



Rijksoverheid

Ministry of Health,  
Welfare and Sport



*Report*

## **Dutch Assessment Procedures for the Reimbursement of Outpatient Medicines**

***Publication***

Joint publication of the Ministry of Health, Welfare and Sport and CVZ

***Date***

March 1th, 2010

***Series number***

2011023491

***Dept.***

ZORG- ZA

***Author***

Dr. Caroline van der Meijden; Carolin Grahlmann, MSc

***Direct line***

Tel. (020) 797 87 45

This publication is available electronically via CVZ's website .  
See [www.cvz.nl](http://www.cvz.nl)

## **Contents:**

*pag.*

	<b>Foreword</b>
2	1. List of abbreviations
3	2. Introduction
5	3. Statutory procedures
6	4. Preliminary stage
6	4.a. Introduction
6	4.b. Exemption from pharmacoeconomic analysis
7	4.c. Scientific advice
9	4.d. Preliminary discussion
10	5. Official assessment
10	5.a. Submitting a formal application
10	5.a.1. Formal application to VWS
11	5.a.2. Data required
15	5.a.3. Supplying the data
17	5.b. CVZ's advice
17	5.b.1. CFH stage
20	5.b.2. CVZ RvB stage
22	5.c. Minister's decision-making
23	6. Reassessment
24	7. Communication
24	7.a. Inter-party communication
24	7.b. Public accessibility
25	7.c. Contacts
26	<b>References</b>
	<i>Appendix/ices</i>
27	1. Laws and legislation
28	2. Assessment criteria of the Medicinal Products Reimbursement Committee
36	3. Time-path and flow-diagram of the GVS assessment route

## Foreword

### *alterations*

This is a new version of Dutch assessment procedures for the reimbursement of outpatient medications. The last booklet on procedures was published in 2007. As several alterations did occur since then, applicants were no longer correctly informed and the procedures required an update.

For example, the way in which applications are submitted has altered and there are new formats for submitting reimbursement files which make it easier for applicants to present all relevant information clearly. Policy on exemption from carrying out pharmacoeconomic analysis has also altered. The application procedures for obtaining exemption are now entirely in the hands of CVZ. Exemption policy has been extended to include medicines whose therapeutic value is equal to that of medicines that have already been accepted into the Medicine Reimbursement System [*Geneesmiddelen-vergoedingssysteem, GVS*] and for which there is evidence that their inclusion will not lead to added costs. Note the risk that should the assessment reveal a therapeutic added value, an extensive economic evaluation will nevertheless be necessary. Another alteration in the procedures is the extra opportunity to temporarily suspend procedures in a case where the Medicinal Products Reimbursement Committee [*Commissie Farmaceutische Hulp, CFH*] has consulted an expert who indicates needing more time to prepare a response. In the past, the CFH only consulted experts (associations) when formulating extra conditions relating to reimbursement. These associations and other relevant parties are currently being asked for their expertise much more frequently. In addition to therapeutic value, the CFH also determines a medicine's place compared with other medicines for the ' Dutch National Drug Formulary [*Farmacotherapeutisch Kompas*]. This was not discussed in the previous procedure. There is also a new CVZ committee, the Appraisal Committee [*Adviescommissie Pakket, ACP*], which plays a role in the new procedures in a number of cases, particularly when evaluating topics with a societal impact. Furthermore, the moment at which a product is eligible for re-assessment has been specified, i.e., a minimum of 6 months after concluding the previous submission. Lastly, the maximum weight for the boxes in which files should be delivered has been altered to 10 kg.

Apart from the authors, the following people have contributed to the renewed procedures: Patrick Kruger, Harrie Storms and Marco van de Velde of the Ministry of Health, Welfare and Sport (VWS) and Jolanda de Boer, Po Kam Cheung, Wim Goettsch, Martin van der Graaff, Arnold van Halteren, Marja Kuijpers and Linda van Saase of the *College voor zorgverzekeringen (CVZ)*. With special thanks to Christene Beddow for translation services.

## 1. List of abbreviations

ACP	Appraisal Committee [ <i>Adviescommissie Pakket</i> ]
ATC	Anatomical Therapeutic Chemical (ATC) classification system
List 1A	list with groups of mutually interchangeable medicines in the GVS
List 1B	list with medicines in the GVS that are not mutually interchangeable
List 2	summary of medicines in the GVS whose reimbursement is subject to conditions (contains products on Lists 1A and 1B)
CBG	Medicines Evaluation Board [ <i>College ter beoordeling van geneesmiddelen</i> ]
CBO	Dutch Institute for Healthcare Improvement [ <i>Kwaliteitsinstituut voor de gezondheidszorg CBO</i> ]
CFH	Medicinal Products Reimbursement Committee [ <i>Commissie Farmaceutische Hulp</i> ]
CHMP	Committee for Medicinal Products for Human Use
CIBG	Central Information point for Healthcare Professions [ <i>Centraal Informatiepunt Beroepen Gezondheidszorg</i> ]
CVZ	Health Care Insurance Board [ <i>College voor zorgverzekeringen</i> ]
DDD	Defined Daily Dose (the proposed average daily maintenance dose of a medicine for the main indication in adults)
EMA	European Medicines Agency
GMT	Medicines and Medical Technology [ <i>Geneesmiddelen en Medische Technologie</i> ], Department of the ministry of Health, Welfare and Sports.
G- standard	Medicinal databank of the Z- index
GVS	Medicine reimbursement system [ <i>Geneesmiddelenvergoedingsstelsel</i> ]
NZa	Dutch Healthcare Authority [ <i>Nederlandse Zorgautoriteit</i> ]
RvB	Executive Board [ <i>Raad van Bestuur</i> ] of Cvz
SmPC	Summary of Product Characteristics
VWS	Ministry of Health, Welfare and Sport
WHO	World Health Organization
Rzv	Health Insurance Regulation [ <i>Regeling zorgverzekering</i> ]
Zvw	Health Care insurance Act [ <i>Zorgverzekeringswet</i> ]

## 2. Introduction

***Aim*** Pharmaceutical care can be provided to inpatients (by a hospital pharmacist) or to outpatients (by an independent pharmacist or a general practitioner with a dispensary). This document relates only to medicines provided to outpatients and describes the procedures for assessing these medicines within the framework of the medicine reimbursement system [*Geneesmiddelenvergoedingssysteem, GVS*]. Different procedures exist for the inclusion of a medicine in the policy regulations for inpatient medicines.

***Registration and reimbursement*** Two important sets of assessment procedures exist for outpatient medicines:

- one for being allowed to market a product;
- one for becoming eligible for reimbursement within the framework of the insured basic package (according to the regulations of the Health Insurance Act [*Zorgverzekeringswet, Zvw*])

These are separate procedures, each with their own assessment criteria.

***Registration*** Permission to market a product involves, in particular, assessing the efficacy, safety and quality of the product. This assessment is carried out by the Medicines Evaluation Board [*College ter Beoordeling van Geneesmiddelen, CBG*] or the European Medicines Agency (EMA), with material support from the Committee for Medicinal Products for Human Use (CHMP). That registration process is not discussed further in this procedure.

***Reimbursement*** Whether a medicine is eligible for reimbursement is largely determined by its therapeutic value in relation to the current standard treatment in the Netherlands and the substantiation of its cost-effectiveness. The decision on inclusion is made by the Minister of Health, Welfare and Sport (VWS), who can first obtain advice from the Health Care Insurance Board [*College voor zorgverzekeringen, CVZ*]. CVZ incorporates the advice of the Medicinal Products Reimbursement Committee [*Commissie Farmaceutische Hulp, CFH*] in their advice. This committee is comprised of 22 external, independent experts whose membership is limited to a maximum of eight years. A medicine must have completed the statutory procedures in order to be included in the GVS (see section 3, Statutory procedures).

***The GVS*** Once a medicine has been included in the GVS, it is eligible for reimbursement. The GVS is part of the Health Insurance Regulation and it includes lists of medicines that are insured benefits within the framework of the Zvw. Products included in the GVS are clustered on list 1A of the Health Insurance Regulation or they appear separately on list 1B. A

reimbursement limit is calculated for medicines on list 1A, but there is no limit for medicines on list 1B. Furthermore, products from lists 1A and 1B can be placed on list 2, which means they are subject to additional conditions (for example, eligibility for reimbursement of the product for the registered indication is limited to a sub- population of patients – not the entire patient population).

***Pharmaco-  
therapeutic  
Compass***

In addition to assessing a product for inclusion in the GVS, the CFH also advises CVZ on the place of each product compared with other medicines within a given indication field. The resulting CFH- advice is addressed to prescribers and is published in the *Farmacotherapeutisch Kompas* [the Dutch National Drug Formulary].

***Alterations in  
Detailed Conditions  
and Reassessment***

In addition to assessing medicines that have recently been granted market permission, the assessment procedures are also used for alterations in the inclusion of products that have previously been assessed for the GVS. The registration-holder's claim may be the same, or it may actually differ from a previous assessment. A reassessment will always require new, published research data (see section 6, Reassessment).

### 3. Statutory procedures

#### ***Summary***

In brief, the procedures are as follows.

