Y (no CI) [+1] | Y (no CI) [+1] | 5 [6] |
| (13) Outcomes identified (e.g QALY, LYG, efficacy endpoints) **[+3]** | Y [+3] | Y [PASI +3] | Y [PASI +3] | Y [PASI +3] | Y [+3] | Y [+3] | 6 [6] |
| (14) Outcomes measured (how and state e.g. utilities) [generic, disease-specif, domain-specif questionnaire+1] | Y [EQ-5D from RCTs +1] | Y [from RCTs, no utilities 0] | Y [published studies, no utilities 0] | Y [published trials, no utilities 0] | P [EQ-5D to PASI mapping; unstated formula 0] | Y [DLQI mapping +1] | 5 [2] |
| (15) Outcomes valued (concrete QALYs gain etc) [QALY+1] | Y (+CI) [+1] | Y (no CI) [PASI 0] | Y (no CI) [PASI 0] | Y (+CI) [PASI 0] | Y (+CI) [+1] | Y (no CI) [+1] | 6 [3] |
| (16) Incremental analysis (with confidence intervals) | Y (+CI) | Y (not CI) | Y (not CI) | Y (not CI) | Y (not CI) | Y (+CI) | 6 |
| (17) Uncertainty analysis (CE plane and ACC curve included?) **[univ./PSA, C&E +2]** | Y [+2] | Y (no CE/ACC) [no PSA 0] | Y (CE, but no ACC) [no drug costs 0] | Y (no CE/ACC) [no PSA 0] | Y (no CE/ACC) [no PSA 0] | Y (CE, but no ACC) [no drug costs 0] | 6 [1] |
| (18) Transparent reporting | Y | Y | P (reference mix-up) | P | P (sens anal + formula not) | P | 2 |
| (19) Conclusions follow data | Y | P (wrong interpretation) | Y | P (wrong calculation) | Y | Y | 4 |
| (20) Transferability addressed | Y | N | N | N | Y | N | 2 |
| (21) Discussion of ethical and distributional issues | N | N | Y | N | P | N | 1 |
| (22) Explicit discussion of bias (includes limitations and assumptions) | Y | Y | Y | Y | Y | Y | 6 |
| (23) Contextual embedding (other studies, threshold) | P (no other studies) | Y | P (no threshold) | P (no threshold) | Y | Y | 3 |
| (24) Funding source and conflict of interest disclosure [stated +1] | Y [+1] | Y [+1] | P [unclear funding but CoI 0] | P [unclear funding but CoI 0] | Y [+1] | N [but industry employees0] | 3 [3] |
| **Total items reported on** (general = 24; specific = [15]) | **20**/24 [**12**/15] | **19**/24 [**8**/15] | **15**/24 [**7**/15] | **12**/24 [**5**/15] | **17**/24 [**10**/15] | **16**/24 [**12**/15] | **16.5**/24 [**9**/15] |
| **Country specific total quality score** | **40/50** | **32/50** | **29/50** | **24/50** | **34/50** | **38/50** | **32.8/50** |

Y= yes, N= no, NA= not applicable, n/a= not available, U=unclear, P=partial, 1 year (for discounting). No, NA, n/a, unclear and partially are regarded negatively and do not give one point.
* Average total score

**Table 27:** Checklist for EEs in PsA (Rodgers), AS (Botteman), PP (Nelson), JIA (Ungar), UC (Xie)

| | *PsA* | | *AS* | | *PP* | | *JIA* | | *UC* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *2004 Rodgers* | **Total items** | *2006 Botteman* | **Total items** | *2008 Nelson* | **Total items** | *2008 Ungar* | **Total items** | *2009 Xie* | **Total items** |
| (1) Audience | Y | 1 | Y | 1 | N | 0 | Y | 1 | N | 0 |
| (2) Study population **[reg.indication+2]** | Y [2nd, 3rd line +2] | 1 [1] | Y [+2] | 1 [1] | Y [+2] | 1 [1] | Y [2nd line +2] | 1 [1] | N [0] | 0 [0] |
| (3) Comparator **[STAND/USUAL+4]** | Y [+4] | 1 [1] | Y [+4] | 1 [1] | Y [0] | 1 [0] | Y [+4] | 1 [1] | Y [+4] | 1 [1] |
| (4) Perspective **[SOC+3]** | 3PP [0] | 1 [0] | 3PP [SOC in sens. anal. +3] | 1 [1] | 3PP [0] | 1 [0] | SOC [+3] | 1 [1] | 3PP [0] | 1 [0] |
| (5) Analysis technique **[CUA/CEA +2]** | CUA [+2] | 1 [1] | CUA [+2] | 1 [1] | CEA [+2] | 1 [1] | CEA [+2] | 1 [1] | CUA [+2] | 1 [1] |
| (6) Analysis time period (allowing time for all relevant and important outcomes) [sufficiently long +1] | lifetime [+1] | 1 [1] | lifetime [+1] | 1 [1] | ≤1 year [0] | 1 [0] | ≤1 year [0] | 1 [0] | 5 years [0] | 1 [0] |
| (7) Modelling **[based on peer-reviewed publ+2]** | Y [+2] | 1 [1] | Y [+2] | 1 [1] | n/a | 0 [0] | Y [+2] | 1 [1] | Y [+2] | 1 [1] |
| (8) Discounting [C 4%, E 1,5% +1] | C/E 3.5% [0] | 1 [0] | C/E 3.5% [0] | 1 [0] | n/a [0] | 0 [0] | n/a [0] | 0 [0] | C/E 5% [0] | 1 [0] |
| (9) Best available effectiveness source [systematic search alg.] | Y | 1 | U | 0 | Y | 1 | U | 0 | U | 0 |
| (10) Costs identified (which cost type) [dir costs inside/outside care; indir costs outside care +1] | Y [0, no indir] | 1 [0] | Y [+1] | 1 [1] | Y [0, no indir] | 1 [0] | Y [+1] | 1 [1] | Y [0, no indir] | 1 [0] |
| (11) Costs measured (cost year and units, and their reference) [units/ unit costs +1] | Y [+1] | 1 [1] | Y [+1] | 1 [1] | Y [+1] | 1 [1] | U (no clear quantities) [0] | 0 [0] | U (no clear quantities) [0] | 0 [0] |
| (12) Costs valued (concrete total costs) [validated source+1] | Y (no CI) [+1] | 1 [1] | Y (+CI) [+1] | 1 [1] | Y (no CI) [+1] | 1 [1] | Y (+CI) [+1] | 1 [1] | Y (+CI) [+1] | 1 [1] |
| (13) Outcomes identified (e.g QALY, LYG, efficacy endpoints) **[+3]** | Y [+3] | 1 [1] | Y [+3] | 1 [1] | Y [+3] | 1 [1] | Y [+3] | 1 [1] | Y [+3] | 1 [1] |
| (14) Outcomes measured (how and state e.g. utilities) [generic, disease-specif, domain-specf questionnaire+1] | Y [1 HAQ DI and PASI; but mapped] | 1 [1] | Y [HUI and mapping from BASDAI/ BASFI +1] | 1 [1] | Y (+CI) [from RCT +1] | 1 [1] | Y (+CI) [from publ. RCT data +1] | 1 [1] | Y [from publ. data +1] | 1 [1] |
| (15) Outcomes valued (concrete QALYs gain etc) [QALY+1] | Y (+CI) [+1] | 1 [1] | Y (+CI) [+1] | 1 [1] | Y (+CI) [0] | 1 [0] | Y (+CI) [+1] | 1 [1] | Y (+CI) [+1] | 1 [1] |
| (16) Incremental analysis (with confidence intervals) | Y (+CI) | 1 | Y (+CI) | 1 | Y (no CI) | 1 | Y (+CI) | 1 | Y (no CI) | 1 |
| (17) Uncertainty analysis (CE plane and ACC curve included?) **[univ./PSA, C&E +2]** | Y (no CE, but ACC) [+2] | 1 [1] | Y (no CE/ACC) [+2] | 1 [1] | Y (no CE/ACC) [+2] | 1 [1] | P (no CE, but ACC) [no costs 0] | 0 [0] | Y (no CE, but ACC) [+2] | 1 [1] |
| (18) Transparent reporting | Y | 1 | Y | 1 | Y | 1 | P | 0 | P | 0 |
| (19) Conclusions follow data | Y | 1 | Y | 1 | Y | 1 | Y | 1 | Y | 1 |
| (20) Transferability addressed | N | 0 | Y | 1 | N | 0 | Y | 1 | N | 0 |
| (21) Discussion of ethical and distributional issues | P (distributional) | 0 | N | 0 | N | 0 | N | 0 | N | 0 |
| (22) Explicit discussion of bias (includes limitations and assumptions) | Y | 1 | Y | 1 | Y | 1 | Y | 1 | Y | 1 |
| (23) Contextual embedding (other studies, threshold) | Y | 1 | Y | 1 | N (no threshold or studies) | 0 | Y | 1 | Y | 1 |
| (24) Funding source and conflict of interest disclosure [if stated +1] | Y [+1] | 1 [1] | Y [+1] | 1 [1] | Y [+1] | 1 [1] | Y [+1] | 1 [1] | P [unclear funding but CoI 0] | 0 [0] |
| **Total items reported on** (general = 24; specific = [15]) | **22**/24 [**12**/15] | | **22**/24 [**14**/15] | | **18**/24 [**8**/15] | | **18**/24 [**11**/15] | | **16**/24 [**8**/15] | |
| **Country specific total quality score** | **43/50** | | **47/50** | | **31/50** | | **39/50** | | **32/50** | |

