



Compassionate Use Programs in Austria

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Introduction

The European legal framework foresees two situations of exceptional application of (as yet) non-licensed medicinal products to patients. Those are „**Compassionate use**” and „**Named Patient Use**”. Reference is made to document “L I236 Information Named Patient Use en.pdf” Information on Named Patient Use in Austria (<https://www.basg.gv.at/en/companies/medicinal-products/compassionate-use-1>).

The scope of this guidance is to detail the definition of the term „Compassionate Use” (CU), and to outline the procedural details for compassionate use applications (CUPs) in Austria.

The purpose of Compassionate Use Programmes is to facilitate access of patients with life-threatening or seriously debilitating disease to as yet unlicensed medicinal products in situations where no alternative therapies are available.

Of note, any English translations of Austrian legal documents are not authorized and therefore not legally binding. The original, legally binding, German text passages are included in the text for reference.

1. Applicability

This guidance outlines the placing on the market within the context of Compassionate Use Programmes (CUPs) according to article 83 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

This Regulation is applicable to medicinal products for human use, which have not been approved or licensed in Austria or other member state or the European Economic area (EEA) and which fulfil the requirements according to article 3 paragraphs 1 and 2 of Regulation (EC) Nr. 726/2004.

2. Definitions and legal Framework

The compassionate use definition is laid down in article 83 of Regulation (EC) No 726/2004.

Article 83 Regulation (EC) No 726/2004 reads:

- (1) By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use.*
- (2) For the purposes of this Article, 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3 (1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life threatening, and who can not be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials*
- (3) When a Member State makes use of the possibility provided for in paragraph 1 it shall notify the Agency.*



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- (4) *When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted. The opinions shall be updated on a regular basis.*
- (5) *Member States shall take account of any available opinions.*
- (6) *The Agency (European Medicines Agency, EMA) shall keep an up-to-date list of the opinions adopted in accordance with paragraph 4, which shall be published on its website. Article 24 (1) and Article 25 shall apply mutatis mutandis.*
- (7) *The opinions referred to in paragraph 4 shall not affect the civil or criminal liability of the manufacturer or of the applicant for marketing authorisation.*
- (8) *Where a compassionate use programme has been set up, the applicant shall ensure that patients taking part also have access to the new medicinal product during the period between authorisation and placing on the market.*
- (9) *This Article shall be without prejudice to Directive 2001/20/EC and to Article 5 of Directive 2001/83/EC.*

This article has been incorporated into the Austrian Medicinal Products Act (AMG). Manufacturers, if they are the sponsor of an authorised clinical trial for the medicinal product concerned, or applicants for a marketing authorisation can apply for a CUP:

§ 8a AMG reads:

- (1) *Arzneispezialitäten, die die Voraussetzungen nach Artikel 3 Abs. 1 oder 2 der Verordnung (EG) Nr. 726/2004 erfüllen, bedürfen keiner Zulassung, wenn das Bundesamt für Sicherheit im Gesundheitswesen unter den in Artikel 83 der Verordnung (EG) Nr. 726/2004 genannten Voraussetzungen eine Genehmigung für deren Inverkehrbringen im Rahmen eines „Compassionate use Programms“ erteilt hat. Das Programm ist für eine **definierte Gruppe von Patienten** festzulegen, die an einer zur Invalidität führenden chronischen oder schweren Erkrankung leiden oder deren Erkrankung lebensbedrohend ist und die mit einer zugelassenen und verfügbaren Arzneispezialität nicht zufriedenstellend behandelt werden können.*
- (2) *Zur Antragstellung auf Erteilung einer Genehmigung nach Abs. 1 berechtigt ist*
 1. *der Hersteller, wenn er Sponsor einer genehmigten klinischen Prüfung für das betreffende Arzneimittel ist, oder*
 2. *der Antragsteller einer Genehmigung für das Inverkehrbringen nach Artikel 6 der Verordnung Nr. 726/2004 für das betreffende Arzneimittel.*
- (4) *Der Inhaber einer Genehmigung für die Durchführung eines „Compassionate use Programms“ hat sicherzustellen, dass die Arzneispezialität den in das Programm eingeschlossenen Patienten auch nach der Erteilung der Genehmigung für das Inverkehrbringen bis zum tatsächlichen Inverkehrbringen zur Verfügung gestellt wird.*