The registration- holder submits to the Minister of VWS an application to designate a medicine as insured Pharmaceutical care (inclusion in the GVS). The registration- holder uses the GVS- application form. This form can be downloaded at: <http://www.farmatec.nl/medicines/prijzenenlimieten/vergoedingssysteem/AanvraagGVS.aspx>

The registration- holder provides the Minister with all the data necessary for making a decision on the application. When the data provided are insufficient, the registration- holder is given the opportunity of completing them. The Minister may send the application to CVZ for advice. After CVZ has assessed the application and advised the Minister, the latter makes a decision. The statutory period between this decision and receipt of the application is 90 days. The Minister informs the registration- holder of the decision. The Minister refers to CVZ's advice, the grounds for the decision and what legal recourses are available.

#### ***Insured benefit***

An insured person's right to the reimbursement of outpatient medicines is laid down in their health insurer's policy. This policy is based on the Zvw, the Health Insurance Decision and the Health Insurance Regulation. An insured person has a right to a registered medicine once it has been designated by the Minister (it has been placed on list 1 of the Health Insurance Regulation) and the product is included in their health insurer's policy. The relevant procedures are governed by Section 1, paragraph 2 of the Health Insurance Regulation (see appendix 1).

## 4. Preliminary stage

### **4.a. Introduction**

**Preliminary stage** CVZ offers the registration-holder the possibility of being exempted from carrying out a pharmacoeconomic analysis (see paragraph 4.b), obtaining scientific advice (see paragraph 4.c), and participating in a preliminary discussion of all aspects of a draft file (see paragraph 4.d). Accepting scientific advice and participating in a preliminary discussion of the draft file do not guarantee that the CFH will not request further data during the course of the procedures, though the chance that this will happen is considerably reduced.

### **4.b. Exemption from pharmacoeconomic analysis**

**Policy on exemption from pharmacoeconomic analysis**

A pharmacoeconomic analysis is required for including a medicine on list 1B and for extending the specific conditions of a product that is already included on list 1A or 1B.

In individual cases, however, CVZ can grant exemption from the obligation to carry out extensive pharmacoeconomic analysis. This requires that the registration-holder submits a written application to CVZ.

Registration-holders can apply for exemption from pharmacoeconomic analysis for three categories of medicines:

- Medicines for which EMA has granted orphan designation;
- Medicines of which the costs are not expected to exceed €500,000 per year at any time within five years after market entry;
- Medicines whose therapeutic value is equivalent to that of products already included in the GVS if no added costs will result from including the new medicines in the GVS.

**Orphan medicines**

Orphan medicines can be granted exemption from pharmacoeconomic analysis. Criteria that play a role in the decision on exemption from carrying out pharmacoeconomic analysis are the number of patients with the disorder, the expected budget impact, the feasibility of research and the availability of other treatments for the disorder.

**Costs lower than €500,000 per year**

CVZ can grant exemption for medicines if their costs are not expected to exceed €500,000 per year at any moment over a period of five years after market entry. This limit applies per (sub)indication for which reimbursement is being requested. When calculating the costs, possible savings due to substitution of other medicines are not taken into account.

**Therapeutically equivalent medicines**

Medicines of therapeutic equal value to medicines which are already included in the GVS, but which cannot be clustered, are eligible for exemption if there is evidence that including the medicine will not lead to added costs. This should also take into account costs incurred outside the pharmacy budget. The request should be accompanied by substantiation of this

claim in the form of a cost- minimisation analysis. The sources for prices and volumes should be clearly stated in this analysis.

***Application procedures***

The registration- holder should submit to CVZ a written request asking for exemption from carrying out a pharmacoeconomic analysis. The request should cover the following matters:

- the (registered) indication(s) for which exemption is being requested;
- substantiation of the number of patients who can be treated with the medicine;
- the price of the medicine;
- the expected budget impact of the medicine;
- the availability of other treatment methods;
- grounds as to why carrying out a pharmacoeconomic analysis is not feasible;
- for orphan medicines: "positive opinion for orphan designation" from the EMA's Committee on Orphan Medicinal Products;
- for medicines with an equal therapeutic value: a cost- minimisation analysis.

***Timing of the application***

The application for exemption can be submitted in advance or simultaneously with the formal application. If exemption is not granted, then a pharmacoeconomic analysis will be required after all. This means that a simultaneous submission involves the risk of delaying assessment of the formal application.

***Exemption***

If exemption is granted, then a detailed budget impact analysis should be supplied with the formal application. The fact that exemption from submitting a pharmacoeconomic analysis has been granted does not mean that cost- effectiveness plays no role in the final assessment and decision- making.

***4.c. Scientific advice***

***Scientific advice***

Registration- holders of medicines can ask CVZ for scientific advice before submitting a formal request for inclusion in the GVS. Via scientific advice CVZ can reveal possible disadvantages and shortcomings in relation to the standard or usual treatment and clinically important outcome parameters. In addition, the advice provides an opportunity to identify and discuss, in advance, methodological problems in applying the pharmacoeconomic guidelines. Scientific advice is always provided in advance of a proposed preliminary discussion of the draft file.

The scientific advice facilitates the compilation of an optimal reimbursement file, thereby aiming to prevent delays in subsequent procedures, e.g., due to a lack of essential data.

Scientific advice can be requested within three years to approximately three months before the expected registration. After obtaining approval by the CFH, CVZ will provide scientific advice in writing.

CVZ's advice is based on current established medical science and medical practice and current guidelines. However, CVZ is unable to anticipate the final assessment. No rights can be derived on the basis of scientific advice.

***Subjects of scientific advice***

Scientific advice can involve a detailed discussion of the following subjects:

- choice of standard or usual treatment,
- relevant outcome parameters,
- design and methodology of the pharmacoeconomic analysis.

Descriptions of these subjects are provided in section 5.a.2. Data Required.

***Application procedures for obtaining scientific advice***

The registration-holder takes the initiative in asking for scientific advice. The application procedures are as follows:

1. The registration-holder sends the completed application form, with relevant documents, in quadruplicate, to the secretary of the CFH, Care Advice Department of CVZ (see contacts). The application form can be found on [www.cvz.nl](http://www.cvz.nl).
2. After the application has been assessed, the registration-holder is informed, within ten weekdays, of its progress.
3. The secretary of the CFH can request a meeting with the registration-holder. This takes place between three and five weeks after receiving the application and lasts at most one-and-a-half hours. On behalf of the CVZ, advisors specialized in pharmacotherapy and pharmacoeconomics and the (deputy) secretary of the CFH will be present. At least two weeks prior to the planned date, a list of persons representing the registration-holder must have been provided and the items stipulated under point 1 must have been fulfilled.
4. If the standard or usual treatment, or the effect parameters are undefined, CVZ can ask scientific associations for advice on the standard or usual treatment or (possible updates of) guidelines.
5. The registration-holder will receive the scientific advice once it has been established by CVZ. The aim is to send it within six weeks of receiving the application or holding the meeting.

<b><i>Procedures for preliminary discussion</i></b>	<p><b><i>4.d. Preliminary discussion</i></b></p> <p>Once the registration- holder has received a positive assessment from the CHMP or the CBG, the draft file can be completed and submitted. The registration- holder should initiate a preliminary discussion with CVZ. In order to make an appointment, the registration- holder must provide CVZ with five copies of the draft file. Without a draft file it is not possible to make an appointment for a preliminary discussion.</p> <p>The aim of the preliminary discussion is to ensure that the reimbursement file handed in for the official assessment will be complete in the sense that it contains all the data necessary for the Minister to make a decision. The registration- holder is responsible for compiling the file.</p> <p>Based on the registration- holder's claim, CVZ advises which data the file should include. During the preliminary discussion, CVZ draws the applicant's attention to matters such as mutual interchangeability, therapeutic value and the cost-effectiveness of the medicine. CVZ also points out possible pitfalls. No rights may be derived on the basis of statements made by CVZ because the final assessment of the file is in the hands of the CFH (after which, CVZ eventually establishes its advice).</p>
<b><i>Meeting data</i></b>	<p>Preliminary discussions with registration- holders are usually held during the afternoon of the first and third Tuesdays of the month and the afternoon of the third Thursday of the month. A written response will follow within two weeks of the discussion.</p>
<b><i>Written comments</i></b>	<p>For medicines with a 1A claim, it is also possible to obtain written comments on the draft file from CVZ without a preliminary discussion.</p>
<b><i>Accelerated assessment</i></b>	<p>In the event of an accelerated assessment, the registration- holder is permitted to submit a draft file before receiving a positive assessment from the Committee for Medicinal Products for Human Use (CHMP) (see the paragraph on accelerated assessment in 5.a.1. Formal application to VWS). The registration- holder remains responsible for compiling the file.</p>
<b><i>Preliminary discussion recommended</i></b>	<p>There is no obligation to follow the above- described preliminary stage when compiling a file. An application can also be submitted without a preliminary discussion. However, a preliminary discussion is highly recommended, as it helps to avoid a suspension in procedures due to a lack of relevant data.</p>

## 5. Official assessment

### ***5.a. Submitting a formal application***

#### *5.a.1. Formal application to VWS*

#### ***Initiating procedures***

The formal application for inclusion in the GVS can start once the registration- holder has proof that the medicine has been granted a marketing permit (i.e., proof of approval by the EMA or the certified registration sheet). An exception is made for medicines that have been granted a marketing permit via accelerated procedures (accelerated marketing authorisation), within the framework of the centralised European registration procedures. See "**accelerated assessment**". Within one week, the Minister of VWS sends the registration- holder confirmation of receipt of the application.