Y= yes, N= no, NA= not applicable, n/a= not available, U=unclear, P=partial, 1 year (for discounting). No, NA, n/a, unclear and partially are regarded negatively and do not give one point. * Average total score

# **Appendix 8**: Cost-effectiveness results for imatinib

**Table 28:** Results of economic evaluation studies for imatinib in CML

| First-line therapy (standard care) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cost-utility analyses** | | | | | | | | | | | | |
| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime) | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
| [1] | Groot et al. (2003) | first-line CML | 32/50* | 2000 € | Conversion: - Inflation: 1.2050 | Interferon-alpha (IFN-α) 3M IE / 5M IE | IFN 3M IE<br>IFN 5M IE<br>Imatinib | 4.98<br>4.98<br>6.67 | *Reference*<br>Unstated<br>Unstated | *Reference*<br>-<br>- | -<br>Unstated<br>Unstated | -<br>-<br>- |
| [2] | Reed et al. (2004) | 1,000 simulated CML patients | 35/50 | 2002 US$ | Conversion: 0.9456 Inflation: 1.1251 | IFN-α+LDAC | IFN-α+LDAC<br>imatinib | 5.17<br>9.06 | *Reference*<br>$43,400 | *Reference*<br>**€51,638** | -<br>$20,500-$67,400 | -<br>**€24,391-€80,194** |
| [3] | Dalziel et al. (2004) | first-line treatment for chronic myeloid leukaemia | 42/50 | 2001-3 £ | Conversion: 0.64756# Inflation: 1.1298# | IFN-α | IFN-α<br>Imatinib | 5.04<br>7.03 | *Reference*<br>£26,180 | *Reference*<br>**€45,676** | -<br>£13,555-£51,870## | -<br>**€23,649**-€90,498 |
| [3] | Dalziel et al. (2004) | Intermediate-risk patients | 39/50* | 2001-3 £ | Conversion: 0.64756# Inflation: 1.1298# | IFN-α | IFN-α<br>Imatinib | 4.50<br>6.30 | *Reference*<br>£29,605 | *Reference*<br>**€51,652** | -<br>Unstated | -<br>- |
| [3] | Dalziel et al. (2004) | high-risk patients | 39/50* | 2001-3 £ | Conversion: 0.64756# Inflation: 1.1298# | IFN-α | IFN-α<br>Imatinib | 4.31<br>6.04 | *Reference*<br>£30,753 | *Reference*<br>**€53,655** | -<br>Unstated | -<br>- |
| [4] | Dalziel et al. (2005) | first-line treatment for chronic myeloid leukaemia | 39/50 | 2001-3 £ | Conversion: 0.64756# Inflation: 1.1298# | IFN-α | IFN-α<br>imatinib | 5.04<br>7.03 | *Reference*<br>£26,180 | *Reference*<br>**€45,676** | -<br>£19,449-£51,870 | -<br>**€33,933**-€90,498 |
| [5] | Groot et al. (2006) | 1,000 hypothetical CML patients | 33/50 | 2002 € | Conversion: - Inflation: 1.1251 | IFN-α+LDAC | IFN-α+LDAC<br>Imatinib | 4.84<br>8.19 | *Reference*<br>€49,021 | *Reference*<br>**€55,154** | -<br>€44,587-€54,758 | -<br>**€50,165-€61,608** |
| [6] | Reed et al. (2008) | 1,000 simulated CML patients | 33/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | IFN-α+LDAC | IFN-α+LDAC<br>imatinib | 5.18<br>10.71 | *Reference*<br>$57,103 | *Reference*<br>**€48,166** | -<br>$52,696-$61,939 | -<br>**€44,449-€52,246** |
| [7] | Chen et al. (2009) | Newly diagnosed chronic CML | 34/50 | [2009] RMB | Conversion: 9.5277 Inflation: 1.0099 | IFN-α+LDAC | IFN-α+LDAC<br>Imatinib | 5.4<br>11.8 | *Reference*<br>RMB73,674 | *Reference*<br>**€7,809** | -<br>RMB10,741-101,110 | -<br>**€1,139-€10,717** |
| **Cost-effectiveness analyses** | | | | | | | | | | | | |
| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | LYG (per lifetime) | ICER (per LYG) | ICER (per LYG) 2010 EURO | Sensitivity analysis (per LYG) | Sensitivity analysis (per LYG) 2010 EURO |
| [2] | Reed et al. (2004) | 1,000 simulated CML patients | 35/50 | 2002 US$ | Conversion: 0.9456 Inflation: 1.1251 | IFN-α+LDAC | IFN-α+LDAC<br>imatinib | 7.48<br>9.06 | *Reference*<br>$43,100 | *Reference*<br>€51,282 | -<br>$20,400-60,900 | -<br>€24,272-€72,460 |
| [5] | Groot et al. (2006) | 1,000 hypothetical CML patients | 33/50 | 2002 € | Conversion: - Inflation: 1.1251 | IFN-α+LDAC | IFN-α+LDAC<br>Imatinib | 7.09<br>10.43 | *Reference*<br>€49,146 | *Reference*<br>€55,294 | -<br>€43,414-57,519# | -<br>€48,845-€64,715 |
| [6] | Reed et al. (2008) | 1,000 simulated CML patients | 33/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | IFN-α+LDAC | IFN-α+LDAC<br>imatinib | 7.49<br>13.39 | *Reference*<br>$53,535 | *Reference*<br>€45,157 | -<br>$49,588-$57,794 | -<br>€41,828-€48,749 |
| [7] | Chen et al. (2009) | Newly diagnosed chronic CML | 31/50* | [2009] RMB | Conversion: 9.5277 Inflation: 1.0099 | IFN-α+LDAC | IFN-α+LDAC<br>Imatinib | 7.9<br>14.2 | *Reference*<br>RMB 74,908 | *Reference*<br>€7,940 | -<br>Unstated | -<br>- |



In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

**Table 29:** Results of economic evaluation studies for imatinib in CML (continued)

First-line therapy (usual care, ordered by comparator)

**Cost-utility analyses**

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime) | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [3] | Dalziel et al. (2004) | first-line treatment for chronic myeloid leukaemia | 39/50* | 2001-3 £ | Conversion: 0.64756# Inflation: 1.1298# | Hydroxy-carbamide (HU) | HU<br>IFN-α<br>Imatinib | 4.99<br>5.04<br>7.03 | *Reference*<br>£2,505,364<br>£86,934 | *Reference*<br>€4,371,117<br>€151,674 | -<br>Unstated<br>Unstated | -<br>-<br>- |
| [3] | Dalziel et al. (2004) | Intermediate-risk patients | 39/50* | 2001-3 £ | Conversion: 0.64756# Inflation: 1.1298# | Hydroxy-carbamide (HU) | HU<br>IFN-α<br>Imatinib | 4.52<br>4.50<br>6.30 | *Reference*<br>£4,507,569<br>£88,459 | *Reference*<br>€7,864,370<br>€154,335 | -<br>Unstated<br>Unstated | -<br>-<br>- |
| [3] | Dalziel et al. (2004) | high-risk patients | 39/50* | 2001-3 £ | Conversion: 0.64756# Inflation: 1.1298# | Hydroxy-carbamide (HU) | HU<br>IFN-α<br>Imatinib | 4.35<br>4.31<br>6.04 | *Reference*<br>£2,120,182<br>£89,045 | *Reference*<br>€3,699,088<br>€155,357 | -<br>Unstated<br>Unstated | -<br>-<br>- |
| [4] | Dalziel et al. (2005) | Patients too frail to tolerate IFN-alfa | 39/50 | 2001-3 £ | Conversion: 0.64756# Inflation: 1.1298# | Hydroxy-carbamide (HU) | HU<br>Imatinib | 4.99<br>7.03 | *Reference*<br>£86,934 | *Reference*<br>€151,674 | -<br>£69,701-£147,095 | -<br>€121,608-€256,637 |
| [9] | Gordois et al. (2003) | Accelerated phase | 33/50 | 2001 £ | Conversion: 0.62187 Inflation: 1.1605 | Conventional care | Convent. care<br>Imatinib *600mg*/day | -0.04<br>2.04 | *Reference*<br>£29,344 | *Reference*<br>**€54,760** | -<br>£9,132-£60,991 | -<br>**€17,042**-€113,818 |
| [9] | Gordois et al. (2003) | Blast phase | 33/50 | 2001 £ | Conversion: 0.62187 Inflation: 1.1605 | Conventional care | Convent. care<br>Imatinib 600mg/day | -0.05<br>0.53 | *Reference*<br>£42,239 | *Reference*<br>**€78,824** | -<br>£11,556-£122,016 | -<br>**€21,565**-€227,700 |
| [8] | Breitscheidel (2008) | Newly diagnosed chronic CML | 36/50 | 2005 € | Conversion: - Inflation: 1.0756 | Stem cell transplant (SCT) | SCT<br>Imatinib | 3.12<br>3.87 | *Reference*<br>€69 754 | *Reference*<br>**€75,027** | -<br>SCT-dominated – €126,139 | -<br>SCT-dominated - €135,675 |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

