Federal Agency for Medicines and Health Products
Avenue Galilée 5/03
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http://www.fagg.be – http://afmps.be

DG Pre/Research & Development/Unmet Medical Need

Guidance on compassionate use and medical need programs

Content

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I. General

The law on medicinal products of the 25th of March 1964 describes how medicinal products that are not authorized in Belgium or only authorized in different indications: For non-authorized medicinal products this can be via a Compassionate Use Program (CUP), a program for a group of patients with a life threatening disease, a chronic disease or a seriously debilitating disease which cannot be satisfactorily treated with a product that is licensed, commercially available in Belgium and reimbursed for this indication. As condition, clinical trials should be running with the medicinal product for the CUP indication or a Marketing Authorisation Application (MAA) should have been submitted to the EMA (Cfr. article 6 of Regulation 726/2004) for the medicinal product for the CUP indication.

- For products authorized in Belgium this can be via a Medical Need Program (MNP), a program for a group of patients with a life threatening disease, a chronic disease or a seriously debilitating disease which cannot be satisfactorily treated with a product that is licensed, commercially available in Belgium and reimbursed for this indication. Additional conditions are :
    - a demand to obtain the MNP indication is being evaluated in a MAA; *or*
    - the MA has been granted for the MNP indication but the medicinal product is not yet marketed with the MNP indication (if the product is commercially available in Belgium for a previous indication we accept that a MNP can run as long as the reimbursement procedure for the MNP indication is ongoing); *or*
    - clinical evidence has been generated in (ongoing) clinical trials for the MNP indication.

Only one indication can be considered per program.
This document provides additional guidance on the application for such programs.

II. Compassionate use programs (CUP)

A. Submission

An applicant can apply for a CUP as described in article 106 of the Royal Decree of 14/12/2006 (see annex I) by submitting a dossier that complies with the requirements as set out below to the Federal Agency for Medicines and Health Products (FAMHP) via the Common European Submission Platform (CESP) following the process as described in Annex IX: e-submission through the CESP.
The FAMHP will contact the applicant within 6 working days to confirm the completeness of the application:

- If the request is not complete, the applicant will be contacted with a list of missing items. The applicant needs to submit the missing items within 30 calendar days. After reception of

the response, the FAMHP confirms completeness within 3 working days, or declares the application invalid.

- If the request is complete, the starting date of the procedure (T0) is confirmed to the applicant by email within 3 working days. The internal processes to gather an opinion from an ethics committee and the Commission for Human Medicines are started.

Within 40 working days after T0, additional questions can be sent to the applicant. The applicant has a maximum of 10 calendar days to respond to the questions. The process timeline is stopped when the applicant's responses are received.
Within 55 working days after T0 (excluding the additional days for responding to questions, see above) a decision is communicated. If not, the request is tacitly approved.
In case of approval, the essential elements of the decision (see below: information for publication) are published through the FAMHP's website within 5 working days after approval.

The FAMHP requests a fee for each file submitted[1]. Please indicate in the cover letter to whom the invoice should be sent and the VAT number. The invoice with structured notice for the payment is sent the month following the validation of the dossier (T0).

B. Content and format of the application

Electronic documents should be adequately named and allow copying. Applications by other electronic means (e.g. email) are not accepted.

The application should contain :

- A cover letter describing the application and outlining where the information can be found
- An application form duly filled in (see annex II)
- The summarized information for publication (see below and annex IV)
- A medicinal product dossier (see below)
- An example of the labels, in line with the requirements of art. 107 §2 (see below and annex V)
- The informed consent form (ICF) in French and Dutch (see below)
- A protocol compiling the information regarding the rationale (see annex III for a template protocol). It would be really appreciated to annex pertinent/essential publications referred to in the protocol to the application.

In order to accelerate your application, please make sure that it is done in the correct manner, including all the requested information in line with the available template documents on the website.