The application should include all data necessary for making a decision regarding inclusion of the medicine in the health care insurance package. CVZ determines whether the file is complete. Paragraph 5.a.2. lists the requirements for compiling the reimbursement file. CVZ sends the registration- holder confirmation of receipt once the application has arrived and assumes sufficient data have been provided. If insufficient data have been provided, CVZ will inform the registration- holder, within two weeks after receipt, along with a summary of which additional data are required.

In principle, valid applications submitted before the 25<sup>th</sup> of a month will be included in the next month's assessment assignment (= Minister's official request to CVZ to assess the medicines).

#### ***Abbreviated procedures***

Abbreviated procedures are sufficient for applications for generics and parallel imports, as well as for new dosages and Pharmaceutical substances that are comparable with medicines already on list 1A. In this case, the registration- holder needs to submit a brief file, in duplicate, to the Minister only, who will decide without first consulting CVZ. The Minister will inform the applicant of the decision in writing. If a registration- holder considers its product eligible for the abbreviated procedures, the registration- holder may propose this to the Ministry of VWS.

#### ***Early assessment***

An early assessment is possible for certain medicines intended for life- threatening and severely debilitating, progressive disorders, under the condition that no other medicines are currently available for these disorders. Furthermore, this only applies to medicines for which the CHMP (based on article 14, ninth paragraph, of Council Regulation 726/2004) has granted marketing permit following accelerated procedures.

An application for these products may start, once they have received a positive assessment from the CHMP. Eligibility for accelerated assessment requires permission by the Minister. Therefore, a written request is to be submitted to the Ministry of VWS, with a copy sent to CVZ. Furthermore, the procedures are the same as those for other applications.

***Requesting extension of a therapeutic indication***

In cases whereby reimbursement has already been obtained for one or more other indications, a reimbursement application for (adding) a new indication for a medicine is also regarded as an application for assessment, though limited to the new indication and list 2. The application should therefore take place in accordance with the procedures described.

***Registration-holder's claim***

*5.a.2. Data required*

The guiding principle for assessing a medicine's place in the GVS is a proposal, with grounds, regarding its classification in a group and, where applicable, the standard dose based on WHO- publications on the DDD and ATC and on relevant literature (see therapeutic value, pages 14- 15).

Compilation of the file depends in part on the claim regarding the medicine's mutual interchangeability (see pharmacoeconomic analysis).

***Pharmacoeconomic analysis***

Pharmacoeconomic analysis is required for the following applications:

1. for including a new product on list 1B.
2. for extending the detailed conditions of a product which is already on list 1A or 1B.

In some cases, the registration- holder can ask CVZ for exemption from pharmacoeconomic analysis (see 4.b. Exemption from pharmacoeconomic analysis).

For the pharmacoeconomic analysis, the registration- holder must use the same comparator as used in the claim regarding the therapeutic value. The analysis must be carried out for the same patient population for which a therapeutic added value is requested.

Pharmacoeconomic analysis should be carried out according to the current 'guidelines for pharmacoeconomic analysis' and the current 'manual for cost research' [handleiding voor kostenonderzoek]. Both publications can be found at [www.cvz.nl](http://www.cvz.nl).

***Patient population***

The best evidence for determining the relative efficacy or cost-effectiveness is research that directly compares the medicine in the same population, with the correct dosage of the standard or usual treatment. If a direct comparison is not possible, CVZ will make an indirect comparison.

Irrespective of whether the registration- holder is claiming a therapeutic added value and/or cost- effectiveness for only a single sub- population, they should also provide data for assessing the therapeutic value for the entire indicated (registered) population.

***Comparison with the standard or usual treatment***

A comparison with the standard or usual treatment is essential for determining the therapeutic value of a new medicine. The standard treatment is the treatment that is regarded as first choice in daily practice, the efficacy of which has been proven. It may be comprised of one or more medicines or forms of treatment with a similar indication to the new medicine.

The registered indications of medicines form the point of departure for determining the standard or usual treatment. Other medicines may be important if they are used in practice, even though they are not registered for the indication concerned. If necessary, CVZ consults (the organisations of) specialists and patients.

The registration- holder's reimbursement proposal should clearly indicate with which other available products, and/or forms of treatment, the new medicine has been compared. It is important to provide grounds for the choice of comparative treatment and keep to generally accepted guidelines and protocols where possible. If a pharmacoeconomic analysis is included, it must be based on the same comparative treatment.

***Relevant outcome parameters***

In addition to comparison with the right standard or usual treatment, it is important to be perfectly clear about the relevant outcome parameters that are necessary for determining therapeutic value.

The registration- holder's proposal should indicate on which effect parameters the cost- effectiveness is based. If a pharmacoeconomic analysis is included, then the health states used should be consistent with the effect parameters used for determining the therapeutic value.

***Conditions to registration***

The registration authorities sometimes attach conditions to the registration of a medicine. For example, 'in exceptional circumstances' the EMA may grant market authorization, but request that a specific study will be conducted by the registration- holder. Where, necessary, CVZ can request additional research data for the assessment.

## **Therapeutic value**

### ***Criteria***

For a definition of therapeutic value and the assessment criteria: see the Pharmacotherapeutic compass, section CFH-criteria for assessing therapeutic value (also available in appendix 2 of these procedures). Submissions should use the "Format farmacotherapeutisch dossier" that can be found on CVZ's website (see also "dossiereisen geneesmiddelen beoordeling"). CVZ advises downloading the format before each new application as it may alter from time to time.

### ***Literature search***

The reimbursement file should include a description of the literature search carried out by the registration-holder (for guidelines, see, e.g., [http://www.york.ac.uk/inst/crd/finding\\_studies\\_systematic\\_reviews.htm](http://www.york.ac.uk/inst/crd/finding_studies_systematic_reviews.htm)). The description of the search strategy must indicate, for each of the databases used (Pubmed and Embase), the search terms and selection criteria, the date on which the search took place and the time-span. The search must involve, at the very least, the name (generic and trade name) of both the medicine for which reimbursement is being requested and the chosen comparative treatment(s).

### ***Most recent data***

The most recently published research data must be included.

### ***Relevant data***

The following data are relevant for assessing the mutual interchangeability and the therapeutic value of a medicine:

- the Summary of Product Characteristics (SmPC) from the registration file of the European Medicines Agency (EMA) or the CBG/MEB.
- The European or National public assessment report (EPAR/NPAR).
- The pharmacological and pharmaco-therapeutical reference books commonly used in medical-pharmaceutical practice (e.g., Martindale, Dutch reference books, Informatorium Medicamentorum).
- WHO- publications on the DDD and ATC.
- Meta- analyses, systematic reviews, observational studies and reports on clinical studies, provided they were published in peer- reviewed journals that are regarded as reliable sources of information in the medical-pharmaceutical practice .
- Guidelines, developed by independent Dutch organisations such as the College of General practitioners [*Nederlands Huisartsen Genootschap*, NHG] and the Dutch Institute for Healthcare Improvement [*Kwaliteitsinstituut voor de Gezondheidszorg*, CBO].
- Foreign data regarding usage, whereby the databank used is indicated and only if the data comes from countries with good post- marketing surveillance (PMS- structure).

<b><i>Non-relevant data</i></b>	<p>In principle, the assessment will not take the following data into consideration:</p> <ul style="list-style-type: none"> <li>• Reports from animal studies.</li> <li>• Clinical studies published in non peer-reviewed supplements of journals. .</li> <li>• Opinion statements from experts consulted by the registration-holder.</li> <li>• 'Expert reports' used during registration, unless no EPAR/NPAR is available.</li> <li>• 'Abstracts'.</li> <li>• 'Posters'.</li> <li>• 'Proceedings'.</li> <li>• 'Data on file'.</li> </ul>
<b><i>Unpublished data</i></b>	<p>Unpublished study reports can only be included in an initial assessment, if the registration-holder provides the full research data in an easily analysable form, and if citation in the CFH report is permitted. The study report should place due emphasis on the following aspects:</p> <ul style="list-style-type: none"> <li>• the selection of patients,</li> <li>• the inclusion and exclusion criteria,</li> <li>• study goal and set-up,</li> <li>• the method,</li> <li>• the clinical outcome parameters,</li> <li>• the analysis method (intention to treat, non-responders),</li> <li>• the efficiency and effectiveness on clinical parameters.</li> <li>• and the adverse events.</li> </ul> <p>Unpublished data have not yet been evaluated or subjected to peer-review, which is why the level of evidence of published material is always considered higher than that of unpublished material.</p>
<b><u>Cost-effectiveness</u></b>	
<b><i>Guidelines for pharmacoeconomic research</i></b>	<p>A pharmacoeconomic analysis and a budget-impact analysis estimate must be provided where there is a claimed therapeutic added value. The pharmacoeconomic analysis must have been carried out in accordance with the current 'guidelines for pharmacoeconomic research' and the relevant 'cost research manual'.</p>
<b><i>English</i></b>	<p>The pharmacoeconomic analysis may be drawn up in both Dutch or English, but English is preferred.</p>
<b><i>Format</i></b>	<p>When compiling the pharmacoeconomic analysis and the budget-impact analysis, the available formats should be used. The "Format for submitting a pharmacoeconomic analysis" and the "Format for submitting a budget impact analysis" are both available on <a href="http://www.cvz.nl">www.cvz.nl</a>.</p>
<b><i>Author(s)</i></b>	<p>There should be transparency regarding who has carried out the pharmacoeconomic analysis and the relationship between the commissioning party and the author(s).</p>

**Electronic model** Appendix 6 of the "Guidelines for pharmacoeconomic research" formulates requirements for reporting pharmacoeconomic analyses. If modelling techniques are used, an unblocked version of the electronic model should be provided in six-fold. The report should specify the transition probabilities used in the model and clearly state all relevant sources and references.