**Table 30:** Results of economic evaluation studies for imatinib in CML (continued)

| Second-line therapy (standard care) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cost-utility analyses** | | | | | | | | | | | | |
| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime) | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
| [10] | Warren et al. (2004) | Chronic CML after IFN-failure | 35/50 | 2001 £ | Conversion: 0.62187 Inflation: 1.1605 | Hydroxy-carbamide (HU) | HU<br>Imatinib | 3.49<br>5.95 | *Reference*<br>£38,468 | *Reference*<br>**€71,787** | -<br>£14,195-£62,745 | -<br>**€26,490**-€117,091 |
| Second-line therapy (usual care) | | | | | | | | | | | | |
| **Cost-utility analyses** | | | | | | | | | | | | |
| [11] | Ghatnekar et al. (2010) | Resistant to standard dose imatinib (<600 mg/kg) | 40/50 | 2008 € | Conversion: - Inflation: 1.0202 | *Imatinib 800mg/day* | Imatinib 800mg/day<br>Dasatinib | 4.57<br>5.19 | *Reference*<br>€6,880 | *Reference*<br>**€7,019** | -<br>Dominant-€70,335 | -<br>Dominant-**€71,756** |
| [5] | Groot et al. (2006) | 2nd line | 30/50* | 2002 € | Conversion: - Inflation: 1.1251 | IFN-α+LDAC (*after IFN-α+LDAC*) | IFN-α+LDAC (*after IFN-α+LDAC*)<br>IFN-α+LDAC (*after imatinib*)<br>Imatinib 400mg/day (*after imatinib*)<br>SCT-Imatinib 800mg/day (*after imatinib*) | 6.73<br>11.96<br>12.15<br>12.99 | *Reference*<br>€53,982<br>€111,600<br>€51,328 | *Reference*<br>**€60,735**<br>€125,561<br>**€57,749** | -<br>Unstated<br>Unstated<br>Unstated | -<br>-<br>-<br>- |
| **Cost-effectiveness analyses** | | | | | | | | | | | | |
| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime) | ICER (per LYG) | ICER (per LYG) 2010 EURO | Sensitivity analysis (per LYG) | Sensitivity analysis (per LYG) 2010 EURO |
| [11] | Ghatnekar et al. (2010) | Resistant to standard dose imatinib (<600 mg/kg) | 37/50* | 2008 € | Conversion: - Inflation: 1.0202 | *Imatinib 800mg/day* | Imatinib 800mg/day<br>Dasatinib | 5.69<br>6.37 | *Reference*<br>€6,332 | *Reference*<br>€6,460 | -<br>Unstated | -<br>- |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

**Table 31:** Results of economic evaluation studies for imatinib in GIST

Second-line therapy (usual care)

**Cost-utility analyses**

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime) | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [12] | Wilson et al. (2005) | unresectable and/or metastatic GIST | 35/50 | Unclear [2005]# £ | Conversion: 0.68380 Inflation: 1.0756 | Control (no therapy) | Control<br>imatinib | 3.39<br>4.85 | *Reference*<br>£29,789 | *Reference*<br>**€46,857** | -<br>£21,404-33,976 | -<br>**€33,668-€53,443** |

**Cost-effectiveness analyses**

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | LYG | ICER (per LYG) | ICER (per LYG) 2010 EURO | Sensitivity analysis (per LYG) | Sensitivity analysis (per LYG) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [13] | Mabasa et al. (2008) | 93 GIST patients | 29/50 | 2006 CA$ | Conversion: 1.4237 Inflation: 1.0591 | Historic control | Historic control<br>Imatinib | 0.64<br>5.56 | *Reference*<br>$15,638 | *Reference*<br>€11,633 | -<br>$0-$50,806## | -<br>€0-€37,795 |
| [14] | Contreras-Hernández et al. (2008) | 21 mostly female GIST patients | 30/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | Sunitinib | Sunitinib<br>Palliative care<br>Imatinib 800mg/day | 1.40<br>1.08<br>1.31 | *Reference*<br>$46,109<br>Dominated | *Reference*<br>€38,893<br>Dominated | -<br>Unclear<br>Unclear | -<br>-<br>- |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.

# Data not clearly stated; the publication date is taken as proxy.
## Only costs discounted with 3%; if outcomes were discounted too, likely to result in higher ICERs (as was shown with point-estimates).

# **Appendix 9**: Cost-effectiveness results for pegfilgrastim

**Table 32:** Results of economic evaluation studies for pegfilgrastim in febrile neutropenia

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs per lifetime | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **First-line therapy (primary prophylaxis)** | | | | | | | | | | | | |
| **Cost-utility analyses** | | | | | | | | | | | | |
| [16] | Eldar-Lissai et al. (2008) | Solid tumour cancer patients aged 18-65 | 34/50 | 2005 US$ | Conversion: 1.2441 Inflation: 1.0756 | Pegfilgrastim | 1P Pegfilgrastim<br>No G-CSF<br>1P Filgrastim | 12.967#<br>12.362#<br>12.698# | *Reference*<br>Dominated<br>Dominated | *Reference*<br>Dominated<br>Dominated | $444-$11,616#<br>Unstated<br>Unstated | **€384-€10,043**<br>-<br>- |
| [17] | Danova et al. (2009) | 45-year (30-80) old women with early-stage breast cancer | 32/50 | [2009] € | Conversion: - Inflation: 1.0099 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 15.22<br>15.32 | *Reference*<br>€429 | *Reference*<br>**€433** | -<br>€-3,000 to +7,500 | -<br>**€-3,030 to €+7,574** |
| [18] | Liu et al. (2009) | 45-year old women with early-stage breast cancer | 31/50* | 2006 £ | Conversion: 0.68173 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 14.302<br>14.354 | *Reference*<br>£8,526 | *Reference*<br>**€13,246** | -<br>Unstated | -<br>- |
| [18] | Liu et al. (2009) | 45-year old women with early-stage breast cancer | 34/50 | 2006 £ | Conversion: 0.68173 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 14.054<br>14.160 | *Reference*<br>£4,161 | *Reference*<br>**€6,464** | -<br>£-10,000 to +30,000 | -<br>**€-15,535 to €46,606** |
| [19] | Lyman et al. (2009a) | 65-year old (6 cycles) with non-Hodgkin's lymphoma | 35/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 7.276<br>7.318 | *Reference*<br>$6,190 | *Reference*<br>**€5,221** | -<br>$-100,000 to $+170,000 | -<br>**€-84,350** to €143,395 |
| [19] | Lyman et al. (2009a) | 65-year old (6 cycles) with non-Hodgkin's lymphoma | 32/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 5.571<br>5.726 | *Reference*<br>$1,677 | *Reference*<br>**€1,415** | -<br>Unstated | -<br>- |
| [20] | Lyman et al. (2009b) | 49-year (30-80) old women with early-stage breast cancer (6 cycles) | 35/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 14.517<br>14.560 | *Reference*<br>$14,538 | *Reference*<br>**€12,263** | -<br>$-60,000 to +190,000 | -<br>**€-50,610** to €160,265 |
| [20] | Lyman et al. (2009b) | 49-year (30-80) old women with early-stage breast cancer (6 cycles) | 32/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 14.286<br>14.380 | *Reference*<br>$14,330 | *Reference*<br>**€12,087** | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 11-day filgrastim | 11-day filgrastim<br>Pegfilgrastim | 12.960<br>12.985 | *Reference*<br>Dominant | *Reference*<br>Dominant | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 11-day filgrastim | 11-day filgrastim<br>Pegfilgrastim | 12.848<br>12.888 | *Reference*<br>Dominant | *Reference*<br>Dominant | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 12.938<br>12.985 | *Reference*<br>€28,851 | *Reference*<br>**€29,137** | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 12.814<br>12.888 | *Reference*<br>€18,324 | *Reference*<br>**€18,505** | -<br>Unstated | -<br>- |
| **Second-line therapy (secondary prophylaxis)** | | | | | | | | | | | | |
| [21] | Ramsey et al. (2009) | 49-year (30-80) old women with early-stage breast cancer (6 cycles) | 30/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | Secondary prophylaxis pegfilgrastim | 2P Pegfilgrastim<br>1P Pegfilgrastim | 14.487<br>14.563 | *Reference*<br>$116,000 | *Reference*<br>€97,846 | -<br>$50,000-300,000 | -<br>**€42,175**-€253,050 |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.