[1] https://www.afmps.be/fr/items-HOME/Redevances

1. The medicinal product dossier

The Royal Decree defines the information that is requested to examine your application. Depending on the case:

- If a centralized procedure was submitted for the concerned medicinal product, please mention in the cover letter that a MAA has been introduced and the reference of the dossier. In this way we can consult the dossier.
- If not
    - a pre-submission dossier in line with the requirements for pre-submission applications in the centralized procedure[2]; *or*
    - relevant quality, non-clinical and clinical data as in the Investigational Medicinal Product Dossier ("IMPD") format as described in the clinical trial guidances[3]. In this case, a clear rationale is expected why this information is sufficient for compassionate use.

2. Information for publication

The Royal Decree describes the information that is part of the decision. In concreto, it concerns the following information:

1. Duration of the program
2. Conditions of use and indication
3. Conditions of distribution
4. Conditions, delays and further rules for participation of patients
5. Responsible person of the program
6. The ICF
7. Modalities for the disposal of non-used medicinal product
8. The Information for registration of suspected unexpected serious adverse reactions (including the list of expected adverse reactions)

To structure the information concerning the program, the applicant should complete the template in annex IV "summarized information for publication" as part of the original submission in Dutch, in French and in English. Explications on the information expected are available in the annex.
The ICF has to be included as well.

Upon approval of the program both the "summarized information for publication" and the ICF are published on the FAMHP's website.

[2] See p 4.1 of chapter 4 of volume IV of Good manufacturing product (GMP)
[3] http://ec.europa.eu/health/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

C. Labelling of the CUP product

The labelling of medicinal products in compassionate use programs needs to be compliant with the requirements as described in EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines annex 13. The summarizing table is annexed (annex V) – the requirement "For clinical trial use only" needs to be replaced by "Compassionate use – cannot be sold".
As a general rule, a labelling in the 3 national languages should be foreseen (Dutch, French, German).
Based on rationale, individual waivers on the language regimen can be requested in the cover letter.

III. Medical need programs (MNP)

A. Submission

An applicant can apply for a MNP as described in article 108 of the Royal Decree of 14/12/2006 (see annex I) by submitting a dossier that complies with the requirements as set out below to the FAMHP via CESP following the process as described in Annex IX: e-submission through the CESP.
The FAMHP will contact the applicant within 6 working days to confirm the completeness of the application.

- If the request is not complete, the applicant will be contacted with a list of missing items. The applicant needs to submit the missing items within 30 calendar days. After reception of the response, the FAMHP confirms completeness within 3 working days, or declares the application invalid.
- If the request is complete, the starting date of the procedure (T0) is confirmed to the applicant by email within 3 working days. The internal processes to gather an opinion from an ethics committee and the Commission for Human Medicines are started.

Within 40 working days after T0, additional questions can be sent to the applicant. The applicant has a maximum of 10 calendar days to respond to the questions. The process timeline is stopped when the applicant's responses are received.
Within 55 working days after T0 (excluding the additional days for responding to questions, see above) a decision is communicated. If not, the request is tacitly approved.
In case of approval, the essential elements of the decision (see below: information for publication) are published through the FAMHP's website within 5 working days after approval.

The FAMHP requests a fee for each file submitted[4]. Please indicate in the cover letter to whom the invoice should be sent and the VAT number. The invoice with structured notice for the payment is sent the month following the validation of the dossier (T0).

B. Content and format of the application

Electronic documents should be adequately named and allow copying. Applications by other electronic means (e.g. email) are not accepted.

The application should contain :

- A cover letter describing the application and outlining where the information can be found
- An application form duly filled in (see annex II)
- The summarized information for publication (see below and annex IV)
- A medicinal product dossier (see below)
- The ICF in French and Dutch (see below)
- A protocol compiling the information regarding the rationale (see annex VI for a template protocol). It would be really appreciated to annex pertinent/essential publications referred to in the protocol to the application.

In order to accelerate your application, please make sure that it is done in the correct manner, including all the requested information in line with the available template documents on the website.

1. The medicinal product dossier

The Royal Decree defines the information that is needed to examine the request. Depending on the case:

- If an application for authorization was submitted for the concerned medicinal product and indication, please mention in the cover letter that a MAA has been introduced and the reference of the dossier. In this way we can consult the dossier.
- If no authorization procedure is ongoing, please submit all relevant results from clinical trials.