*5.a.3. Supplying the data*

**Background information** Not all data are equally relevant for assessment by the CFH, though they may be relevant when CVZ- employees are preparing the draft reports. Technical specifications of the model used in the pharmacoeconomic analysis may be supplied separately. The registration- holder can suffice by sending six copies of the background information, including a copy of the electronic model.

**Standard lay- out** The registration- holder should use the "Format Pharmacotherapeutical File" (available on [www.cvz.nl](http://www.cvz.nl)) and the reimbursement file must include the following items:

1. A summary of the contents.
2. A fully completed "GVS application form" (see: <http://www.farmatec.nl/medicines/prijzenenlimieten/vergoedingssysteem/AanvraagGVS.aspx>).
3. A proposal, with grounds, relating to the GVS- group classification, standard dose, comparative treatment, effect parameters used and therapeutic value.
4. The front page of the certification or proof that it has been approved by the EMA and the "Summary of Product Characteristics" (SmPC).
5. The EPAR/NPAR.
6. Budget impact analysis (where applicable).
7. A pharmacoeconomic analysis (where applicable), including information on the author(s) of the pharmacoeconomic analysis and the relationship between the commissioning party and the author(s).
8. A description and the results of the literature search.
9. The literature lists from the proposal (with grounds) and the pharmacoeconomic analysis, numbered according to the sequence in which they will be discussed, whereby each literature reference is given a separate numbered tab.

The file must contain all publications discussed. The following information must be supplied, on paper, for the pharmacotherapeutical file:

- All relevant clinical studies of the product being assessed and the comparative treatment(s) (published or in compact analysable form), incl. reviews/meta-analyses and relevant guidelines of the professional group;
- The EPAR (on paper) should be included in the file;

•The SmPC (on paper) should be included in the file  
Other references may be supplied on CD-rom (in 34- fold).

Literature relating only to the pharmacoeconomic analysis can be supplied electronically. Background information for the pharmacoeconomic analysis include:

1. Technical appendices relating to the pharmacoeconomic analysis, where applicable: copies of questionnaires and measuring instruments, technical specifications of the model used in the pharmacoeconomic evaluation, etc.
2. Publications cited in the pharmacoeconomic analysis, but which are not included in the reimbursement file.

***Delivery***

The registration- holder should deliver the files in as compact a form as possible for sending agenda items to members of the CFH. Copies should be double- sided (A4 format). A quick- binder is preferred for thin files. The registration- holder should also use tabs to separate all sections and individual publications.

The registration- holder should send two copies of the reimbursement file to the Ministry of VWS (CIBG, Pharma- cluster (Farmatec)) and 34 copies, together with six copies of the pharmacoeconomic background information, directly to CVZ. Files should be delivered in boxes with a maximum weight of 10 kg. The mail room will not accept boxes heavier than this. If several boxes are to be delivered to CVZ, please indicate the contents of each box.

***Incomplete files***

The registration- holder is responsible for supplying complete reimbursement files. If the Ministry of VWS or the CVZ believes that the files supplied with the application are incomplete, then the registration- holder is responsible for replacing or supplementing them.

### **5.b. CVZ's advice**

Within CVZ there are two sequential assessment stages that are linked to one another: the CFH stage and the CVZ RvB stage (see 5.b.1. and 5.b.2.).

#### **5.b.1. CFH stage**

##### ***Report with appendices from the CFH***

The actual assessment of the new medicine starts after the Minister has received the request. CVZ advisors draw up reports which are subsequently approved during meetings held by the CFH.

##### ***CFH-report***

The first step in the assessment is determining whether a product can be clustered. This is done using the GVS- criteria. The outcome is described in the CFH-report. The GVS- criteria are listed in the Health Insurance Regulation, article 2.40. If the medicine is not mutually interchangeable, it cannot be clustered. The CFH then assesses the medicine according to a number of criteria that are important for possible inclusion in the GVS. These criteria are its therapeutic value, substantiation of its cost- effectiveness and the budget impact of inclusion in the GVS, which can be found in, respectively, the pharmacotherapeutic (FT) report, the pharmacoeconomic (FE) report and the budget impact analysis report (KCR). In the report, the CFH also discusses the registration- holder's arguments regarding the medicine's place in the GVS.

##### ***Pharmaco-therapeutic report***

The pharmacotherapeutic report discusses the manufacturer's claim regarding the medicine's therapeutic value. This report is drawn up, where necessary following consultations with external experts. The system used is described in the section "CFH- criteria for assessing therapeutic value" in the Pharmacotherapeutic Compass (see also appendix 2). This report contains a systematic and transparent description of the committee's opinion on the medicine's therapeutic value, substantiated by references to the literature.

##### ***Pharmacoeconomic report***

The pharmacoeconomic report discusses the pharmacoeconomic analysis carried out by the registration- holder. In addition to assessing whether the research was carried out in accordance with the guidelines for pharmacoeconomic analysis, the report also pays attention to facts and uncertainties that are relevant to the Minister's decision. The conclusion discusses whether the pharmacoeconomic analysis provided has sufficiently substantiated the registration- holder's claim in relation to cost- effectiveness.

##### ***Costs***

The basis for calculating the costs of a medicine is the official reimbursement price as quoted in the G- standard of the Z- index. If the medicine has not yet been included in the G- standard, then the price is the one provided by the registration- holder on the GVS- form.

***Budget impact analysis (KCR)***

The CFH draws up a budget impact analysis based on data supplied in the GVS- form and the pharmacoeconomic analysis provided.

In order to estimate the budget impact of including a medicine in the GVS, the CFH distinguishes between the budget impact for:

- the patient;
- the pharmacy budget;
- the health care budget (the Budgeted Health Care Framework).

A variety of factors are taken into account when determining budget impact. The aim of the budget impact analysis is to estimate the cost consequences for use of the medicine in daily practice. Factors that play a role are the expected number of patients, possible substitution of current treatment, degree of market penetration, the risk of 'off-label' usage, the costs of administering the medicine and possible additional costs or savings.

Data from the pharmacoeconomic analysis are particularly important for estimating costs and savings that are closely linked to a medicine's cost-effectiveness, such as those relating to delayed operations or reduced absenteeism.

***CFH meeting on draft reports***

The CFH discusses the preliminary reports and the registration-holder's file. After establishing the preliminary reports, the CFH sends them in confidence for review to the registration-holder - and to other stakeholders for comments.

***Comments from stakeholders***

Stakeholders could be the associations of the professionals, patients and health insurers. The CFH determines which parties in the field will be invited to comment on preliminary reports. The period for responding is often limited to 5 week-days in order to be able to discuss the comments of those consulted during the next meeting. If the registration-holder exceeds the stipulated period of time, then it is extended to 30 days. A registration-holder can also apply for a maximum clockstop of 90 days.

***Clockstop***

If it becomes clear during the CFH meeting that they will need additional data from the registration-holder for the assessment, then they will inform him in writing. The application procedures are suspended until the requested data have been received (see: Health Insurance Regulation, article 2.50). If the manufacturer wants to supply newly published data relevant to questions posed by the CFH, then it is possible to request an extended clockstop. Otherwise, if the data are not received after three months, the CFH will round off the assessment and CVZ will approve the reports as they stand.

Furthermore, CVZ can order a clockstop or request an extension if a reply from the parties in the field is delayed and it is deemed indispensable.

***Altered circumstances***

If, during the procedures, altered circumstances should arise that could be relevant to the assessment (e.g., extending the indication, price alterations), then the registration-holder should contact CVZ (see section 7.3, Contacts).

***Lack of a pharmacoeconomic analysis***

If mutual interchangeability is being claimed by the registration holder and CVZ and the CFH reach the conclusion that the medicine is not mutually interchangeable, then a pharmacoeconomic analysis will be necessary after all, and the reimbursement file is, by definition, incomplete. CVZ will complete the procedures without publishing the assessment of the therapeutic value and cost-effectiveness. A new assessment will be initiated once the file is complete.

***Meeting dates***

The CFH meets, barring exceptions, every fourth Monday in the month. Meetings of the CFH are held behind closed doors.