* Three points deducted from baseline total score due to the missing uncertainty analysis.

# Eldar-Lissai: QALDs instead of QALYs.

**Table 33:** Results of economic evaluation studies for pegfilgrastim in febrile neutropenia (continued)

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | LYG | ICER (per LYG) | ICER (per LYG) 2010 EURO | Sensitivity analysis (per LYG) | Sensitivity analysis (per LYG) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **First-line therapy (primary prophylaxis)** | | | | | | | | | | | | |
| **Cost-effectiveness analyses** | | | | | | | | | | | | |
| [17] | Danova et al. (2009) | 45-year (30-80) old women with early-stage breast cancer | 29/50* | [2009] € | Conversion: - Inflation: 1.0099 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 16.35<br>16.47 | *Reference*<br>€409 | *Reference*<br>€413 | -<br>Unstated | -<br>- |
| [18] | Liu et al. (2009) | 45-year old women with early-stage breast cancer | 31/50* | 2006 £ | Conversion: 0.68173 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 15.385<br>15.440 | *Reference*<br>£8,075 | *Reference*<br>€12,545 | -<br>Unstated | -<br>- |
| [18] | Liu et al. (2009) | 45-year old women with early-stage breast cancer | 31/50* | 2006 £ | Conversion: 0.68173 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 15.126<br>15.238 | *Reference*<br>£3,955 | *Reference*<br>€6,144 | -<br>Unstated | -<br>- |
| [19] | Lyman et al. (2009a) | 65-year old (6 cycles) with non-Hodgkin's lymphoma | 32/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 8.389<br>8.436 | *Reference*<br>$5,532 | *Reference*<br>€4,666 | -<br>Unstated | -<br>- |
| [19] | Lyman et al. (2009a) | 65-year old (6 cycles) with non-Hodgkin's lymphoma | 32/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 6.473<br>6.647 | *Reference*<br>$1,494 | *Reference*<br>€1,260 | -<br>Unstated | -<br>- |
| [20] | Lyman et al. (2009b) | 49-year (30-80) old women with early-stage breast cancer (6 cycles) | 32/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 15.653<br>15.699 | *Reference*<br>$29,456 | *Reference*<br>€24,846 | -<br>Unstated | -<br>- |
| [20] | Lyman et al. (2009b) | 49-year (30-80) old women with early-stage breast cancer (6 cycles) | 32/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 15.411<br>15.510 | *Reference*<br>$13,687 | *Reference*<br>€11,545 | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 11-day filgrastim | 11-day filgrastim<br>Pegfilgrastim | 13.999<br>14.025 | *Reference*<br>Dominant | *Reference*<br>Dominant | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 11-day filgrastim | 11-day filgrastim<br>Pegfilgrastim | 13.882<br>13.924 | *Reference*<br>Dominant | *Reference*<br>Dominant | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 13.975<br>14.025 | *Reference*<br>€27,120 | *Reference*<br>€27,388 | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 13.845<br>13.924 | *Reference*<br>€17,165 | *Reference*<br>€17,335 | -<br>Unstated | -<br>- |
| **Second-line therapy (secondary prophylaxis)** | | | | | | | | | | | | |
| [21] | Ramsey et al. (2009) | 49-year (30-80) old women with early-stage breast cancer (6 cycles) | 27/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | Secondary prophylaxis pegfilgrastim | 2P Pegfilgrastim<br>1P Pegfilgrastim | 15.622<br>15.701 | *Reference*<br>$110,000 | *Reference*<br>€92,785 | -<br>Unstated | -<br>- |

In squared brackets are the most likely assumptions depicted as made by the author of this thesis.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

**Table 34:** Results of economic evaluation studies for pegfilgrastim in febrile neutropenia (continued)

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | **FN risk (%)** | ICER (cost per FN event avoided) | ICER (per FN event avoided) 2010 EURO | Sensitivity analysis | Sensitivity analysis 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **First-line therapy (primary prophylaxis)** | | | | | | | | | | | | |
| **Cost-effectiveness analyses** | | | | | | | | | | | | |
| [18] | Liu et al. (2009) | 45-year old women with early-stage breast cancer | 31/50* | 2006 £ | Conversion: 0.68173 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 17.5<br>7 | *Reference*<br>£4,200 | *Reference*<br>€6,525 | -<br>Unstated | -<br>- |
| [19] | Lyman et al. (2009a) | 65-year old (6 cycles) with non-Hodgkin's lymphoma | 32/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 25.1<br>13.1 | *Reference*<br>$2,167 | *Reference*<br>€1,828 | -<br>Unstated | -<br>- |
| [20] | Lyman et al. (2009b) | 49-year (30-80) old women with early-stage breast cancer (6 cycles) | 32/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 17.5<br>7 | *Reference*<br>$12,904 | *Reference*<br>€10,885 | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 11-day filgrastim | 11-day filgrastim<br>Pegfilgrastim | 12.5<br>7 | *Reference*<br>Dominant | *Reference*<br>Dominant | -<br>Unstated | -<br>- |
| [22] | Sehouli et al. (2009) | 45-year (30-80) old women with early-stage breast cancer (4 cycles) | 28/50 | [2009] € | Conversion: - Inflation: 1.0099 | 6-day filgrastim | 6-day filgrastim<br>Pegfilgrastim | 17.5<br>7 | *Reference*<br>12,914 | *Reference*<br>€13,042 | -<br>Unstated | -<br>- |
| **Second-line therapy (secondary prophylaxis)** | | | | | | | | | | | | |
| [21] | Ramsey et al. (2009) | 49-year (30-80) old women with early-stage breast cancer (6 cycles) | 27/50* | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | Secondary prophylaxis pegfilgrastim | 2P Pegfilgrastim<br>1P Pegfilgrastim | 24.6<br>6.5 | *Reference*<br>$48,000 | *Reference*<br>€40,488 | -<br>Unstated | -<br>- |

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | **FN hospitalisations** | ICER (cost per hospitalisation for FN) | ICER (per FN hospitalisation) 2010 EURO | Sensitivity analysis | Sensitivity analysis 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [15] | Numnum et al. (2007) | *Average*-risk cohort of 10,000 patients with epithelial ovarian carcinoma | 27/50 | [2007] US$ | Conversion: 1.3705 Inflation: 1.0430 | No G-CSF | No G-CSF<br>2P pegfilgrastim<br>1P pegfilgrastim | 2,860<br>2,719<br>1,171 | *Reference*<br>$76,288<br>$47,343 | *Reference*<br>€58,058<br>€36,030 | -<br>Unclear<br>Unclear | -<br>-<br>- |
| [15] | Numnum et al. (2007) | *High*-risk cohort of 10,000 patients with epithelial ovarian carcinoma | 27/50 | [2007] US$ | Conversion: 1.3705 Inflation: 1.0430 | No G-CSF | No G-CSF<br>2P pegfilgrastim<br>1P pegfilgrastim | 8,044<br>7,071<br>2,860 | Dominated<br>Dominated<br>- | Dominated<br>Dominated<br>- | Unstated<br>Unstated<br>Unstated | -<br>-<br>- |

In squared brackets are the most likely assumptions depicted as made by the author of this thesis.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