2. Information for publication

The Royal Decree describes the information that is part of the decision. In concreto, it concerns the following information:

1) Duration of the program
2) Conditions of use and indication
3) Conditions of distribution
4) Conditions, delays and further rules for participation of patients

[4] https://www.afmps.be/fr/items-HOME/Redevances

5) Responsible person of the program
6) The ICF
7) Modalities for the disposal of non-used medicinal product
8) The information for registration of suspected unexpected serious adverse reactions (including the list of expected adverse reactions)

To structure the information concerning the program, the applicant should complete the template in annex IV "summarized information for publication" as part of the original submission in Dutch, in French and in English. Explications on the information expected are available in the annex.
The ICF is to be included as well.

Upon approval of the program both the "summarized information for publication" and the ICF are published on the FAMHP's website.

C. Labelling of the MNP product

The labelling of medicinal products in medical need programs needs to be the same as the one of the product authorized in Belgium. Nevertheless, a labelling could be added on the package to make a distinction between medicinal product used within a program and others.
If no Belgian labelling is available yet, the labelling of medicinal products needs to be compliant with the requirements as described in EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines annex 13. The summarizing table is annexed (annex V) – the requirement "For clinical trial use only" needs to be replaced by "Medical Need Program – cannot be sold".
As a general rule, a labelling in the 3 national languages should be foreseen (Dutch, French, German).
Based on rationale, individual waivers on the language regimen can be requested in the cover letter.

IV. Process to include patients in a CUP/MNP

The treating physician informs the patient or its legal representative regarding the lack of therapeutic alternative to treat the pathology, the modalities to make the medicine available and the benefit and the risk of this new treatment. If the patient gives truly informed and voluntary his written consent, the treating physician sends a written request to the responsible physician of the program. This request includes :

- A copy of the identity card of the patient and if applicable the number of social security
- A motivation to enroll the patient within this program and the evidence that the inclusion/exclusion criteria of the program are fulfilled
- A declaration of the treating physician stating that he/she is aware that he/she is personally responsible for the use of an unauthorized medicine or the use of an authorized medicine in an non-authorized indication.

- The ICF signed by the patient

The responsible physician gives his advice regarding the admissibility of the patient taking into consideration the possibility to include the patient in an ongoing clinical trial[5] in Belgium. He provides his reasoned advice as soon as possible to the responsible of the program. The responsible of the program only makes available the medicinal product to the treating physician if the advice of the responsible physician is positive.
The responsible physician stores the written requests from the treating physicians (including the four annexes) during 10 years.

V. Substantial amendment

A substantial amendment is a modification to the program regarding the safety or the physical and mental integrity of the patient, the course of the program or the quality or safety of the medicinal product used in the program.
Submission should be done via CESP following the process as described in Annex IX: e-submission through the CESP.
Electronic documents should be adequately named and allow copying. Applications by other electronic means (e.g. email) will not be accepted.
The application form (annex II) used for initial submission should be used in which you have to indicate that it concerns an amendment. All documents necessary to evaluate the amendment and updates of the documents provided in the initial submission (track changes and clean version) need to be provided. The timelines for reviewing amendments are the same as the initial submission of a CUP/MNP program.

VI. Pharmacovigilance

The regular pharmacovigilance duties for pre-registered investigational medicinal products or the duties for post-marketing products for the registration holder have to be applied, this means that any adverse drug reaction has to be recorded in the post market Eudravigilance database[6]. The reporting within a CUP or MNP is solicited. Please note that notifications with an investigational medicine that is also used in a Clinical Trial (=with an Eu(dra)CT number) should be reported as SUSARs (EVCTMPROD (this is the Production Environment of EVCTM (EudraVigilance Clinical Trial Module))) if this is required by the Clinical Trial protocol. Notifications with medicines that are not included in a Clinical Trial for which the protocol requests such reporting should be sent as post marketing cases (EVHUMAN (this is the Production Environment of EVPM (EudraVigilance Post-authorisation Module))).

