CBG MEB

MEDICINES EVALUATION BOARD

Policy document

Compassionate Use Programme

MEB 49

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1 Contents

2 Abbreviations and definitions

aRMM	Additional Risk Minimisation Material (educational material)
B/R	Benefit/Risk
MEB	Medicines Evaluation Board
CESP	Common European Submission Portal
CHMP	Committee for Medicinal Products for Human Use (CHMP)
CUP	Compassionate Use Programme
DSUR	Development Safety Update Report
EMA	European Medicines Agency
GVP	Guideline on good pharmacovigilance practices
IGJ	Health and Youth Care Inspectorate (*Inspectie Gezondheidszorg en Jeugd*)
SmPC	Summary of product characteristics
PSUR	Periodic Safety Update Report
ZIN	The National Health Care Institute (*Zorginstituut Nederland*)

3 Introduction

Medicinal products may only be marketed if a marketing authorisation has been granted. In cases of compassionate use, medicinal products for which no marketing authorisation has yet been granted may be made available to patients suffering from a serious disease for which there is no authorised medicinal product.
To this end, manufacturers of medicinal products can submit an application to the Medicines Evaluation Board for approval of a Compassionate Use Programme (CUP).

An alternative to make medicinal products without a marketing authorisation available to individual patients is on a named patient basis. To request approval for this, you can contact the Health and Youth Care Inspectorate (IGJ). For more information, please consult the website of IGJ.

4 The legal framework

In the Netherlands the MEB is the competent authority for approval of CUP. The legal framework originates from Article 83 of Regulation (EC) No. 726/2004, read in conjunction with Section 40(3), preamble and f of the Medicines Act and Section 3.18 of the Medicine Law Regulation.

Article 83 of the Regulation covers use of medicinal products for which no marketing authorisation has been granted in cases of compassionate use. Once a marketing authorisation has been granted, this legal framework no longer applies. However, once a CUP has been set up, the applicant will ensure that the patients included in the programme will keep access to the medicinal product during the period between the medicinal product being allowed on the market and actually being marketed. This is in accordance with Article 83(8) of this Regulation.

5 Criteria for a CUP

For a medicinal product to be eligible for a CUP, three criteria apply.

1. The medicinal product must be intended for treatment of a group of patients (cohort) suffering from a chronic disease, a disease that is detrimental to their health or a life-threatening disease.
2. This disease cannot be treated satisfactorily using an authorised medicinal product.
3. An application for a marketing authorisation for the medicinal product has been submitted, or clinical tests to support such an application are still ongoing.

Further explanation:

- With regard to the second criterion: there should be sufficient evidence that the Benefit/Risk balance of the medicinal product in the CUP is positive.
- It is important to submit a CUP application in time. Several factors are relevant in this regard. If the application is submitted too soon, it can be difficult for the MEB to properly weigh the benefit and risks. The assessment of the Marketing Authorisation application by the EMA may be considered. If the application is submitted too late and an application for a marketing authorisation has also been submitted, the marketing authorisation may be granted before the CUP application can be approved. In that case the MEB will terminate the assessment of the CUP application.

The applicant can contact the MEB using the contact form on the MEB's website to receive advice in advance.

- With regard to the second criterion: if a another medicinal product has been authorised for the same indication, but it is not yet available in the Netherlands, this should not hinder approval of the CUP.
- An application for a CUP for a medicinal product for which a marketing authorisation has already been granted, with the CUP application relating to a new indication, cannot be accepted for consideration by the MEB. After all, doctors are allowed to prescribe this medicinal product for off-label use for indications that have not yet been included in the SmPC/patient information leaflet, in accordance with the provisions of Section 68 of the Medicines Act.
- The purpose of the clinical tests mentioned in the third criterion is to support an application for a marketing authorisation. If the studies have already been concluded and the application for a marketing authorisation has not yet been submitted, an application for a CUP can already be submitted and will be assessed by the MEB

6 Application, validation and assessment of a CUP

6.1 CUP application

A manufacturer of medicinal products that wants to make a medicinal product available through a CUP must submit an application to the MEB. The application should at least include a description of the following components:

- a substantiation of the importance of making the medicinal product available;
- a description of the patient group for which the medicinal product will be made available in the CUP;
- all available data for an assessment of the relationship between the efficacy and safety of the medicinal product (if an application for a marketing authorisation has already been submitted, the applicant can refer to this) and the applicant's substantiation for why making the medicinal product available will have a net positive result.
- the agreements between the applicant and the prescribers and patients involved with regard to the patients reporting adverse reactions relating to pharmacovigilance and/or the collection of clinical data during the CUP.

Complete the **application form** and have it sent to your email address. Submit the application through CESP, together with the completed application form and the accompanying documentation.

6.2 Validation

Once the application has been received, the MEB will check whether it has all data it needs to accept the application for consideration. The MEB will inform the applicant as soon as possible, within two weeks at the latest, whether the application can be assessed or whether the applicant needs to provide supplementary information or a further explanation.

6.3 Assessment

The MEB will assess the CUP application based on the criteria and the applicant's substantiation. The MEB will inform the applicant of the result of the assessment as soon as possible, within six weeks of completing the validation at the latest.

