

Guidance on compassionate use and medical need programs.

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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), can be provided to patients under certain conditions :

- For non-authorized medicinal products this can be done for compassionate reasons ("compassionate use") for a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorization by the centralized procedure (Cfr. article 6 of Regulation 726/2004) or must be undergoing clinical trials for the related indication.
- For products authorized in Belgium, this can be done in cases where a patient has a chronic disease, a disease with a serious impact or a life threatening disease that cannot be treated satisfactory by a product that is authorized for this indication (and commercially available) in Belgium ("medical need programs"). Additional conditions are :
 - o a demand to obtain authorization for the indication in question needs to be in process
 - o or the indication has been authorized but the product is not yet commercially available
 - o or clinical trials are ongoing in this indication or clinical trials have demonstrated the relevance of the use of the medicine in the envisaged indication

Only a single indication can be approved 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 compassionate use program as described in article 106 of the Royal Decree of 14/12/2006 as changed by the Royal Decree of 25/04/2014 (see annex I). A dossier that complies with the requirements as set out below, needs to be submitted to the FAMHP.

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 missing items need to be submitted 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 the T0, additional questions can be sent to the applicant. The applicant will have a maximum of 10 calendar days to respond to the questions. The process timeline is stopped until the applicant's responses have been received.

After a maximum of 55 working days after T0 (excluding the additional days for responses to questions, see above) the request is tacitly approved, or a decision is communicated.

5 working days later, the essential elements of the decision (see below: program information for publication and ICF) are published through the FAMHP's website in case of approval.

B. Content and format of the application

From May 15th until September 30th 2018, there are 2 possible options for submission:

1) By post : only the cover letter is to be submitted in hard copy together with a CD-ROM or USB containing the dossier to the following address :

FAGG-AFMPS
Division R&D – unit “unmet medical need”
Place V. Hortaplein 40,40
1060 Bruxelles/Brussel

2) Via CESP: electronically only and following the process as described in Annex IX: e-submission through the Common European Submission Portal.

However we ask the applicants to only use one of the 2 possibilities for the submission.

From October 1st 2018 only the submission via CESP will be accepted.

Electronic documents should be adequately named and need to allow copying. Applications by other electronic means (e.g. email) will not be 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)
- A proof of payment (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 in French and Dutch (see below)
- A protocol compiling the information regarding the rationale. Please find an example in annex III

1. The medicinal product dossier

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

- If a centralized procedure was submitted for the concerned medicinal product, the same information as mentioned in Regulation 726/2004, article 6

- If not
 - o a pre-submission dossier in line with the requirements for pre-submission applications in the centralized procedure¹; or
 - o relevant quality, non-clinical and clinical data as in the Investigational Medicinal Product Dossier ("IMPD") format as described in the clinical trial guidances². 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 informed consent form
- 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 template in annex IV "summarized information for publication" should be filled in by the applicant as part of the original submission, both in Dutch and French. Explications on the information expected are available as well.

The informed consent form has to be included as well. The FAMHP published templates for informed consent that could be adapted for CUP or MNP. http://www.famhp.be/en/human_use/medicines/medicines/research_development/ethic_committee/templates_inform_med_consent/

Upon approval of the program both the "summarized information for publication" and the informed consent form will be published on the FAMHP's website.

C. Labeling of the unmet medical need medicinal product

The labeling of medicinal products in compassionate use programs needs to be compliant with the requirements as described in GMP 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 labeling in the 3 national languages should be foreseen (Dutch, French, German). Individual waivers on the language regimen can be requested in the cover letter.

¹ See p 4.1 of chapter 4 of volume IV of Good manufacturing product (GMP)

² http://ec.europa.eu/health/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

III. Medical need programs (MNP)

A. Submission

An applicant can apply for a medical need program as described in article 108 of the Royal Decree of 14/12/2006 as changed by the Royal Decree of 25/04/2014 (see annex I). A submission that complies with the requirements as set out below, needs to be submitted to the FAMHP.

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 missing items need to be submitted 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 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 will have a maximum of 10 calendar days to respond to the questions. The process timeline is stopped until the applicant's responses have been received.

After a maximum of 55 working days after T0 (excluding the additional days for responses on questions, see above) the request is tacitly approved, or a decision is communicated.

5 working days later, the essential elements of the decision (see below: program information for publication and ICF) are published through the FAMHP's website in case of approval.