# **Appendix 10**: Cost-effectiveness results for adalimumab

**Table 35:** Results of economic evaluation studies for adalimumab in RA

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime) | ICER (per QALY) | ICER (per QALY) 2010 EUR | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EUR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **First-line therapy (non-biologic comparator)** | | | | | | | | | | | | |
| **Cost-utility analysis** | | | | | | | | | | | | |
| [24] | Chen et al. (2006) | 400,000 RA patients (~2/3 female) | 41/50 | 2004 £ | Conversion: 0.67866 Inflation: 1.0904 | Trad. DMARDs | Trad. DMARDs | 8.3166 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 8.9674 | £52,600 | €84,513 | £27,000 - £122,00000 | **€44,481**-€196,017 |
| | | | | | | | ETA | 9.3005 | £49,400 | **€79,370** | £23,500 - £0,119,000 | **€37,757**-€191,197 |
| | | | | | | | INFL+MTX | 8.3682 | £654,000 | €1,050,779 | £44,600 - Dominated | **€71,659**-Dominated |
| | | | | | | | ADA+MTX | 8.5176 | £171,000 | €274,745 | £37,600 - Dominated | **€60,412**-Dominated |
| | | | | | | | ETA+MTX | 8.9408 | £78,100 | €125,483 | £28,000 - Dominated | **€44,987**-Dominated |
| [25] | Spalding et al. (2006) | Unnumerated cohort of women (men in sens. anal.) | 38/50 | 2005 US$ | Conversion: 1.2441 Inflation: 1.0756 | MTX | MTX | No QALYs transparently reported | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | | $ 63,769 | **€55,132** | N/A - $ 65,919 | N/A - **€ 56,991** |
| | | | | | | | ETA | | $ 89,772 | **€77,613** | $ 78,961 - $104,803 | **€ 68,267**-€ 90,609 |
| | | | | | | | ADA+MTX | | $ 194,589 | €168,234 | N/A - $198,541 | € N/A - €171,651 |
| | | | | | | | INFL+MTX | | $409,523 | €354,057 | $409,425 - $556,405 | €353,973-€481,046 |
| **Second-line therapy (non-biologic comparator)** | | | | | | | | | | | | |
| [26] | Bansback et al. (2005) | ACR50 (= DAS28 good) | 44/50 | 2001 € | Conversion: - Inflation: 1.1605 | Trad. DMARDs | Trad. DMARDs | 1.1818 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 1.6551 | €41,561 | **€48,232** | Unspecified | - |
| | | | | | | | ETA | 2.0493 | €36,927 | **€42,854** | Unspecified | - |
| | | | | | | | ADA+MTX (1) | 2.3114 | €34,167 | **€39,651** | €17,000 - €38,000## | **€19,729-€44,099** |
| | | | | | | | ADA+MTX (2)# | 2.1045 | €34,922 | **€40,527** | | |
| | | | | | | | ETAN+MTX | 2.0974 | €35,760 | **€41,499** | Unspecified | - |
| | | | | | | | INFL+MTX | 1.8379 | €48,333 | **€56,090** | Unspecified | - |
| [26] | Bansback et al. (2005) | ACR20 (= DAS28 moderate) | 41/50* | 2001 € | Conversion: - Inflation: 1.1605 | Trad. DMARDs | Trad. DMARDs | 1.7041 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 2.4321 | €65,499 | **€76,012** | Unspecified | - |
| | | | | | | | ETA | 2.7303 | €42,480 | **€49,298** | Unspecified | - |
| | | | | | | | ADA+MTX (1) | 2.9083 | €40,875 | **€47,435** | Unspecified## | - |
| | | | | | | | ADA+MTX (2)# | 2.7424 | €44,018 | **€51,083** | | |
| | | | | | | | ETAN+MTX | 2.9515 | €51,976 | **€60,318** | Unspecified | - |
| | | | | | | | INFL+MTX | 2.4121 | €64,935 | **€75,357** | Unspecified | - |
| [24] | Chen et al. (2006) | 100,000 early RA patients | 41/50 | 2004 £ | Conversion: 0.67866 Inflation: 1.0904 | Trad. DMARDs | Trad. DMARDs | 5.3995 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 6.3183 | £34,600 | **€55,592** | £21,200-£ 54,600 | **€34,062**-€87,726 |
| | | | | | | | ETA | 6.8617 | £30,400 | **€48,844** | £18,700-£ 45,600 | **€30,045-€73,265** |
| | | | | | | | INFL+MTX | 6.4405 | £30,400 | **€48,844** | £19,500-£ 45,300 | **€31,331-€72,783** |
| | | | | | | | ADAL+MTX | 6.4613 | £30,200 | **€48,522** | £19,100-£ 43,200 | **€30,688-€69,409** |
| | | | | | | | ETAN+MTX | 6.9715 | £28,500 | **€45,791** | £17,800-£ 42,000 | **€28,599-€67,481** |
| [24] | Chen et al. (2006) | 40,000 late RA patients | 41/50 | 2004 £ | Conversion: 0.67866 Inflation: 1.0904 | Trad. DMARDs | Trad. DMARDs | 5.4169 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 5.6365 | £141,000 | €226,544 | £41,500 - Dominated | **€66,678**-Dominated |
| | | | | | | | ETA | 6.3415 | £ 47,400 | **€ 76,157** | £24,400 - £ 95,400 | **€39,203**-€153,279 |
| | | | | | | | INFL+MTX | 5.6380 | £139,000 | €223,331 | £39,400 - Dominated | **€63,304**-Dominated |
| | | | | | | | ADA+MTX | 5.9053 | £ 64,400 | €103,471 | £30,200 - £150,000 | **€48,522**-€241,004 |
| | | | | | | | ETA+MTX | 6.2974 | £ 49,800 | **€ 80,013** | £24,600 - £ 96,100 | **€39,525**-€154,403 |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

#Adalimumab (2) contained values from a pooled analysis.
## Unclear whether for ADAL+MTX (1) or (2) and whether univariate sensitivity analysis was conducted for ACR20 or ACR50, but most likely ACR50 as PSA was also related to that response rate.
For Bansback, total costs and benefits are higher for ACR20 than ACR50 as more patients respond to the less restrictive ACR20 threshold and therefore continued with treatment.