***Pharmaco-therapeutic Compass***

CFH-advice that has been approved by the committee is provided as an appendix to the pharmacotherapeutic report. This advice relates to the place of each medicine relative to other medicines within a therapeutic area. This CFH-advice is addressed to prescribers and is incorporated in the Pharmacotherapeutic compass.

***Assessment of content***

After discussing the comments of stakeholders, the definitive reports are approved during meetings of the CFH. The CFH limits its opinion to whether the medicine is mutually interchangeable, the standard dose, and, in the event it is not mutually interchangeable, its therapeutic value and substantiation of the cost-effectiveness and the budget impact upon including it in the package.

The CFH advises CVZ's *Raad van Bestuur* [RvB, Executive Board] of their assessment. CVZ's RvB approves the definitive advice to (be sent to) the Minister (see 5.b.2. CVZ RvB stage) and sends it, by way of notification, to the registration-holder. As a rule, CVZ's RvB adhere to the CFH's advice in their advisory report to the Minister.

The regulations of the CFH can be found on CVZ's website.

### *5.b.2. CVZ RvB stage*

Based on the CFH's advice, CVZ's RvB draws up their definitive advice on including a medicine in the GVS. In addition to the CFH's content-related opinion, CVZ also considers other socially and administratively relevant aspects. As package manager, CVZ provides well-founded advice on whether or not a medicine should be included in the package, a possible cluster classification and, if necessary, suggestions for imposing specific stipulations relating to its reimbursement.

#### ***Advice to the minister***

The letter of tender with the definitive advice to the Minister contains not only information about the outcomes of the CFH-stage. The advice can also include considerations relating to policy, administration or society. These aspects are part of the CVZ's integral assessment within the framework of their administrative responsibility in relation to developing and guaranteeing the public preconditions of the health care insurance system.

#### ***ACP***

The Minister of VWS has set up the Appraisal Committee [*Advicemissie Pakket, ACP*] in order to shed light on societal considerations in relation to proposed advice. Its task is to advise CVZ's RvB over the societal consequences of the advice regarding the basic health care package. Meetings of the ACP are public. The committee's agenda can be found on CVZ's website one week before each meeting.

There are a number of variations in the course of the CVZ RvB stage, i.e., on behalf of the RvB and via the RvB and with or without ACP advice. This is apparent from the Participation Protocol for the CVZ RvB stage, advice on applying for the reimbursement of outpatient medicines 2010.

#### ***On behalf of the RvB***

This variation applies where the chair of the RvB has assessed that he/she can deal with the CVZ Executive Board stage of an application for reimbursement personally, on behalf of the RvB. This relates to advice that does not provoke a discussion, such as applications whereby the registration-holder is reporting a medicine for reimbursement on List 1A or applications whereby the CFH has established a lower therapeutic value than the standard treatment.

#### ***Via the RvB***

This variation applies where the chairman of the RvB has decided that the reimbursement application needs to be discussed at a meeting of the RvB. This could occur in the following cases:

- there may be procedural shortcomings or inadequacies surrounding the assessment of this medicine by the CFH.
- at the request of a member of the RvB, or if the chairman feels that there are administrative arguments for it.

When processing takes place via the RvB, the chairman of the RvB can ask the ACP for advice. This applies to reimbursement

applications that could provoke a public discussion (see the Regulations on the Appraisal Committee).

***Participation procedures***

When the chair of the RvB decides to introduce an application for reimbursement into an RvB meeting, this constitutes the initiation of participation procedures. This involves providing the registration-holder of the medicine and others whom the chairman regard as stakeholders with an opportunity to respond to the draft advice. The purpose of providing an opportunity to participate is to support meticulous decision-making by CVZ. If the advice is also to be dealt with at a meeting of the ACP, then this does not represent another opportunity for participation, unless the chairman decides otherwise.

***Written response***

In the event that CVZ's RvB wants to start participation procedures, the registration-holder and other interested organisations receive an invitation to respond, in writing, before a certain date, to the draft letter of tender. The CFH-report is enclosed, by way of notification, as a background document.

***Hearing***

If the chair considers it necessary, he/she can decide to grant parties an opportunity to explain their written comments in person during a hearing. This will happen if a hearing can be expected to contribute to meticulous decision-making by the RvB. The chair takes the initiative for holding a hearing. He/she will take into consideration factors relating to public interest, the importance of obtaining support and the importance of disseminating knowledge about the subject concerned. During the hearing, the CFH-report, including its appendices, is no longer a matter of discussion. No more discussions will be entered concerning the therapeutic value, cost-effectiveness or budget impact, since this opportunity was available to the parties during the CFH stage.

***RvB meetings***

Meetings of the RvB are private and take place once per fortnight. As soon as the advice has been approved and sent to the Minister, CVZ sends the definitive documents, including all (references to) related appendices, by way of notification, to the registration-holder and all parties who responded to a request for comments. They are also published on CVZ's website, [www.cvz.nl](http://www.cvz.nl).

The "Participation protocol (administrative route) for advice on applications for the reimbursement of medicines 2010" [in Dutch] and the "Regulations on the Appraisal Committee" [in Dutch] can be downloaded from CVZ's website ([www.cvz.nl](http://www.cvz.nl)). In the Regulations and the Participation protocol the term "administrative stage" is employed for the term "CVZ executive board stage".

### ***5.c. Minister's decision- making***

***Publication in the  
Government  
Gazette***

The point of departure for the Minister's decision- making on applications for reimbursement is the advice of CVZ and the underlying reports as well as advice of the CFH and, in some cases, the ACP. The decisions come into force via an amendment to the Health Insurance Regulation. These amendments are published online, in the Government Gazette (*Staatscourant*), together with other amendments that did not require an examination by CVZ.

***Publication of a  
decision***

The Minister informs the registration- holder about the decision in writing. CVZ's advice, and the CFH- report, including appendices, are published on CVZ's website, under publications of CFH- reports. (see: <http://www.cvz.nl>).

## 6. Reassessment

<b><i>New data</i></b>	Any request for reassessment of a decision regarding an application for reimbursement, must be submitted in writing to the Minister. It should include information on new facts and altered circumstances. A request for reassessment may only be based on data published since submitting the previous reimbursement application. This applies not only when the pharmacotherapeutic part of a file was rejected, but also when the pharmacoeconomic analysis formed the ground for rejection. The procedures when requesting reassessment are, furthermore, identical to the procedures for a normal application for reimbursement (see section 5, Official assessment).
<b><i>Obligation in the event of alteration in treatment guidelines</i></b>	The registration-holder is also responsible for submitting an application for reassessment, when within a therapeutic indication an alteration occurs due to a change in a therapeutic guideline for a medicine which is already included in List 2 of the GVS. If the specific conditions which apply to a medicine that is already on List 2 of the GVS need to be adjusted, the manufacturer is responsible for applying for reassessment and for providing a pharmacoeconomic analysis that substantiates extending the List 2 conditions. This applies to both List 1A medicines and List 1B medicines. This obligation does not exist in the case of a List 1A medicine, whereby the adjustment in the specific conditions has already been included for a different product in the same cluster on List 2.
<b><i>Timing of the request</i></b>	A request for reassessment will not be accepted for processing within 6 months after a previous reimbursement decision of the Minister.

## **7. Communication**

### ***7.a. Inter- party communication***

#### ***Inter- party communication***

All parties (VWS, CVZ, registration- holders, prescribers, patients and health- insurers) benefit from rapid, transparent procedures, preferably with a highly predictable outcome. Smooth procedures require transparency regarding the degree to which the discussion is public and the lines of contact between the registration- holder, the Minister of VWS, and CVZ.

### ***7.b. Public accessibility***

#### ***Confidentiality of the assessment***

The observance of confidentiality requires that the various phases of an assessment are distinguishable.

1. During the phase of developing a medicine, up to the submission of a test- file, the Ministry of VWS and CVZ may publicly formulate factual discussion points relating to a new medicine. They will, however, guard against making statements about the possible results of the discussion on therapeutic value and the reimbursement status.
2. Public statements about therapeutic value, cost- effectiveness and the medicine's reimbursement status are no longer relevant at the moment that the (test- ) file has been submitted.

The day after the CFH meeting, the registration- holder may approach the secretary to enquire about the results of the discussion within the CFH and about subsequent procedures. During the procedures, all parties involved, i.e., even the registration- holder, should observe confidentiality with respect to the committee's provisional assessment. However, this does not preclude the CFH and the registration- holder from consulting external experts during the procedures. Starting January 1st 2010, parts of the minutes of the CFH will be publicly available.

#### ***Transparency***

In the interests of transparency, when drawing up advice, the CFH uses only public data in the file. Public data are data that can be accessed by any interested party, the main outlines of which can be cited. As it is not possible to cite from confidential information, and such citation could endanger future publication of data, the degree to which unpublished research reports can be used is limited (see 5.a.2. Required data, paragraph "unpublished data").

## **7.c. Contacts**

### ***Permanent contacts***

It is important that communication about the assessment procedures takes place via regular contacts. For the Ministry of VWS these are representatives on behalf of the Department of Medicines and Medical Technology (GMT) and the Farmatec unit (CIBG).