[5] Website tools : https://www.clinicaltrialsregister.eu and http://clinicaltrials.gov/
[6] See section VI.C.6.2.2.1 from module VI of GVP

Besides this, as long as the program is open for new patients, the unmet medical need and the benefit/risk balance of the medicinal product will be evaluated periodically by the FAMHP. This evaluation will be based on safety reporting and the state of the art. The safety reporting is based on the safety register (see Chapter VII) requested in the legal framework.
The sponsor should submit the safety report via CESP following the process as described in Annex IX.

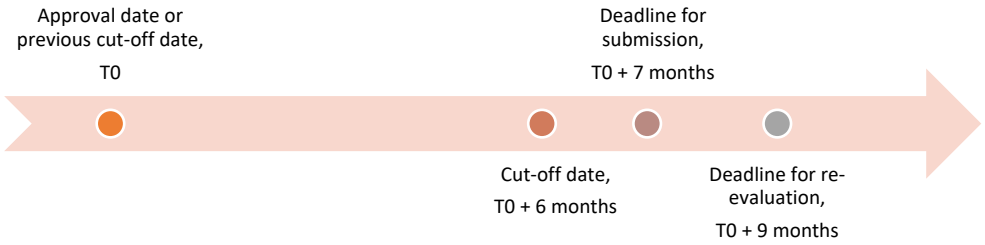
The safety reporting should consist of:

- An application form (annex X) duly filled in
- The latest Development Safety Update Report (DSUR) and/or Periodic Safety Update Report (PSUR) (if you have not already submitted it). The safety information should be mentioned in the DSUR in accordance with ICH E2F guideline on DSUR[7]. Point 3.8.4 is dedicated to "other therapeutic use of investigational drug" and should include clinically important safety information regarding compassionate use programs. The clinical important safety information should be mentioned in the PSUR in accordance with "ICH Topic E2F Note for guidance on PSUR[8]". The PSUR subsection VII.B.5.7.4. "Other therapeutic use of medicinal product" should include clinically important safety information from programs.
- A line listing of SUSARs that are not yet recorded within the DSUR/PSUR to cover the period between the last update of DSUR/PSUR and the cut-off date (see below). Line listings should include SUSARs that occurred worldwide in clinical trials and compassionate use programs with the medicinal product.
- The last version of the Investigators Brochure (IB) unless you have already submitted the IB for a clinical trial application in Belgium and no new version is available.
- Updates of the documents provided in the initial or amended submission (track changes and clean version).

Timelines:
The approval date of the program is the starting point for the cycle of re-evaluation during the program.
The safety reporting should be submitted only if the program is still open for new patients at the following time points:

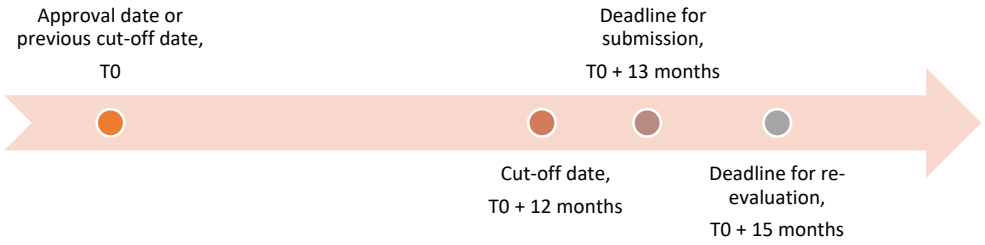
- If no centralized procedure has been submitted for the concerned medicinal product in the concerned indication half-yearly evaluation is planned. The re-evaluation dossier should be submitted between the 6th and 7th month after the approval date or the previous re-evaluation cut-off date. The timeline is as following:

[7] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf
[8] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129136.pdf



The pharmacovigilance deadlines change if a MA is requested during the program for the same medicinal product in the same indication. However the upcoming deadline for pharmacovigilance reporting (6 months after the approval date or the previous re-evaluation cut-off date) is maintained. Annual reporting is planned from then on (see next point).

- If a centralized procedure has been submitted for the concerned medicinal product in the concerned indication annual evaluation is planned. The re-evaluation dossier should be submitted between the 12th and 13th month after the approval date or the previous re-evaluation cut-off date . The timeline is as following:



VII. Registers

Two different registers should be set-up: one central register and one safety register. The applicant (who is the responsible of program) is responsible for the maintenance of these registers that have to be archived at least 10 years after the end of the program.