**Table 36:** Results of economic evaluation studies for adalimumab in RA (continued)

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime) | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Second line therapy (non-biologic comparator) (continued)** | | | | | | | | | | | | |
| [27] | Hallinen et al. (2010) | 3,000; 33% male and 67% female; aged 48 | 45/50 | 2008 € | Conversion: - Inflation: 1.0202 | BSC (=MTX) | BSC | 2.69 | *Reference* | *Reference* | - | - |
| | | | | | | | 1) INFL+MTX 2) BSC | 3.15 | €36,121 | **€36,851** | €31,930-€42,794 | **€32,575-€43,658** |
| | | | | | | | 1) ADA+MTX 2) BSC | 3.19 | €50,941 | **€51,970** | €43,218-€60,842 | **€44,091-€62,071** |
| | | | | | | | 1) ETA+MTX 2) BSC | 3.22 | €50,372 | **€51,390** | €42,628-€60,273 | **€43,489-€61,491** |
| | | | | | | | 1) ABA+MTX 2) BSC | 3.31 | €67,003 | **€68,356** | €57,578-€79,647 | **€58,741**-€81,256 |
| | | | | | | | 1) RTX+MTX 2) BSC | 3.39 | €30,248 | **€30,859** | €22,004-€46,719 | **€22,448-€47,663** |
| [24] | Chen et al. (2006) | 20,000 RA patients; (TNF as 'last-resort') | 41/50 | 2004 £ | Conversion: 0.67866 Inflation: 1.0904 | Trad. DMARDs | Trad. DMARDs | 1.0317 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 1.8631 | £40,100 | **€64,428** | £27,100-64,100 | **€43,541**-€102,989 |
| | | | | | | | ETA | 2.9877 | £23,700 | **€38,079** | £18,100-33,400 | **€29,081-€53,664** |
| | | | | | | | INFL+MTX | 1.9166 | £37,900 | **€60,894** | £25,700-60,500 | **€41,292**-€97,205 |
| | | | | | | | ADA+MTX | 2.1607 | £29,700 | **€47,719** | £22,100-43,000 | **€35,508-€69,088** |
| | | | | | | | ETAN+MTX | 2.9836 | £23,800 | **€38,239** | £18,000-34,000 | **€28,921-€54,628** |
| **Second-line therapy (biologic comparator)** | | | | | | | | | | | | |
| [28] | Wailoo et al. (2008) | National Databank for Rheumatic Diseases (1,490 ETA, 1,403 INFL, 74 ANA, 160 ADA) | 37/50 | 2005 US$ | Conversion: 1.2441 Inflation: 1.0756 | INFL | INFL | 7,64 | *Reference* | *Reference* | - | - |
| | | | | | | | ANAK | 7,44 | $216,573 | €187,241 | *(Reference)* | - |
| | | | | | | | ADA | 7,64 | Dominates infliximab | Dominates infliximab | Vs anakinra: $142,726 | €123,395 |
| | | | | | | | ETAN | 7,66 | Dominates infliximab | Dominates infliximab | Vs adalimumab: $92,058† | **€79,590** |
| [29] | Chiou et al. (2004) | Moderate-to-severe RA, deemed candidate for biologics | 27/50 | 2003 US$ | Conversion: 1.1312 Inflation: 1.1038 | ANA (due to lowest costs) | ANA | 0.5733# | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 0.5842# | Dominated by ETA | Dominated by ETA | Not dominated by ETA | Not dominated by ETA |
| | | | | | | | ETA | 0.6421# | $13,387 | **€13,063** | Unspecified | - |
| | | | | | | ANA+MTX (due to lowest costs) | ANA+MTX | 0.5772# | *Reference* | *Reference* | - | - |
| | | | | | | | INFL+MTX | 0.5949# | Dominated | Dominated | Dominates ANA+MTX | Dominates ANA+MTX |
| | | | | | | | ADA+MTX | 0.6608# | Dominated by ETA+MTX | Dominated by ETA+MTX | Dominates ANA+MTX | Dominates ANA+MTX |
| | | | | | | | ETA+MTX | 0.6919# | $7,925 | **€7,733** | Dominates ANA+MTX | Dominates ANA+MTX |
| **Third-line therapy (non-biologic comparator)** | | | | | | | | | | | | |
| [24] | Chen et al. (2006) | From the 40,000 late RA patients | 38/50* | 2004 £ | Conversion: 0.67866 Inflation: 1.0904 | Trad. DMARDs return | Base | 4.6988-4.9302 | *Reference* | *Reference* | - | - |
| | | | | | | | 1) ADA 2) ETA | 5.7622 | £ 51,600 | € 82,905 | Unstated | - |
| | | | | | | | 1) ADA 2) INFL | 5.0558 | £239,000 | €384,000 | Unstated | - |
| | | | | | | | 1) ETA 2) ADA | 4.8230 | £242,000 | €388,820 | Unstated | - |
| | | | | | | | 1) ETA 2) INFL | 4.8559 | £190,000 | €305,272 | Unstated | - |
| | | | | | | | 1) INFL 2) ADA | 5.1019 | £141,000 | €226,544 | Unstated | - |
| | | | | | | | 1) INFL 2) ETA | 5.7985 | £47,000 | **€ 75,515** | Unstated | - |
| [30] | Malottki et al. (2011) | failure of a first TNF inhibitor | 43/50 | 2008 £ | Conversion: 0.79628 Inflation: 1.0202 | DMARDs (after TNF-failure) | DMARDs | 2.13 | *Reference* | *Reference* | - | - |
| | | | | | | | ETA | 2.80 | £38,900 | **€49,839** | £31,100-£76,300 | **€39,846**-€97,756 |
| | | | | | | | INFL | 2.80 | £36,100 | **€46,252** | £28,800-£68,900 | **€36,899**-€88,275 |
| | | | | | | | ADA | 2.89 | £34,300 | **€43,945** | £28,100-£61,300 | **€36,002-€78,538** |
| | | | | | | | RTX | 3.10 | £21,100 | **€27,033** | £11,400-£46,000 | **€14,606-€58,936** |
| | | | | | | | ABT | 3.28 | £38,400 | **€49,198** | £32,100-£63,300 | **€41,127**-€81,100 |
| [27] | Hallinen et al. (2010) | 3,000; 33% male and 67% female; aged 48 | 42/50* | 2008 € | Conversion: - Inflation: 1.0202 | BSC | 1) BSC | 3.39 | *Reference* | *Reference* | - | - |
| | | | | | | | 1) RTX 2) INFL 3) BSC | 3.77 | €32,621 | **€33,280** | - | - |
| | | | | | | | 1) RTX 2) ADA 3) BSC | 3.79 | €38,235 | **€39,007** | - | - |
| | | | | | | | 1) RTX 2) ETA 3) BSC | 3.83 | €38,938 | **€39,725** | - | - |
| | | | | | | | 1) RTX 2) ABA 3) BSC | 3.91 | €46,367 | **€47,304** | - | - |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

† Compared to first against infliximab (the reimbursed standard therapy), then against anakinra (ADAL + ETAN) and against adalimumab (ETAN).
#Annual total costs and QALYs, not per lifetime.

**Table 37:** Results of economic evaluation studies for adalimumab in RA (continued)

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime) | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Third-line therapy (biologic comparator)** | | | | | | | | | | | | |
| [31] | Walsh et al. (2007) | At least 12 weeks treatment with infliximab before switch | 27/50 | 2006 € | Conversion: - Inflation: 1.0591 | INFL | INFL<br>ADA | Not specified (insignificant differences) | *Reference*<br>Dominates INFL | *Reference*<br>Dominates INFL | -<br>Not specified | -<br>- |
| [27] | Hallinen et al. (2010) | 3,000; 33% male and 67% female; aged 48 | 42/50* | 2008 € | Conversion: - Inflation: 1.0202 | 1) RTX+MTX 2) BSC (smallest ICER in previous scenario) | 1) RTX 2) BSC | N/A | *Reference* | - | - | - |
| | | | | | | | 1) RTX 2) INFL 3) BSC | N/A | €37,013 | **€37,761** | - | - |
| | | | | | | | 1) RTX 2) ADA 3) BSC | N/A | €52,021 | **€53,072** | - | - |
| | | | | | | | 1) RTX 2) ETA 3) BSC | N/A | €52,698 | **€53,762** | - | - |
| | | | | | | | 1) RTX 2) ABA 3) BSC | N/A | €68,100 | **€69,476** | - | - |
| **Fourth-line therapy (non-biologic comparator)** | | | | | | | | | | | | |
| [24] | Chen et al. (2006) | From the 40,000 late RA patients | 38/50* | 2004 £ | Conversion: 0.67866 Inflation: 1.0904 | Trad. DMARDs return | Base | 4.3218-4.4850 | *Reference* | *Reference* | - | - |
| | | | | | | | 1) ADA 2) ETA 3) INFL | 4.3990 | £414,000 | €665,172 | Unstated | - |
| | | | | | | | 1) ADA 2) INFL 3) ETA | 5.2256 | £ 54,900 | € 88,208 | Unstated | - |
| | | | | | | | 1) ETA 2) ADA 3) INFL | 4.4228 | £290,000 | €465,942 | Unstated | - |
| | | | | | | | 1) ETA 2) INFL 3) ADA | 4.3904 | £437,000 | €702,126 | Unstated | - |
| | | | | | | | 1) INFL 2) ADA 3) ETA | 5.2257 | £ 55,800 | € 89,654 | Unstated | - |
| | | | | | | | 1) INFL 2) ETA 3) ADA | 4.3794 | £506,000 | €812,988 | Unstated | - |
| [27] | Hallinen et al. (2010) | 3,000; 33% male and 67% female; aged 48 | 42/50* | 2008 € | Conversion: - Inflation: 1.0202 | RTX>INFL>BSC | RTX>INFL>BSC | 3.77 | *Reference* | *Reference* | - | - |
| | | | | | | | RTX>INFL>ADA>BSC | 4.14 | €38,329 | **€39,103** | - | - |
| | | | | | | | RTX>INFL>ETA>BSC | 4.18 | €38,785 | **€39,568** | - | - |
| | | | | | | | RTX>INFL>ABA>BSC | 4.26 | €44,466 | **€45,364** | - | - |
| **Fourth-line therapy (biologic comparator)** | | | | | | | | | | | | |
| [27] | Hallinen et al. (2010) | 3,000; 33% male and 67% female; aged 48 | 42/50* | 2008 € | Conversion: - Inflation: 1.0202 | RTX+MTX> INFL+MTX>BSC (smallest ICER in previous scenario) | RTX>INFL>BSC | N/A | *Reference* | *Reference* | - | - |
| | | | | | | | RTX>INFL>ADA>BSC | N/A | €54,701 | **€55,806** | - | - |
| | | | | | | | RTX>INFL>ETA>BSC | N/A | €54,836 | **€55,944** | - | - |
| | | | | | | | RTX>INFL>ABA>BSC | N/A | €70,616 | **€72,042** | - | - |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