B. Content and format of the application

From May 15th until September 30th 2018, there are 2 possible options for submission:

1) By post : only the cover letter is to be submitted in hard copy together with a CD-ROM or USB containing the dossier to the following address :

FAGG-AFMPS
Division R&D – unit “unmet medical need”
Place V. Hortaplein 40,40
1060 Bruxelles/Brussel

2) Via CESP: electronically only and following the process as described in Annex IX: e-submission through the Common European Submission Portal.

However we ask the applicants to only use one of the 2 possibilities for the submission.

From October 1st 2018 only the submission via CESP will be accepted.

Electronic documents should be adequately named and need to allow copying. Applications by other electronic means (e.g. email) will not be 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)
- A proof of payment (see below)
- The Informed consent form in French and Dutch (see below)
- A protocol compiling the information regarding the rationale. Please find an example in annex VI

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 for the same indication: please mention this in the cover letter. The dossier should not be provided by the marketing authorization holder as we have access to this.
- If no authorization procedure is ongoing, please submit all relevant results from clinical trials.

2. Summarized 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 informed consent form
- 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 template in annex IV "summarized information for publication" should be filled in by the applicant as part of the original submission, both in Dutch and French. Explications on the information expected are available as well.

The informed consent form is to be included as well.

The FAMHP published templates for informed consent that could be adapted for CU or MNP.
https://www.famhp.be/en/human_use/medicines/medicines/research_development/ethic_committee/templates_informed_consent

C. Labeling of the unmet medical need medicinal product

The labeling of medicinal products in medical need programs needs to be the same as the one of the product authorized in Belgium. Nevertheless, a labeling could be added on the package to make a distinction between medicinal product used within a program and others.

IV. Process to include patients in a CU/MN Program

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
- 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 informed consent 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 trial³ 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 as described in art. 106 §5 subsection 6.

³ Website tools : <https://www.clinicaltrialsregister.eu> and <http://clinicaltrials.gov/>

From May 15th until September 30th 2018, there are 2 possible options for submission:

- 1) By post : only the cover letter is to be submitted in hard copy together with a CD-ROM or USB containing the dossier to the following address :

FAGG-AFMPS
Division R&D – unit “unmet medical need”
Place V. Hortapplein 40,40
1060 Bruxelles/Brussel

- 2) Via CESP: electronically only and following the process as described in Annex IX: e-submission through the Common European Submission Portal.

However we ask the applicants to only use one of the 2 possibilities for the submission.

From October 1st 2018 only the submission via CESP will be accepted.

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

The [application form](#) 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 as well as updates of the documents provided in the initial submission (track changes and clean version) and the proof of payment need to be provided. Please refer to chapter VIII for the specifications needed for the fee. The timelines for reviewing amendments are the same as the initial submission of an UMN 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 database⁴.

The sponsor should submit available data to the Unmet Medical Need team at the FAMHP.

From May 15th until September 30th 2018, there are 2 possible options for submission:

- 1) By post : only the cover letter is to be submitted in hard copy together with a CD-ROM or USB containing the dossier to the following address :

FAGG-AFMPS
Division R&D – unit “unmet medical need”
Place V. Hortapplein 40,40

⁴ See section VI.C.6.2.2.1 from module VI of GVP



1060 Bruxelles/Brussel

2) Via CESP: electronically only and following the process as described in Annex IX: e-submission through the Common European Submission Portal.

However we ask the applicants to only use one of the 2 possibilities for the submission.

From October 1st 2018 only the submission via CESP will be accepted.

The submission should be accompanied by the application form (annex VI).

As long as the program is ongoing, 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 requested in the legal framework.

Therefore, depending on the program, the following information on top of the application form duly filled in, should be submitted:

In the context of a Compassionate Use Program (CUP), the safety information will be mentioned in the Development Safety Update Report (**DSUR**) in accordance with ICH E2F guideline on DSUR⁵. Point 3.8.4 is dedicated to “other therapeutic use of investigational drug” and should include clinically important safety information regarding compassionate use programs. A listing of SUSARs that are not yet recorded within the DSUR have to be provided to cover the period between the last update of DSUR and the cut-off date as defined in the line listing requirements of art. 106 §5 alinea 3 of the modified Royal Decree dated 25/04/2014. Nevertheless, if you have already submitted the DSUR one time for the periodic review of the program and no new version is available at the time of the next periodic evaluation, it is not necessary to provide the same DSUR again.