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3. Requirements according to EMA Guideline

Taking into consideration the "Guideline on Compassionate Use of Medicinal Products, Pursuant to Article 83 of Regulation (EC) No 726/2004 (Doc. Ref: EMEA/27170/2006)" the requirements can be summarized as follows:

1. Art 3 para 1 and 2 of Regulation (EC) No 726/2004 has to apply to the medicinal product in question (see 3.1.). Therefore, CUPs are only possible for medicinal products for which an application for centralized approval can be submitted to the European Medicines Agency (EMA). A CUP cannot be applied to a medicinal product, which has already been authorised via the centralised procedure, even if the proposed conditions of use and target population are different from those of the marketing authorisation.
2. Proof that the patients to be treated (Patient group) suffers from a chronically or seriously debilitating disease, or a life threatening disease;
3. **Proof that the patient group cannot be treated satisfactorily by an authorised medicinal product in Europe;**
4. Documentation that the medicinal product is either the subject of an application for a centralised marketing authorisation in accordance with Article 6 of Regulation (EC) No 726/2004 or is undergoing clinical trials in the European Union and/or elsewhere;
5. Generally, the results of a „mature randomised phase III trial“ should be available. If patient safety is guaranteed, this requirement can be handled on a case-by-case approach (appropriate data from Phase II studies);
6. Confirmation that the applicant will make the medicinal product available to patients in the interim time between approval of the marketing authorization application and introduction to the market;
7. Assurance of compliance with pharmacovigilance requirements according to article 24 para 1 and article of Regulation (EC) No 726/2004 in the context of the CUP.

Note: Medicinal Products that may be licensed according to article 3 paragraphs 1 and 2 of Reg. (EC) No 726/ 2004

CUPs can be applied for medicinal products for human use for which either article 3 para 1 of Regulation (EC) No 726/2004 of article 3 para 2 apply.

Article 3 paragraph 2 of Regulation (EC) No 726/2004:

Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, if:

- (a) the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or*
- (b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community level.*

Medicinal products for which a centralized marketing authorization is obligatory are listed in the Annex to Regulation (EC) No 726/2004: This concerns the following medicinal products for human use:



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1. Medicinal products developed by means of one of the following biotechnological processes:
 - recombinant DNA technology,
 - controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
 - hybridoma and monoclonal antibody methods.
2. (Veterinary products).
3. Medicinal products for human use containing a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community, for which the therapeutic indication is the treatment of any of the following diseases:
 - acquired immune deficiency syndrome,
 - cancer,
 - neurodegenerative disorder,
 - diabetes,
 - auto-immune diseases and other immune dysfunctions,
 - viral diseases
4. Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

4. CUP Application in Austria

4.1. General

The application for a CUP can either be submitted at the same time as a Marketing Authorization Application (MAA), or earlier, provided that the applicant commits to the submission of an MAA according to article 6 of Regulation (EC) No 726/2004 in the foreseeable future in writing. The provisional timeframe should be noted.

The conduct of a CUP has to be preceded by a written approval by the Austrian Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen, BASG).

BASG evaluation is based on the requirements of art. 83 of Regulation (EC) No 726/2004, and the framework outlined in the relevant Guidance and Questions & Answers of the European Medicines Agency (EMA):

- Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation (EC) no 726/2004
- Question and Answer document on Compassionate use for centralized medicinal products

These documents are publicly available on the website of the EMA www.ema.europa.eu

The placing on the market of a medicinal product within a CUP is approved by the BASG until regular availability on the national market after granting of the marketing authorisation. The approval of an application is contingent on the provision of a protocol of the intended treatment. In the interest of public health CUP approval can be modified or withdrawn, if the approval conditions are no longer met.



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4.2. Submission

The application for a CUP is to be submitted electronically to the BASG via the following e-mail: compassionate-use@basg.gv.at. Receipt of the submission documents will be confirmed electronically.