**Table 38:** Results of economic evaluation studies for adalimumab in CD

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs (per lifetime)## | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Second-line therapy (non-biologic comparator)** | | | | | | | | | | | | |
| [36] | Bodger et al. (2009) | moderate-to-severe CD (maintenance) | 39/50 | 2006/7 £ | Conversion: 0.683035# Inflation: 1.05105# | Standard Care (=non-biologic medication; plus surgery) | SC | 14.209 | *Reference* | *Reference* | - | - |
| | | | | | | | INFL 1y. | 14.568 | £19,050 | **€29,314** | £18,600 - dominated | **€28,622**-dominated |
| | | | | | | | INFL 2y. | 14.901 | £21,300 | **€32,776** | | |
| | | | | | | | ADA 1y. | 14.682 | £ 7,190 | **€11,064** | £7,560 - 181,620 | **€11,633**-€279,476 |
| | | | | | | | ADA 2y. | 15.156 | £10,310 | **€15,865** | | |
| [37] | Loftus et al. (2009) | moderate-to-severe CD (maintenance) | 41/50 | 2006 £ | Conversion: 0.68173 Inflation: 1.0591 | Standard Care (=non-biologic medication and surgery) | SC | 0.7743 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 0.8647 | £33,731 | **€52,403** | £17,873-57,571 | **€27,767**-€89,439 |
| [38] | Dretzke et al. (2011) | moderate CD | 39/50* | 2005/6 £ | Conversion: 0.682765# Inflation: 1.06735 | Standard Care (=non-biologic medication and surgery) | SC | 0.8926 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA induction | 0.9231 | dominant | dominant | - | - |
| | | | | | | | ADA maintenance | 0.9236 | £160,079 | €250,248 | - | - |
| | | | | | | | INFL induction | 0.9240 | £ 94,321 | €147,450 | - | - |
| | | | | | | | INFL maintenance | 0.9245 | £317,991 | €497,108 | - | - |
| [38] | Dretzke et al. (2011) | severe CD | 42/50 | 2005/6 £ | Conversion: 0.682765# Inflation: 1.06735 | Standard Care (=non-biologic medication and surgery) | SC | 0.8119 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA induction | 0.8942 | dominant | dominant | always dominant | always dominant |
| | | | | | | | ADA maintenance | 0.8956 | £ 7,749 | **€12,114** | dominant - £ 32,759 | dominant - **€51,211** |
| | | | | | | | INFL induction | 0.8943 | dominant | dominant | dominant - £ 71,315 | dominant - €111,485 |
| | | | | | | | INFL maintenance | 0.8957 | £68,315 | €106,795 | £55,119 - £181,475 | €86,166-€283,695 |
| [37] | Loftus et al. (2009) | severe CD (maintenance) | 41/50 | 2006 £ | Conversion: 0.68173 Inflation: 1.0591 | Standard Care (=non-biologic medication and surgery) | SC | 0.7339 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 0.8516 | £16,064 | **€24,956** | dominant - £34,230 | Dominant - **€53,178** |
| **Second-line therapy (biologic comparator)** | | | | | | | | | | | | |
| [39] | Yu et al. (2009) | moderate-to-severe CD (maintenance) | 37/50 | 2006/7 US$ | Conversion: 1.31305# Inflation: 1.05105# | INFL 5mg/kg | INFL 5mg/kg | 0.851 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA 40mg eow | 0.865 | Dominant ($-4,852) | Dominant **( €-3,884 )** | Dominant ($-5,760 to $-1,038) | Dominant (**€-4,611 to -831**) |
| [38] | Dretzke et al. (2011) | moderate CD | 39/50* | 2005/6 £ | Conversion: 0.682765# Inflation: 1.06735# | ADA / INFL induction therapy | ADA induction | 0.9231 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA maintenance | 0.9236 | £13.9M | €21.7M | - | - |
| | | | | | | | INFL induction | 0.9240 | *Reference* | *Reference* | - | - |
| | | | | | | | INFL maintenance | 0.9245 | £13.9M | €21.7M | - | - |
| [38] | Dretzke et al. (2011) | severe CD | 42/50 | 2005/6 £ | Conversion: 0.682765# Inflation: 1.06735# | ADA / INFL induction therapy | ADA induction | 0.8942 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA maintenance | 0.8956 | £4.98M | €7.79M | £320,000-£4.96M | €500,248-€7.75M |
| | | | | | | | INFL induction | 0.8943 | *Reference* | *Reference* | - | - |
| | | | | | | | INFL maintenance | 0.8957 | £5.03M | €7.86M | £443,000-£5.1M | €692,531-€7.97M |
| **Third-line therapy (after infliximab 5mg/kg-failure)** | | | | | | | | | | | | |
| [40] | Kaplan et al. (2007) | 3rd line (INF 5mg/kg failure) | 31/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | ADA | ADA | 0.76 | *Reference* | *Reference* | - | - |
| | | | | | | | INFL 10mg/kg | 0.79 | $332,032 | €267,815 | $49,962 - dominated | **€42,143** - dominated |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.
* Three points deducted from baseline total score due to the missing uncertainty analysis.

# Conversion and inflation rate are the average of both cost years.
## Only for Bodger (Loftus and Dretzke examined lifetime in sensitivity analyses)

**Table 39:** Results of economic evaluation studies for adalimumab in PP

**Second-line therapy (non-biologic comparator)**

**Cost-utility analyses**

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs per lifetime | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [41] | Sizto 2009 | mod-to-sev PP (DLQI≥10) | 40/50 | 2005/6 £ | Conversion: 0.682765# Inflation: 1.06735# | Supportive Care (SC) | SC | 0 | *Reference* | *Reference* | - | - |
| | | | | | | | ETA## | 0.134 | £37,676 | **€58,898** | £ 8,138- 92,387 | **€12,722**-€144,426 |
| | | | | | | | ADA | 0.164 | £30,538 | **€47,739** | £ 4,782- 80,124 | **€ 7,476**-€125,256 |
| | | | | | | | INFL | 0.182 | £42,492 | **€66,427** | £18,790-116,073 | **€29,374**-€181,454 |
| [42] | Knight 2011 | mod-to-sev PP | 38/50 | [2008] (SEK) € | Conversion: - Inflation: 1.0202 | Non-systemic therapy | non-systemic | 5.97 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 6.74 | €46,087 | **€47,018** | €30,438-€55,834 | **€31,053-€56,962** |
| | | | | | | | ETA (intermittent) | 6.56 | € 9,925 | **€10,125** | € 8,683-€16,626 | **€ 8,858-€16,962** |

**Cost-effectiveness analyses**

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | % patient achieving PASI-75 | ICER ( per PASI-75 responder) | ICER ( per PASI-75 responder) 2010 EURO | Sensitivity analysis ( per PASI-75 responder) | Sensitivity analysis ( per PASI-75 responder) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [43] | Greiner 2009 | mod-to-sev PP, 2nd line | 32/50 | 2006 CHF | Conversion: 1.5729 Inflation: 1.0591 | Placebo | ETA | 46 (51) | CHF35,399 | €23,836 | 26,549-44,249 | €17,877-€29,795 |
| | | | | | | | ADA | 56 (62) | CHF29,254 | €19,698 | 21,940-36,567 | €14,773-€24,622 |
| | | | | | | | INFL | 78 (78) | CHF29,826 | €20,083 | 22,369-37,282 | €15,062-€25,104 |
| [44] | Schmitt-Rau 2010 | mod-to-sev PP, 2nd line | 24/50 | [2009] € | Conversion: - Inflation: 1.0099 | Placebo | ADA | 62 | €11,287 | €11,399 | -8% to +6%** | - |
| | | | | | | | ETA 25mg biw | 31 | €16,896 | €17,063 | -17% to +13%** | - |
| | | | | | | | ETA 50mg biw | 46 | €22,725 | €22,950 | -11% to +9%** | - |
| | | | | | | | INFL 3mg/kg | 68 | €10,568 | €10,673 | -8% to +7%** | - |
| | | | | | | | INFL 5mg/kg | 77 | €12,501 | €12,625 | -7% to +6%** | - |
| | | | | | | | USTE 45mg | 63 | €13,099 | €13,229 | -8% to +7%** | - |
| | | | | | | | USTE 90mg | 69 | €12,089 | €12,209 | -8% to +7%** | - |