In principle, contact with CVZ always takes place via the secretary of the CFH or the deputy secretary. For questions regarding submission of files CVZ should be contacted. The Ministry and CVZ would prefer a single contact on behalf of the registration-holder. Preferably, this person is the person responsible for submitting reimbursement applications within the company.

### ***Contact data***

#### **Ministry of VWS, GMT Department:**

- P.P. Kruger, senior policy advisor  
tel. (070) 340 6876  
e-mail: [pp.kruger@minvws.nl](mailto:pp.kruger@minvws.nl)
- Dr. H.F. Storms, senior policy advisor  
tel. (070) 340 7620  
e-mail: [hf.storms@minvws.nl](mailto:hf.storms@minvws.nl)

#### **Ministry of VWS, CIBG (Farmatec)**

Dr. M.J. van de Velde, cluster head  
tel. (070) 340 7330  
e-mail: [mj.vd.velde@minvws.nl](mailto:mj.vd.velde@minvws.nl)

#### **CVZ, Care Advice Department (Pharmacy):**

- Dr. M. van der Graaff, secretary to the CFH  
tel. (020) 797 8892  
e-mail: [MGraaff@cvz.nl](mailto:MGraaff@cvz.nl)
- Ms. J.E. de Boer, MD, deputy secretary to the CFH  
tel. (020) 797 8523  
e-mail: [JEBoer@cvz.nl](mailto:JEBoer@cvz.nl)
- Dr. W.G. Goettsch, deputy secretary to the CFH  
tel. (020) 797 8057  
e-mail: [wgoettsch@cvz.nl](mailto:wgoettsch@cvz.nl)
- Secretariat of the Care Advice Department (Pharmacy)  
tel. (020) 797 8959  
fax.(020) 797 8993  
e-mail: [infocfh@cvz.nl](mailto:infocfh@cvz.nl)

## References

CVZ has published the following documents which can be found, via the search function, on the website (<http://www.cvz.nl>):

1. Dossiereisen geneesmiddelenbeoordeling. Diemen, College voor zorgverzekeringen, 2010' [File requirements, assessment of medicines] (provided on the website) [Regulations for the Appraisal Committee]
2. Format farmacotherapeutisch dossier. 2010. [Format Pharmacotherapeutical File]
3. Format indiening farmaco- economisch dossier. 2010. [Format Pharmacoeconomic File]
4. Format indiening kostenconsequentieraming. 2010. [Format Budget- impact estimate]
5. Richtlijnen voor farmaco- economisch onderzoek. Diemen, College voor zorgverzekeringen, 2006. [Guidelines for Pharmacoeconomic research]
6. Handleiding voor kostenonderzoek; methoden en richtlijnrijzen voor economische evaluaties in de gezondheidszorg, College voor zorgverzekeringen, geactualiseerde versie 2010. [Manual for cost- effectiveness research]
7. Reglement van de Commissie Farmaceutische Hulp Diemen, College voor zorgverzekeringen, 2010. [Regulations for the Committee Pharmaceuticals]
8. CFH- criteria voor beoordeling therapeutische waarde Diemen, College voor zorgverzekeringen, 2010. [CFH- criteria for assessing therapeutic value]
9. Reglement Adviescommissie Pakket, Diemen, College voor zorgverzekeringen, 2008. [Regulations for the Appraisal Committee]
10. Inspraakprotocol bestuurlijk traject. Diemen, College voor zorgverzekeringen, 2010. [Protocol of Participation Administrative Stage]

Also, on the CIBG website (<http://www.farmatec.nl>), the application form for inclusion in the GVS.

Sections of the law relevant to Pharmaceutical products can be found on the central government's website (<http://www.overheid.nl>).

Law texts, formats and other documents are subject to alteration. The most recent publications should always be used when making a submission.

## Appendix 1: Laws and regulations

Health Insurance Act [*Zorgverzekeringswet, ZvW*] (article 10, subsection c)

Health Insurance Decision [*Besluit zorgverzekering*] (article 2.8)

Health Insurance Regulation [*Regeling zorgverzekering*] (starts at article 2.40)

***Health Insurance Act*** The new Health Insurance Act came into force as of 1<sup>st</sup> January 2006. This brought to an end the Benefits Decision [*Verstrekkingenbesluit*] and the Pharmaceutical Care Regulation [*Regeling farmaceutische hulp*] relating to the Sickness Fund Insurance Act. These were replaced by the Health Insurance Decision [*Besluit zorgverzekering*] and the Health Insurance Regulation [*Regeling zorgverzekering*].

Articles relevant to Pharmaceutical products can be found on the central government's website: '<http://www.overheid.nl>'. For the Health Insurance Act [*Zorgverzekeringswet, ZvW*], this is article 10, subsection c .

Sections 1 and 2 of the Health Insurance Decision are particularly important.

Relevant information of the Health Insurance Regulation can be found in sections 1 and 2.

Lists 1A ,1B and 2 can be found on the following websites: <http://www.overheid.nl> and <http://www.farmatec.nl/>

## Appendix 2: Assessment criteria of the CFH

("CFH- criteria for assessing therapeutic value")

### ***Introduction***

The Medicinal Products Reimbursement Committee [*Commissie Farmaceutische Hulp*, CFH] has two goals in assessing medicines. One of these is to providing prescribers with advice by clearly defining the place of each medicine in relation to other medicines for the same indication. The other is to advise on reimbursement within the framework of inclusion in the GVS, the inclusion of expensive intramural (orphan) medicines in the NZa policy regulations and for certain pharmacy preparations. The pharmacotherapeutic report contains the results of the assessment of a medicine. This can be found at [www.cvz.nl](http://www.cvz.nl), under CFH- reports or by clicking on the product test at [www.fk.cvz.nl](http://www.fk.cvz.nl). The focal point is the assessment of a medicine's therapeutic value.

### ***Therapeutic value***

The therapeutic value is the sum of the assessment of all properties of a medicine that are relevant to treatment, which together determine the place of a medicine within therapy relative to other recommended methods of treatment that are available.

The therapeutic value of a medicine is primarily determined by the balance between the *intended and unintended* effects of the medicine in relation to those of the standard or usual treatment. The value of a statement on therapeutic value is limited when few data are available on clinically relevant outcome parameters and if there is as yet insufficient experience for shedding light on important, though rare, side effects. Where the balance between intended and unintended effects is comparable, a role may be played by the other assessment criteria (*applicability, experience and ease of use*), in as far as these become apparent via the intended and/or unintended effects. Costs play no role whatsoever in determining therapeutic value.

Medicines are subsequently divided into three categories:

- Medicines with a therapeutic value lower than other treatment possibilities included in the package. This is the case if:
  - The product has important disadvantages in the intended and/or unintended effects in comparison with the standard or usual treatment;
  - Insufficient scientific data are available in comparison with the evidence for the standard or usual treatment;
- Medicines with a therapeutic value which is comparable to that of other treatment possibilities included in the package. This is the case if the

medicine has no relevant differences in advantages and disadvantages in intended or unintended effects in comparison with the standard or usual treatment;

- Medicines with an added therapeutic value in comparison with that of other treatment possibilities included in the package. This is the case if the medicine has relevant advantages in relation to the intended and/or unintended effects in comparison with the standard or usual treatment.

The CFH assumes that a relevant and specific category of patients must be involved. The size of the group of patients and the severity of the disorder being treated play an important role in determining a possible added therapeutic value.

***The comparative treatment and the therapeutic indication***

In order to determine the therapeutic value for a given indication, the medicine has to be compared with the standard treatment, or failing that, the usual treatment.

The standard treatment is the treatment regarded as first-choice treatment according to current relevant guidelines, the efficacy of which has been proven. If no standard treatment can be determined, then comparison takes place with the usual treatment. That is, the treatment that is regarded in daily practice as first-choice treatment, the efficacy of which has not (yet) been scientifically proven. This usual treatment must be used in practice on a substantial number of patients with the indication concerned.

The CFH establishes the standard treatment, whereby the most important sources are: The standards of the Dutch G.P. Association (NHG), the CBO- guidelines or the National Transmural Agreements (LTA), the *Farmacotherapeutisch Kompas* [Dutch National Drug Formulary]. The guidelines of the professional groups within the Order of Medical Specialists are also important. Lastly, foreign guidelines are relevant. The standard treatment for a given indication may be comprised of more than one medicine or non-medicinal treatment or a policy of 'wait-and-see' or best possible supportive care. The registered indications of medicines form the point of departure for determining the standard or usual treatment. Medicines that are not registered for the indication concerned, but which are used in practice, are also important. Medicines used 'off-label' can only be considered as comparative treatment if their use for the indication concerned is sufficiently substantiated by clinical research and their use as usual treatment in daily practice is accepted, or described in guidelines and/or protocols approved by the professional group.

In practice a number of problems can occur when choosing the

comparative treatment. For example, therapeutic insights may alter over the course of time. This means that opinions about the most suitable comparative treatment may also alter. A well-founded choice of comparative treatment for clinical research is not necessarily the most suitable treatment upon completion of the clinical research or at the moment of applying for inclusion in the insured package.