Should the information be too extensive for transfer per e-mail, a submission via CESP is possible.

4.3. Fees

With the coming into force of the amended Regulations regarding the Schedule of Fees of the BASG according to the Act on Safety in Health and Food on November 7th 2012, fees have been established for compassionate use applications. The applicable fees are indexed and cited in the Regulation issued by the Federal Office for Safety in Health Care and may be found at this internet site: www.basg.gv.at/en/about-us/fees/

4.4. Requirements

According to § 8a paragraph 2 AMG the applicant for a CUP can either be a manufacturer, if also the sponsor of approved clinical trials for the respective medicinal product, or the applicant for a marketing authorization according to article 6 Regulation (EC) 726/2004 for the respective medicinal product.

The following documents are required for the application:

Treatment protocol

It is the applicant's task to write the treatment protocol for the CUP. The purpose of this document is to provide relevant information on the medicinal product and its indication to the authorities and to treating physicians. Further, the treatment protocol includes the provisions for patient treatment and data collection within the CUP.

The treatment protocol should contain at least the following information:

1. Contact details for the person responsible and, if applicable, the legal representative located within the European Union or a member state of the European Economic Area;
Further, contact details need to be provided for the person to be named on the BASG Website as National contact for the public.
Confirmation from this contact person, and the person responsible for the CUP, is required that the publication of name and contact details on the BASG website does not violate any personal rights with regard to data protection.
2. Name of the medicinal product, declaration of active substance and composition, mode of application, dosing and therapeutic application,
3. Description of the disease and justification that the patients for whom the medicinal product is intended suffer from a chronically or seriously debilitating disease, or a life-threatening disease (definition of target population);
4. Criteria for patient selection and estimate of patient number;
5. Justification, why the patients of the target group cannot be treated satisfactorily with a medicinal product authorized for marketing in Austria; If there are authorized medicinal products available for the indication, it is required to define the target group by addition of a clarification like e.g. "Patients with [disease XY] for whom an alternative



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treatment option with authorized medicinal products is not indicated based on clinical judgement of the treating physician.”

6. Justification, why the patients of the target group cannot be included in a currently active clinical trial;
7. Justification and data illustrating the safety and efficacy of the medicinal product in the proposed indication, generally through the provision of results of pivotal clinical trials,
8. Details on
 - a) the approved pivotal clinical trial with the medicinal product in the proposed indication referenced by its EU CT number or the previously assigned EudraCT number, or
 - b) the approved pivotal clinical trial of the medicinal product in the proposed indication in a third country and proof that this trial has been conducted according to the internationally harmonized requirements of Good Clinical Practice (GCP), or
 - c) the marketing authorization application submitted to EMA;
9. The demands on the medical facilities and the qualifications of participating physicians;
10. Criteria leading to the interruption or early termination of the CUP;
11. If an application for marketing authorization of the medicinal product has been refused, withdrawn, revoked or suspended, or if the approval of a clinical trial has been refused, withdrawn, revoked or suspended, the reasons for the respective decisions must be given. The applicant must explain why, despite these facts, a CUP for this medicinal product appears to be justified in Austria.
12. Description of which data is collected within the framework of the CUP
13. The commitment that pharmacovigilance requirements will be fulfilled according to articles 24 and 25 of Regulation (EC) 726/2004 and that safety related information collected in the CUP will be integrated in the DSUR/annual safety report and submitted to the BASG. The pharmacovigilance requirements for use under the CUP are therefore the same as those for drugs with marketing authorization.

Further documents:

1. Patient information and consent form:
All information and documents that patients receive within the framework of the CUP must be submitted in German. The consent to treatment within the framework of the CUP must be documented after the physician has informed the patient, usually by means of a dated signature of the patient and the informing physician on a declaration of consent, which is to be provided in addition to the documentation obligation according to the valid version of the Medical Act;
2. List of currently approved CUPs in other member states of the European Union or the EEA (if applicable) and, when available, the opinion of the Committee for Human Medicinal Products (CHMP) according to article 83 of Regulation (EC) No 726/2004;
3. Latest version of the Investigator's Brochure, and if applicable, the draft Summary of Product Characteristics (SmPC) provided in the marketing authorization application.;
4. Manufacturing documentation (IMPD), including a statement by a qualified person according to § 7 Arzneimittelbetriebsordnung (AMBO) that the medicinal product has been manufactured according to the principles and requirements of Good Manufacturing Practice. In cases where the medicinal product previously has been assessed as part



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of a BASG procedure, reference to the documentation of that procedure is sufficient, taking potential updates into consideration.