**Second-line therapy (biologic comparator)**

**Cost-utility analyses**

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs per lifetime | ICER point-estimate (per QALY) | ICER point-estimate (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [45] | Anis 2011 | mod-to-sev PP | 34/50 | Unclear [2007] US$ | Conversion: 1.3705 Inflation: 1.0430 | ETA (least costly) | ETA (1) | 0,092† | *Reference* | *Reference* | N/A-$47,200†† | N/A-**€35,921** |
| | | | | | | | ADA | 0,113† | $ 544 | **€ 414** | $373-$22,513†† | **€284-€17,133** |
| | | | | | | | ETA (2) | 0,103† | $ -163,900 | **€ -124,733** | N/A-N/A†† | N/A-N/A |
| | | | | | | | INFL | 0,125† | $ 293,283 | € 223,199 | $2,877-$39,763†† | **€2,190-€30,261** |

**Cost-effectiveness analyses**

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | % patient achieving PASI-75 | ICER ( per PASI-75 responder) | ICER ( per PASI-75 responder) 2010 EURO | Sensitivity analysis | Sensitivity analysis ( per PASI-75 responder) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [46] | de Portu 2010 | mod-to-sev PP | 29/50 | Unclear [2008] € | Conversion: - Inflation: 1.0202 | | INFL | 82 (71)‡ | - | - | - | - |
| | | | | | | ETA 25mg biw | | 44 ( - )‡ | € 9,647 | €9,842 | €5,916-€15,430 | €6,036-€15,742 |
| | | | | | | ETA step down | | 54 (54)‡ | € 2,840 | €2,897 | Dominated-€21,841 | Dominated - €22,282 |
| | | | | | | ETA 50mg biw | | 60 (63)‡ | Dominated by INFL | Dominated by INFL | Dominated | Dominated |
| | | | | | | ADA | | 64 (58)‡ | €16,069 | €16,394 | €7,133-€74,878 | €7,277-€76,391 |
| | | | | | | ETA 50mg ew | | 71 ( - )‡ | €33,632 | €34,311 | €14,311-€170,311 | €14,600-€173,751 |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.
Efalizumab and alefacept have been removed from analyses due to the fact that they are not registered in Europe (anymore). That was possible without substantially altering outcomes of the other interventions or comparators (it was never used as such).

# Conversion and inflation rate are the average of both cost years.
† Anis: average annualized costs and QALYs; ICERs only first sequence reported in table. Etanercept (1) taken as reference as least costly. Eta (2) contained high-dosed etanercept of 50mg biw instead of 25 mg biw (= ETA1).
‡ ICERs are calculated as infliximab versus all other TNF-inhibitors. In round brackets the values of 48-50 weeks, outside the brackets of 24 weeks. Excluded hospitalisation costs.
†† Sensitivity analysis outcomes not always clearly reported but declared as the 'least costly' option from all; no absolute values.
## No real difference in results with intermittent or continuous use.
** Sensitivity analysis of varying PASI-75 responders only reported in percentage change; rounded here.

**Table 40:** Results of economic evaluation studies for adalimumab in PsA, AS, JIA, PP [available at t=0], and UC [off-label indication]

Second-line therapy (non-biologic comparator) – PsA

**Cost-utility analyses**

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs per lifetime‡ | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [34] | Rodgers et al. (2011) | 2nd/3rd line trad DMARDs failure (47 years old, at least 7 years PsA) | 43/50 | 2008/9 £ | Conversion: 0.84361# Inflation: 1.01505# | Palliative care (=no therapy) | Palliative care | 5.171 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 6.580 | Dominated extendedly## | **[ €22,604 ]**† | £9,787-18,296 | **€11,776-€22,014** |
| | | | | | | | ETA | 7.001 | £17,853 | **€21,481** | £9,194-36,408 | **€11,062-€43,807** |
| | | | | | | | INFL | 7.308 | £44,326 | **€53,334** | £13,557-122,073 | **€16,312**-€146,881 |

Second-line use (non-biologic comparator) – AS

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs per lifetime‡ | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [35] | Botteman et al. (2007) | active AS, inadequate response to NSAIDs | 47/50 | 2004 £ | Conversion: 0.67866 Inflation: 1.0904 | Conventional therapy (=NSAID or DMARD) | Conv. therapy | 8.1891 | *Reference* | *Reference* | - | - |
| | | | | | | | ADA | 9.2220 | £23,097 | **€37,110** | £5,093-62,679 | **€8,183**-€100,706 |

Second-line therapy (non-biologic comparator) – UC [off-label]

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | QALYs per lifetime‡ | ICER (per QALY) | ICER (per QALY) 2010 EURO | Sensitivity analysis (per QALY) | Sensitivity analysis (per QALY) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [49] | Xie et al. (2009) | mean 80kg; aged 40 years | 32/50 | 2008 CA$ | Conversion: 1.5594 Inflation: 1.0202 | Usual care | Usual care | 2.015 | *Reference* | *Reference* | - | - |
| | | | | | | | 5mg INFL > ADA | 2.178 | $358,088 | €234,270 | $273,081-$527,236 | €178,657-€344,931 |
| | | | | | | | 5mg INFL > 10mg INFL > ADA | 2.149 | $575,540 | €376,533 | $428,676-$889,227 | €280,451-€581,755 |

**Cost-effectiveness analyses**

Second-line therapy (non-biologic comparator) – JIA

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | ACR Pedi 30 responders | ICER point-estimate (per ACR Pedi 30 responder) | ICER point-estimate (per ACR Pedi 30 responder) 2010 EURO | Sensitivity analysis (per ACR Pedi 30 responder) | Sensitivity analysis (per ACR Pedi 30 responder) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [48] | Ungar et al. (2011) | mean 40kg; aged <1 to 14 years | 39/50 | 2008 CA$ | Conversion: 1.5594 Inflation: 1.0202 | MTX | MTX | Unclear | *Reference* | *Reference* | - | - |
| | | | | | | | ABA | 65% | $16,204 | €10,601 | $ 6,964-$22,608 | €4,556-€14,791 |
| | | | | | | | ETA | 74% | $26,061 | €17,050 | $11,914-$41,834 | €7,794-€27,369 |
| | | | | | | | INFL | 75% | $31,209 | €20,418 | $12,121-$66,220 | €7,930-€43,323 |
| | | | | | | | ADA | 84% | $46,711 | €30,560 | $18,071-$75,787 | €11,823-€49,582 |

Second-line therapy (non-biologic comparator) – PP [study available at t=0]

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | Mean unit DLQI improvement | ICER (per patient achieving DLQI MID) | ICER (per patient achieving DLQI MID) 2010 EURO | Sensitivity analysis (per patient achieving DLQI MID) | Sensitivity analysis (per patient achieving DLQI MID) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [47] | Nelson et al. (2008) | moderate to severe psoriasis (weight 80kg) | 31/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | Placebo | ETA | 5.8-7.5 | $2,250-$6,645 | €1,898-€5,605 | - | - |
| | | | | | | | INFL | 9.0-9.7 | $3,508-$4,322 | €2,959-€3,646 | - | - |
| | | | | | | | ADA | 9.5-10.2 | $3,511-$5,662 | €2,962-€4,776 | - | - |

| Ref. | Article | Study population | NL-TQS | Currency & year | Conversion & Inflation rates | Comparator | Interventions | % patients achieving PASI-75 | ICER (per patient achieving PASI-75) | ICER (per patient achieving PASI-75) 2010 EURO | Sensitivity analysis (per patient achieving PASI-75) | Sensitivity analysis (per patient achieving PASI-75) 2010 EURO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [47] | Nelson et al. (2008) | moderate to severe psoriasis (weight 80kg) | 31/50 | 2006 US$ | Conversion: 1.2556 Inflation: 1.0591 | Placebo | ETA | 14.4-49.2 | $14,254-$19,111 | €12,023-€16,120 | - | - |
| | | | | | | | INFL | 70.6-79.1 | $8,797-$10,422 | € 7,420-€ 8,791 | - | - |
| | | | | | | | ADA | 53.3-80.0 | $11,657-$13,243 | € 9,833-€11,170 | - | - |

In **bold** are cost-effective options indicated according to a threshold of €80,000/QALY.

# Conversion and inflation rate are the average of 2008 and 2009.
## Adalimumab was dominated based on *extended dominance* of a linear combination between palliative care and etanercept; i.e. that etanercept was expected to give more QALY gains at a lower ICER versus palliative care. Adalimumab's ICER would be £18,786/QALY compared to palliative care.
† ICER converted and inflated for £18,786/QALY. Adalimumab would still be extendedly dominated by palliative care and etanercept.
‡ Xie et al.: Outcomes and costs only measured for a short-term duration of 1 year, not per lifetime. Nelson: Outcomes and costs only measured for a short-term duration of 12 weeks. Efalizumab and alefacept have been removed from analyses due to the fact that they are not registered in Europe (anymore). That was possible without substantially altering outcomes of the other interventions or comparators (it was never used as such).