Line listings should include SUSARs that occurred worldwide in clinical trials and compassionate use programs with the medicinal product. If there is no new information in this line listing since the last submission for the periodic review, it is not necessary to provide it again. It is requested to mention it in the cover letter.

The last version of the Investigators Brochure (IB) should accompany this package. Nevertheless, if you have already submitted the IB one time for a clinical trial application in Belgium and no new version is available at the time of the periodic evaluation, it is not necessary to provide the same IB again.

The submission should be accompanied of a cover in which it is expected :

- A summary of new safety issues that could have an impact on the safety of patients

⁵ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf

recruited in the program. The impact on the benefit/risk should be discussed.

- A summary of the current understanding and management of **identified and potential risks**.
- An update on the **status** of the clinical investigation/development program and study results if applicable

In the context of a Medical Need Program (MNP), the clinical important safety information will be mentioned in the Periodic Safety Update Report (**PSUR**) in accordance with "ICH Topic E2F Note for guidance on PSUR⁶". The PSUR subsection VII.B.5.7.4. "Other therapeutic use of medicinal product" should include clinically important safety information from programs.

Nevertheless, if you have already submitted the PSUR one time for the periodic review at the FAMHP and that the same version still applies at the time of new evaluation, it is not necessary to provide it again. It is requested to mention it in the cover letter.

SUSARs that are not already recorded within the PSUR have to be provided to cover the period between the last update of PSUR and the cut-off date as defined in the line listing requirements of art. 108 §5 alinea 3 of the modified Royal Decree dated 25/04/2014.

Line listings should include SUSARs that occurred worldwide including those in this medical need program. The Investigator Brochure will accompany this package if it is not older than 2 years.

The submission should be accompanied of a cover in which it is expected :

- A summary of new safety issues that could have an impact on the safety of patients recruited in the program. The impact on the benefit/risk should be discussed.
- A summary of the current understanding and management of **identified and potential risks**.
- An update on the **status** of the clinical investigation/development program and study results if applicable

Timelines:

Depending on the status of the marketing authorization application, the DSUR or PSUR, IB, and the appropriate line listing should be submitted,

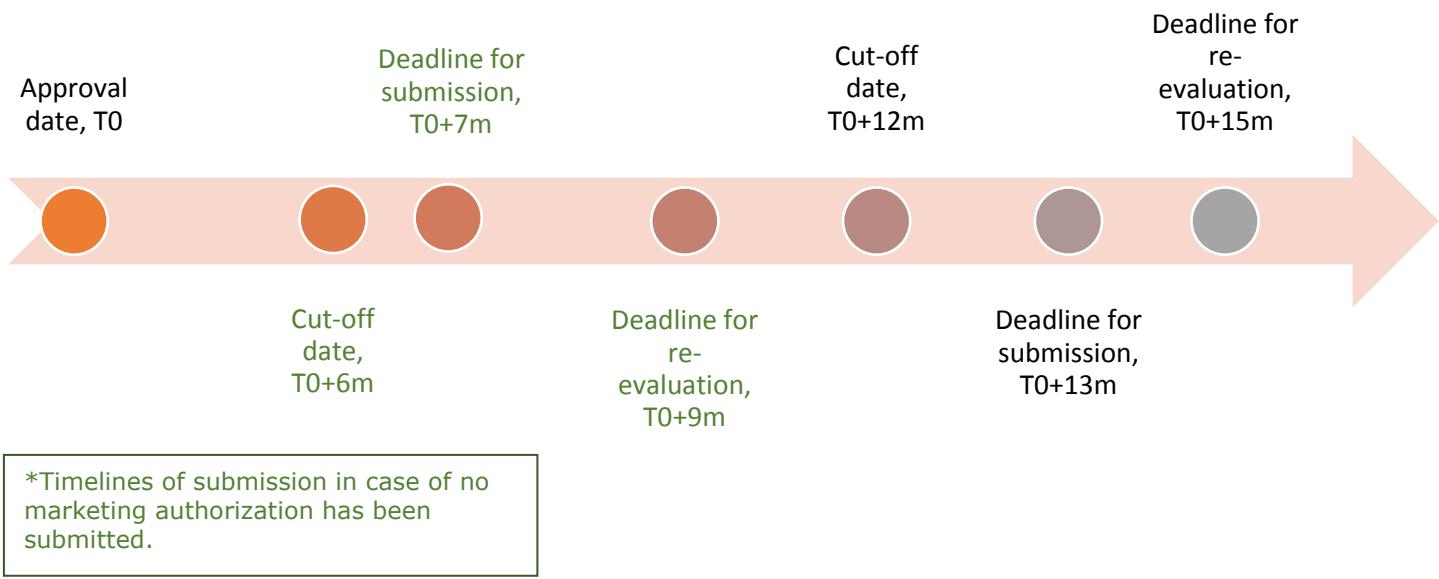
- Between the 6th and 7th month post approval date of the program if no centralized procedure has been submitted for the concerned medicinal product or the concerned new indication; or
- Between 12th and 13th month post approval date of the program if a centralized procedure has been submitted for the concerned medicinal product, or the