4.5. Exceptional case of compassionate use with a medicinal product fulfilling the definition of a genetically modified organism

In case of CUP with a medicinal product fulfills the definition of a genetically modified organism according to § 4 of the Austrian Gene Technology Act (Gentechnikgesetz, GTG), the requirements of both the AMG and the GTG apply, in particular, §74 on the use of GMOs for therapeutic purposes.

Further information on the submission can be found on the website

<https://www.verbrauchergesundheit.gv.at/gesundheit/gentechnik/gvo/gvotherapie.html>

5. Assessment of applications and approval procedure

The application documents form the basis of the evaluation. In particular, the quality, safety and efficacy of the medicinal product in the proposed target population are verified through the dossiers provided.

Generally, the efficacy of a medicinal product should be supported by results from randomized phase III studies, but adequate results from phase II or subgroup analysis of phase III studies might also be acceptable. The safety for participating patients is to be ensured through the provision of all data that have potential relevance for the CUP, including the most recent annual safety report for clinical trials in DSUR format.

5.1. Initiation of the CUP / Rejection

1. The BASG will confirm the valid submission and date of the CUP application electronically. The applicant will be requested to submit additional documents, if the information submitted is incomplete or if the application does not meet all criteria for CUP approval. In such cases, a confirmation of receipt will be issued after the relevant requested information is received.
2. **The CUP can be initiated upon receipt of the positive notification by the BASG**
3. A CUP application will not be approved, if the prerequisites for the conduct of CUP are not fulfilled. If compassionate use requirements cease to be met, the BASG can withdraw CUP approval (e.g. change in benefit-risk). The interdiction of a CUP will only be issued after contact with the applicants.

5.2. Duration of validity of CUP approval

1. A CUP approval is valid until availability of the medicinal product on the market unless terminated early or stopped by the agency, or by premature termination by the "CUP-Sponsor".
2. CUP approval is contingent on the obligation to submit DSURs. These DSURs should be submitted via compassionate-use@basg.gv.at or CESP. Information of national interest concerning the ongoing CUP (e.g. number of Austrian patients treated) should be included in the cover letter of this DSUR submission. It should be noted that non-compliance regarding DSUR submission might result in interdiction of the CUP. In case of a negative change in the benefit/risk a CUP can be interdicted by the agency anytime.



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3. This DSUR assessment is currently included in the fee for CUP.

5.3. Publication

Approved CUPs will be listed on the BASG Homepage and the BASG will inform EMA on these approvals.
<https://www.basg.gv.at/en/companies/medicinal-products/compassionate-use-1>

6. Reporting obligations during CUPs

1. It is the obligation of the holder of the CUP to:
 - a. document and electronically submit every suspected serious adverse reaction, that has been communicated to CUP holder by participating physicians or other ways as soon as possible, at the latest within 15 days to the Eudravigilance Postmarketing module;
 - b. immediately submit substantial amendments of the submitted documents to the BASG, i.e. those with potential impact on patient safety, via compassionate-use@basg.gv.at and to include all relevant information;
 - c. immediately notify a premature termination of a CUP to the BASG including the justification for this measure
 - d. submit annual safety reports (DSURs)
 - e. submit a final safety report (DSUR) to the BASG after finalisation of the CUP;
 - f. immediately notify BASG of any new assessments according to article 83 paragraph 4 Regulation (EC) No 726/2004 and newly generated knowledge relevant for patient safety from CUPs approved in other European member states of member state of the EEA.
2. Intended changes of the target population, dose or formulation of the medicinal product within the CUP require confirmed BASG acknowledgement prior to implementation.
3. The applicant is obliged to communicate emerging risks associated with the medicinal product to the BASG immediately and to ensure that measures for risk mitigation are taken immediately.