- Central register

The central register should contain for each patient included in the program:

- The copy of the signed ICF
- The name and National Institute for Health and Disability Insurance (NIHDI/INAMI/RIZIV) number of the treating physician
- The name and address of the patient

This central register should be managed by the responsible physician under the responsibility of the responsible of program.

The main goal of the central register is to ensure the traceability of medicines delivered under the program.
The data from the central register must be coded by the responsible physician. The codes should be used for the set-up of the safety register.
Managing such a register with nominative patient data could raise major deontological and practical/technical issues for companies, as the privacy information which is processed in the framework of the central register goes beyond the processing usually carried out by pharmaceutical companies in Belgium. Therefore the FAMHP accepts a waiver on request to set-up a central register with nominative data of patients. This waiver must be requested at the time of program submission, together with the description of the alternative central register of encoded patient data and the procedure **to ensure the traceability of the medicinal products supplied** under the program. This waiver can only be granted if the applicant does not request a cohort from the NIHDI/RIZIV/INAMI.

- Safety register

This register should contain at least the Suspected Unexpected Serious Adverse Reactions (SUSARs) that took place in all unmet need programs and clinical trials worldwide with the medicinal product for the given indication. Serious adverse drug reactions should be collected in a solicited way. This data processing is separate from the central register and the processing is done on the basis of coded personal data, such that the suspicions can only be can be linked by means of a code to the data recorded in the central register.
Be advised that in case of request for cohort, the NIHDI/INAMI/RIZIV can request an adaptation of recorded data in the safety register.

VIII. Urgent situations

Exceptionally, in urgent cases, a medicinal product without a marketing authorisation can be used without requesting a CUP. It has to be motivated by the fact that a patient is in immediate risk of dying or that the risk of non-treatment is higher than the inherent risks of the treatment.
Additionally the following conditions should be met:
1. The medicinal product in question is not a drug used in a CUP, in a clinical trial (or if the patient could not be enrolled within such a CUP or clinical trial) or/and is not a drug for which a registration or a marketing authorization is not required;
2. The patient cannot be treated with a marketed medicinal product, a product under hospital exemption or with a magisterial preparation;
3. It is impossible to import a marketed medicinal product with the same qualitative and quantitative composition of active drug substance and the same pharmaceutical form (as stated in article 105 of the Royal Decree of 14/12/2006);

4. No submission can be made for a CUP, unless such an application has been made or if you have the intention to submit such a request. If you have the intention to recruit several patients via this urgent situations pathway, you have to apply for a CUP following point II of this guidance.

A **notification** to the FAMHP is strongly recommended. . It is advised that the treating physician checks with the institution's rules if a notification to the local Ethics Committee is needed.

This notification should consist of:

- the name of the sponsor
- the name of the treating physician
- a sworn statement from the physician that the informed consent was obtained in accordance with the law of 22 August 2002 on patient rights
- the indication
- the motivation that without appropriate treatment, it is expected that the patient's death occurs in a short delay or that the risk for the consequences of the absence of treatment is greater than the risk for the consequences of starting the treatment is included. Please discuss the indication of the patient as well as the previous treatments that the patient received, the unmet need and the benefit/risk balance of treatment along with the urgency for this treatment.

Spontaneous safety reports should be submitted via EudraVigilanceHUMAN by the Sponsor/Pharmaceutical company.

IX. Frequently Asked Questions (FAQ)

A FAQ is published and regularly updated on our website.

If you still have a question, you can send it to umn@afmps-fagg.be

X. Abbreviations

CESP	Common European Submission Platform
CUP	Compassionate Use Program
DSUR	Development Safety Update Report
FAMHP	Federal Agency for Medicines and Health Products
FAQ	Frequently Asked Questions
GMP	Good Manufacturing Practices
IB	Investigators Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MA	Marketing Authorisation
MAA	Marketing Authorisation Application

MNP	Medical Need Program
NIHDI/INAMI/RIZIV	National Institute for Health and Disability Insurance (also referred to as INAMI/RIZIV)
UMN	Unmet Medical Need