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http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129136.pdf

concerned new indication.

The approval date of the program is the starting point for the cycle of re-evaluation during the program.



NB : Cut-off date should be T0 + 6 months for a half-yearly evaluation and T0+12 months for an annual evaluation.

T0 is defined as the approval date or one day after the legal deadline (in case of tacit approval) .

VII. Registers

The new legal framework requests the set-up of two different registers: 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 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 registry 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 data of patients could raise major deontological and practical/technical issues for companies, since the privacy information which is processed in the framework of the central register goes beyond the processing that is usually done by pharmaceutical companies in Belgium. Therefore the FAMHP could accept a waiver upon request for the set-up of a central register with nominative data of the patients with the proposal of an alternative central register (i.e. with coded patient data) in case the applicant will not request for cohort at RIZIV/INAMI. This waiver should be requested at the submission of the pro

gram together with the description of the process to ensure the traceability of the medicines delivered under the program.

- Safety register

This register should contain at least the suspected unexpected serious adverse reaction (SUSAR) 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. These data should be coded and managed independently from the central register.

Be advised that in case of request for cohort, the National Institute of Disability Health Insurance (INAMI/RIZIV) can request an adaptation of recorded data in the safety register.



VIII. Fees

The fees related to submissions as described in articles 106 and 108 of the Royal Decree are defined in a separate Royal Decree (Royal Decree 25/04/2014 – see annex I; changed by the new financing law of the FAMHP 26/03/2018) and needs to be paid on the following account number :

fagg/afmps

IBAN : BE84 6790 0015 1459

BIC : PCHQBEBB

The amounts to be paid are :

Submission type	Fees	Payments communication
Initial request Compassionate use program	18525 EUR	The name of the active substance – CUP
Initial request Medical need program	11296 EUR	The name of the active substance – MNP
Reporting of suspected unexpected serious adverse reactions Compassionate use program	2671 EUR	CUP ASR/SSR (fagg internal reference: CUP -XXXXXX)
Reporting of suspected unexpected serious adverse reactions Medical Need Program	2410 EUR	MNP ASR/SSR (fagg internal reference: MNP-XXXXXX)
Substantial modifications	4635,82 €	UMN Amendment (fagg internal reference: CUP/MNP-XXXXXX)

The applicant is requested to provide the name of the active substance (or medicinal product, if available), together with the letters "CUP" or "MNP" in the payment's communication. For modifications, the identifier "UMN amendment" should be used. Please also add the internal FAMHP number of the program. This will be communicated at the moment of the validation of the program. For payments related to the submission of the annual or biannual pharmacovigilance data, the identifier "CUP ASR/SSR" or "MNP ASR/SSR" is expected. Please also add the internal FAMHP number of the program. For substantial amendments and periodical reporting of adverse reactions, the applicant should be aware that the FAMHP will automatically use the deposit available on the FAMHP's bank account if the fee has not been received within 2 weeks. This is, however, not possible for initial applications. Furthermore, applicants need to be aware that a proof of payment is an essential part of the initial submission package.



IX. Programs submitted before 01st July 2014

Programs submitted before the entry into force of the changed Royal Decree can continue to run under the old regime. Modifications to these programs can be submitted under the old legislation, provided that there are no **major changes**. Typical examples of major changes requiring a new submission under the new legislation would be the addition of new patient populations or the shift in authorization status (compassionate use to medical need). In case of doubt, the FAMHP can be contacted free of charge for a confirmation of the correct steps.

X. Urgent situations

Exceptionally, in urgent cases, a medicinal product which is not available on the market 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 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 in this urgent program, you have to apply for a CUP following point II of this guidance.

A **notification** to the FAMHP and the ethics committee of the site concerned is strongly recommended, but is not required to start the treatment.

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.

XI. 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