This can result in the following outcomes:

- The CUP application can be approved after the first round of assessment.
- The application cannot be approved, due to other concerns. The MEB will inform the applicant that the application can be approved once these other concerns have been resolved. The applicant must satisfactorily deal with these questions with a single response.
- The application cannot be approved, due to both major objections and possibly other concerns. The MEB will inform the applicant that it intends to reject the application. The applicant will have the opportunity to respond to the questions, either in writing or in a hearing.
  After the applicant's response has been assessed, the MEB can make the following decisions:
  - The CUP application can be approved.
  - The major objections have been resolved, but some other concerns remain. The applicant must satisfactorily deal with these other concerns within a single response.
  - The MEB rejects the application.
- The MEB terminates the processing of the application, because the marketing authorisation for the medicinal product has been granted before a decision is taken on the CUP.

The applicant will receive the decision in writing.

An objection or appeal can be lodged against the approval or rejection of a CUP application.

6.4 Publication of the decision

The MEB publishes approved Compassionate Use Programmes on the website: https://www.cbg-meb.nl/onderwerpen/hv-compassionate-use-programma/overzicht-goedgekeurde-cup.

7 Duration, conditions and termination of the CUP

7.1 Duration

The medicinal product can be made available to patients following the approval of the CUP.

Also, after the marketing authorisation has been granted, the applicant should ensure that the medicinal product remains available to the patients in the programme.[1] Where possible, after the marketing authorisation has been granted, the medicinal product can also be made available to new patients.

Termination of the CUP will take place in coordination with the MEB (see 7.3).

7.2 Conditions associated with approval of a CUP

With the decision to approve a CUP the MEB sets specific conditions to the CUP, such as:

- the indication for which the CUP is approved,
- the applicant will register any adverse reactions (see 8.1),
- that a CUP will not prevent patients from participating in a study with this medicinal product in the Netherlands
- that the manufacturer will inform the MEB when serious adverse reactions are reported during the CUP that necessitate reconsideration of the CUP decision (see 7.3).

If the medicinal product supplied in a CUP is granted a marketing authorisation, and educational material (aRMM) has been set as a condition for the marketing authorisation, the manufacturer must implement the aRMM immediately, as soon as the MEB has approved the aRMM (conform MEB 45: National implementation of aRMM) without waiting until the commercial launch of the medicinal product.

7.3 Early termination of the CUP

The manufacturer of the medicinal product will inform the MEB if it intends to terminate the supply of the medicinal product following the approval of a CUP.

In addition, the MEB can withdraw its approval of a CUP early. For example, the MEB may decide to do so in coordination with the manufacturer in the event that:

- the patients in the cohort can be treated using a newly authorised medicinal product, which was not available when the CUP was approved. Upon learning of such a medicinal product, the MEB or the manufacturer will contact the other party. In this case, it may be possible to change the indication of the CUP.
- the manufacturer does not submit an marketing application to the EMA or withdraws the application;
- Newly reported serious adverse events necessitate a reconsideration of the Benefit/Risk balance.
    - The manufacturer of the medicinal product will directly inform the MEB of any serious adverse reactions.

[1] In accordance with Article 83(8) of Regulation (EC) No. 726/2004: If a programme is set up for cases of compassionate use, the applicant will ensure that the patients included in the programme also have access to the new medicinal product during the period betweenmarketing authorisation and actually being brought on the market.

- The MEB can also be informed in other ways (for example, through the EMA) of new data giving cause to reconsider the B/R. The MEB will then contact the manufacturer to discuss this.

The MEB and the manufacturer will coordinate the consequences of terminating the CUP for the treatment of patients. Input from other parties may be requested for this process.

8 Other remarks

8.1 Reporting adverse reactions

The manufacturer that has been granted the CUP approval is required to collect all information about suspected adverse reactions. The applicant/marketing authorisation holder will send any adverse reactions that may have been caused by the medicinal product (according to the primary reporter, or the applicant/marketing authorisation holder) to EudraVigilance. In this context, the Good Vigilance Practice Module VI guidelines must be the guiding principle.
If the programme runs for more than a year, the manufacturer will submit a safety report with recent data (in the PSUR format, in accordance with GVP Module VII, or in the DSUR format, in accordance with ICH E2F). The obligation to submit PSURs will apply after the marketing authorisation has been granted.

8.2 The CHMP's advisory role

The CHMP can advise the nationally competent authority (in the Netherlands, this is the MEB) to allow a Compassionate Use Programme. The manufacturer of the medicinal product must in this case still submit the CUP application to the MEB. The MEB will take the CHMP's advice into account.

8.3 The IGJ

The MEB will inform the IGJ of the CUP applications submitted and the outcome of the associated assessments.

9 Related documents

1. Regulation (EC) No. 726/2004;
2. Medicines Act;
3. Medicine Law Regulation;
4. EMA Guideline on Compassionate Use;
5. guidelines in the Good Vigilance Practice Module VI;
6. GVP Module VII;
7. ICH E2F.
8. MEB 45: National implementation of additional risk minimisation measures