***Assessment criteria for therapeutic value***

The assessment criteria that jointly determine therapeutic value are discussed below: intended effects, unintended effects, experience, applicability and ease of use.

***Intended effects***

The gold standard for determining the intended effects of treatment is randomised, double-blind, comparative research. Intended effects should, preferably, be expressed in clinically relevant outcome parameters that are noticeable for the patient, such as degree of morbidity, mortality and/or quality of life.

Clinically relevant outcome parameters are often not yet available at the moment of assessment (e.g., for preventative cardiovascular medicines). Such clinical studies tend to provide only surrogate (also known as intermediary) outcome parameters. In such cases, surrogate outcome parameters (e.g., a laboratory result, or a physical characteristic) form the only useable parameters for assessing intended effects. It should be mentioned that a demonstrable relationship must exist between this surrogate parameter and a clinically relevant outcome parameter. Surrogate outcome parameters are not always noticeable by patients. In order to establish relevant outcome measures, the CFH can use the guidelines of the EMA and the treatment guidelines of care-providers.

When determining the place of a medicine in the pharmacotherapy, comparison with the standard and/or usual treatment is important for determining the relative efficacy. The best evidence is formed by a study in which the same population is directly compared with the standard or usual treatment at the right dose. A comparison with placebo alone is less valuable unless no treatment is available or the new medicine is being added to an existing therapy ('add-on' or combination therapy).

The evidential value of indirect comparisons between medicines, which generally involve different populations and study circumstances, is lower. Very little research is undertaken that explicitly focuses on quality of life. However, the added value of a medicine may actually be expressed in the form of an improved quality of life. Consequently, it is always worthwhile mentioning relevant data on this aspect. Firm conclusions cannot always be determined based on the

results of research in which quality of life is a secondary parameter.

Finally, the comment should be placed that although randomised clinical studies (RCTs) are essential for a proper assessment, there is also an important limitation to this form of research. RCTs are carried out under controlled circumstances: an homogenous, limited group of patients, experienced and expert researchers, proper supervision, etc. These circumstances differ from those of daily practice, under which, for example, there is no question of the inclusion and exclusion criteria that applied in the clinical research. This could lead to different results in daily practice, but data on this are often not yet available at the time of marketing.

### *Unintended effects*

An unintended effect is an effect that is not intended yet occurs in a patient when the correct dose of a medicine is used for the prevention, diagnosis or treatment of an illness or disorder. Although most unintended effects are the side effects of medicines, effects such as the development of bacterial resistance due to using antibiotics are also regarded as unintended effects. While all medicines have unintended effects, the unintended effects may differ in nature, severity, frequency and clinical relevance. The less severe the disorder, the lower the acceptability of adverse events.

When comparing the different unintended effects, especially the serious adverse events and the adverse events that occur with the highest frequency will be regarded. A serious adverse event is defined as a side effect that leads to mortality, a life-threatening situation, invalidity or a disability, admission to hospital or lengthening the period of hospitalisation. An unexpected adverse event is a side effect that is not described in the official registration text. The risk of unexpected adverse events reduces when the experience with a medicine increases. Therefore, statements regarding a medicine's safety should always be relative to the experience obtained with them.

An important limitation of clinical research is that the populations involved are usually too small and too homogenous to bring to light adverse events that occur infrequently. Furthermore, the follow-up of clinical studies is usually too short to shed light on adverse events that only occur after long-term use. For this reason, reporting and registering adverse events is extremely important for improving our knowledge of every medicine. Furthermore, on the grounds of comparable medicines with known side effects, it is sometimes possible to voice expectations regarding unintended effects that have not yet been observed or studied (extrapolation is important here).

The assessment of adverse events should be based on all the information available from randomised clinical and observational research and voluntary reports from daily practice for which causality has been established. An important item in the comparison of the differences in adverse events between two medicines, is the number of patients that are forced to prematurely terminate participation in a clinical study as a result of adverse events.

A separate aspect that is regarded as a disadvantageous property is toxicity as a result of overdose. Lastly, medicines with a broad therapeutic application are preferred to medicines with a limited therapeutic application.

### ***Experience***

Experience in using a medicine is important because it provides greater clarity about its intended effects, the risk of unexpected unintended effects, its applicability and the ease of use. More experience provides prescribers and patients with more confidence in the therapeutic value of a medicine.

The experience that can be obtained using a medicine is determined by the length of time it has been available and the number of patients treated with it during that period of time. Experience per therapeutic indication may differ, as medicines often have a variety of indications and the therapeutic are can be expanded over time. That is why statements on adverse events and the safety of medicines should always take into consideration whether the experience obtained is sufficient to notice the most important rare adverse events.

Essential data for an assessment of experience are the period of time that a medicine has been on the market and the number of prescriptions or patient years. The CFH also makes use of data from abroad [other countries with an adequate system for registering adverse events].

The CFH postulates that after three years *sufficient experience* is obtained for a medicine if either more than 100,000 prescriptions have been supplied for a non- chronic indication, or a minimum of 20,000 patient years in case of chronic indication. After ten years one can speak of *considerable* experience. Experience with a medicine for a given indication is regarded as *limited* if it has been on the market for less than three years or if it does not fulfil the use- standard of 100,000 prescriptions or 20,000 patient years.

It may be that in the comparison between two different medicines less experience is obtained for one medication than for the other. Nevertheless, the experience for this medicine may still be considered sufficient or considerable.

The above- mentioned limits do not always apply. For example, it may be the case that, due to the rareness of the indication, a

medicine is hardly ever prescribed. Therefore, a relative comparison with the prescription data of the standard treatment should be made available. On the other hand, the experience with a new product may be considered limited, in spite of the fact that it has already been used by tens of thousands of patients. This happens when a medicine is used on an extremely large scale, with millions of users throughout the world. Due to this expected large-scale use, the limited experience will nevertheless carry a lot of weight.

### ***Applicability***

Not every medicine for the treatment of a given disorder can be used for all patients with this disorder. If the medicine has only been studied among a select group of patients, as evident from the inclusion and exclusion criteria of a clinical study, then in principle, its application should also be limited to that group.

The first question when assessing the applicability of a specific medicine is which properties are relevant in view of the product's therapeutic indication area: its applicability for children and the elderly, for organ function disorders, during pregnancy and lactation, and the presence of contraindications and interactions. The medicine being assessed is subsequently compared, per relevant property, with the standard or usual treatment. This will eventually result in the conclusion that the applicability of the product is *less broad, comparable or broader* than the applicability of the standard or usual treatment.

The applicability of a medicine is limited if it cannot be administered to a significant category of patients. Medicines that can be used on broad groups of possible users are preferred. A product may have a therapeutic added value for a specific, relatively large sub-group of patients who can not be treated with the standard or usual treatment.

### ***Ease of use***

Dose frequency, time of administration, mode of administration, taste, packaging, etc. are properties that affect the ease with which patients can use a medicine. There may be individual differences between medicines. Ease of use can play a role in a patient's therapy compliance, which will have consequences for the course of treatment and its eventual effect.

Differences in ease of use can be important when choosing between various medicines. Advantages in ease of use should be evident from a clinically relevant improvement in intended or unintended effects in order to be able to speak of a therapeutic added value in comparison with the standard or usual treatment.

**Comparison**

In order to determine the therapeutic value of a medicine in comparison with that of the standard or usual treatment, the said criteria (intended effects, unintended effects and, if relevant, experience, applicability and ease of use) of the individual products will have to be compared with one another. Intended and unintended effects are deemed of the greatest importance in this comparison. When making the comparison, the CFH takes many aspects into account, such as disease burden, chronicity of the disorder and the availability of alternatives.

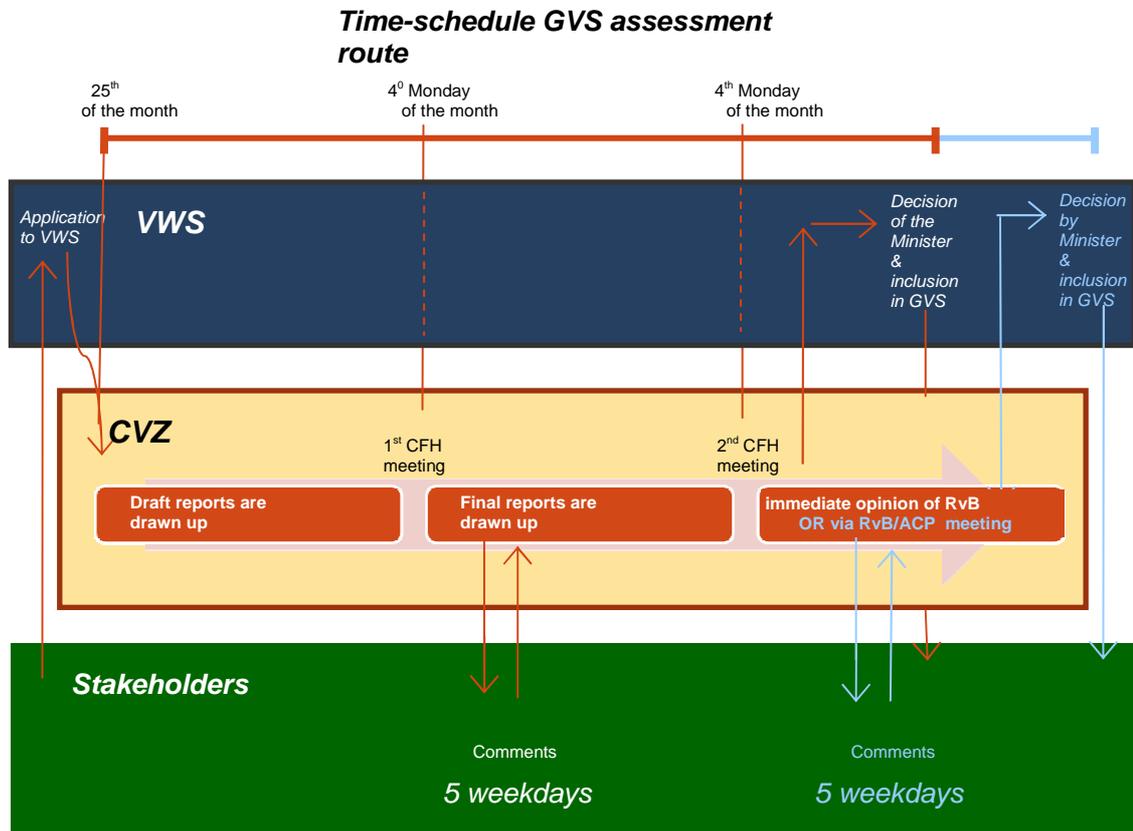
**Table 1: Definitions of important concepts and criteria**

<b>Concept</b>	<b>Meaning</b>
Standard and usual treatment	<i>Standard treatment</i> is the treatment regarded in daily practice as treatment of first choice, the efficacy of which has been proven. <i>Usual treatment</i> is the treatment regarded in daily practice as treatment of first choice, the efficacy of which has not (yet) been scientifically proven. This must be used in practice for a substantial number of patients with the indication concerned.
Clinically relevant outcome parameter	A clinically relevant outcome parameter is an outcome parameter that reflects the degree of morbidity, mortality or quality of life due to a treatment.
Surrogate outcome	A surrogate outcome is an outcome that is not directly noticeable for the patient, but which is correlated with a clinically relevant outcome parameter.
Intended effects	Intended effects are the positive effects of a medicine, expressed in clinically relevant outcome parameters, or – where these are lacking - in surrogate outcome parameters.
Systematic summary and meta-analysis	A systematic summary reflects established medical scientific research. A systematic summary is transparent and reproducible and is based on answering an explicit question, an extensive search strategy, unequivocal procedures for selecting studies, an assessment of the quality of the studies and a transparent presentation of the results. Quantification of the results is also provided in a meta-analysis. A meta-analysis combines the individual results to form a total estimate – weighted according to study size – of the effect of the intervention being studied.
Unintended effects	Unintended effects are effects that are unintended but which nevertheless occur in patients when a medicine is used.
Experience	The experience obtained with a medicine is the degree (limited, sufficient, ample) to which the advantages and disadvantages of its use in daily practice have – as far as possible – emerged and been dealt with.
Applicability	The applicability of a medicine is the degree to which its use in various (groups of) patients is limited or facilitated. Examples are its applicability in a given age group, organ function disorder, during pregnancy and lactation. Limitations as a result of contraindications and interactions are also important.
Ease of use	Ease of use is the degree of user- friendliness. Ease of use is reduced by increases in the burden on patients when using a medicine.
Quality of life	Quality of life relates to a patient's state of health and is defined as the physical, psychological and social aspects of how a patient functions. These matters can even be sub- divided into more specific territories, such as physical functioning and pain, both of which are aspects of the physical side of quality of life. Aspects that are not directly related to illness and health care are not taken into consideration.
Therapeutic value	A medicine's therapeutic value is the sum of the evaluation of all properties (intended and unintended effects, experience, ease of use and applicability) that are relevant to the treatment and which together determine its place in therapy in comparison with other treatment possibilities that are available and recommended.
Statistical significance	Statistical significance can be defined as the chance that is only just still considered acceptable that an intended or unintended effect observed is actually non- existent.
Clinical relevance	Clinical relevance relates to a medicine's importance for clinical practice.

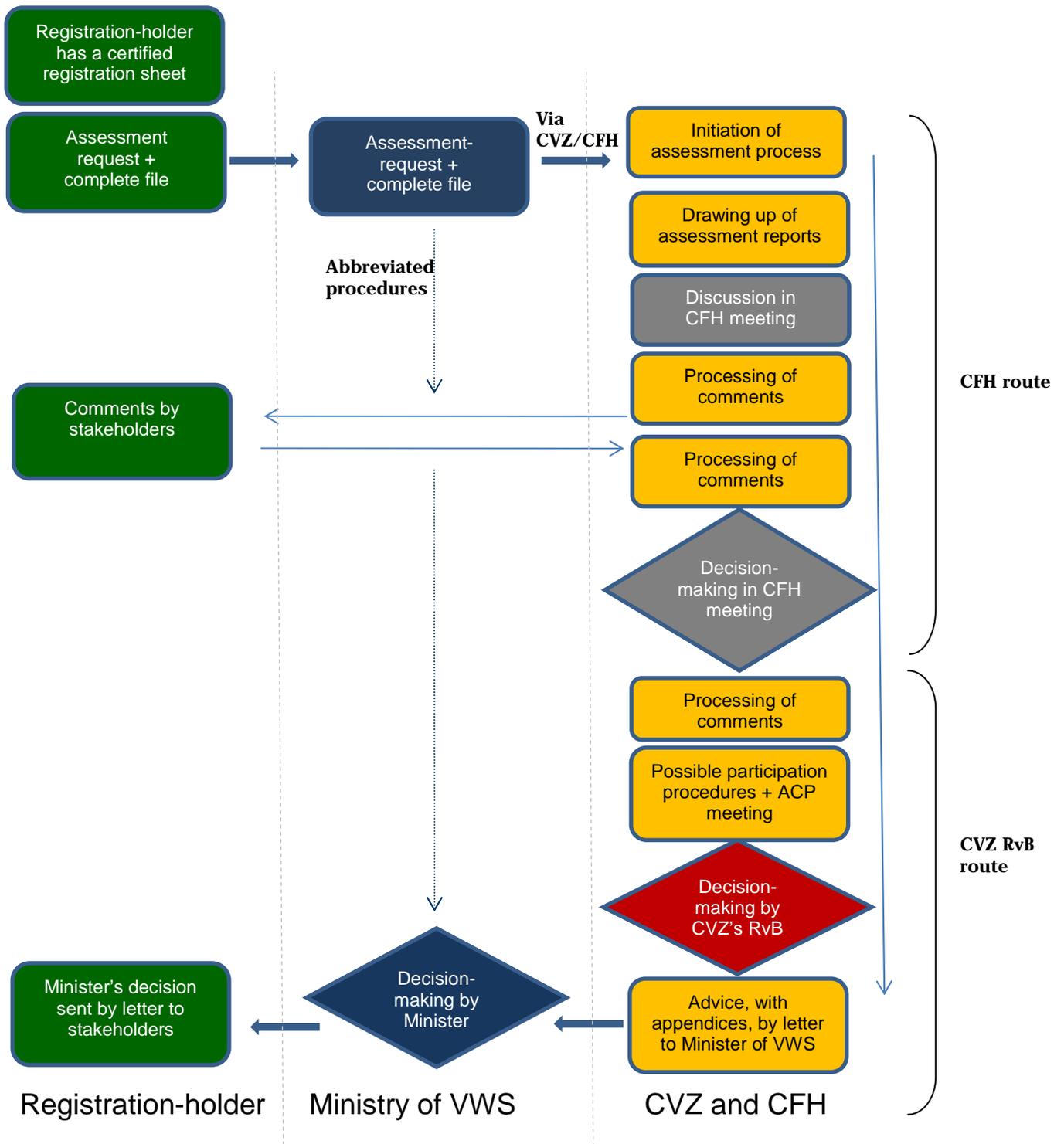
### Appendix 3: Summary of the GVS assessment route.

**Figures 1 and 2: Time- schedule and flow- diagram of the official GVS assessment route.**

The parties involved are stakeholders (green), the Ministry of VWS (blue) and CVZ (yellow). An interested party submits an application to the Ministry of VWS. The route commences on the 25<sup>th</sup> of every month. CVZ compiles the draft assessment reports during the period leading up to the 1<sup>st</sup> CFH meeting. The CFH assesses the draft reports during its meeting. After the meeting, any necessary alterations are made to the draft reports and the secretary of the CFH sends these documents to stakeholders, who then have 5 weekdays in which to comment on the draft documents. Stakeholders who require more time can apply for a suspension (lasting a maximum of 3 months). CVZ incorporates comments received and discusses them in the 2<sup>nd</sup> CFH meeting. Several CFH meetings may be necessary in order to arrive at a final opinion on the reports. After this, the final reports can be sent to the Ministry or the CVZ RvB stage can be started. The entire procedures must have been completed within 90 days.



**Fig. 1: Time- schedule of the GVS assessment route**



**Fig. 2: Flow diagram of the GVS assessment route**