7. Responsibilities of the CUP holder

The holder of an approved CUP has to ensure

1. that CUP implementation follows the relevant requirements;
2. that all conditions and limitations in the context of the safe and efficacious administration for the medicinal product are followed and that the persons involved receive the relevant information
3. that the medicinal product is supplied with adequate labelling
4. that the manufacture and release of the medicinal product have been conducted according to the requirements for investigational products according to the AMG and AMBO
5. that pharmacovigilance requirements are fulfilled according to articles 24 and 25 of Regulation (EC) 726/2004



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6. that the essential documentation associated with the CUP are archived for at least 15 years after the finalization or early termination of a CUP. This has no bearing on other requirements associated with the archiving of medical documentation
7. that the medicinal product provided in the CUP is also made available to patients after licensing prior to introduction to the market. (§ 8. 1a paragraph 4 AMG). It should be noted, however, that according to the current legal interpretation in Austria, no further patients may be treated under the approved CUP once marketing authorisation has been granted.

8. Involvement of the European Medicines Agency (EMA)

8.1. Fulfilment of requirements

Contacting the EMA is suggested in case of doubts whether a given medicinal product is eligible for a centralized marketing application

The BASG will inform the EMA on CUPs approved and terminated in Austria according to article 83 para 3 of Regulation (EC) 726/2004. Therefore, the holder of an approved CUP does not need to inform the EMA.

8.2. CHMP Opinion

The EMA Committee for Medicinal Products for Human Use (CHMP) is authorized to provide opinions on applications for compassionate use programmes for medicinal products in clinical trials or undergoing a MAA according to article 83 paragraph 4 Regulation (EC) 726/2004. These opinions will be reviewed regularly and can be found on the EMA Website.

This is based on the legal text of article 83 para 4:

When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted. The opinions shall be updated on a regular basis.

The BASG will take CHMP opinions into consideration during the application procedure.

9. Import of medicinal products in the context of a CUP

Medicinal products that are shipped to or imported into Austria in the context of an approved CUP are exempted from the requirements of the Medicinal Products Importation Act (Arzneiwareneinfuhrgesetz 2010, BGBl. I No 79/2010), according to article 11 para 1.3. Therefore, no shipment notification or import application to the BASG is required.

10. Advertising

The AMG permits „advertising“ only in the context of „advertising for licensed or registered medicinal products“ Advertising is defined as measures to promote information, market investigation and cultivation and the creation of incentives to promote the prescription, dispensing, sale or use of medicinal products.



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11. Switching from Compassionate Use to Marketing

The medicinal product must be made available to the patients included in the CUP even after the marketing authorisation has been granted until it is actually placed on the market (Section 8.1a para. 4 AMG). It should be noted, however, that according to the current legal interpretation in Austria, no further patients may be treated under the authorised CUP once marketing authorisation has been granted.

Once marketing approval is granted for a medicinal product with an existing CUP in Austria, the authorization holder is required to inform the BASG on the actual availability of the product on the Austrian market. This date will be considered as the termination date for the CUP. The termination message is sent via compassionate-use@basg.gv.at.

12. Demarcations

12.1. Compassionate Use versus Named Patient Use (= Heilversuch)

As noted at the beginning, the definition for named patient use is found in article 5 of directive 2001/83/EC.

A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive (2001/83/EC) medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.

This text has been translated into National Law in § 8 article 1 (2) AMG:

§ 8. (1) Arzneispezialitäten bedürfen keiner Zulassung, wenn ...

2. ein zur selbständigen Berufsausübung im Inland berechtigter Arzt, Zahnarzt oder Tierarzt bescheinigt, dass die Arzneispezialität zur Abwehr einer Lebensbedrohung oder schweren gesundheitlichen Schädigung dringend benötigt wird und dieser Erfolg mit einer zugelassenen und verfügbaren Arzneispezialität nach dem Stand der Wissenschaft voraussichtlich nicht erzielt werden kann

In contrast to compassionate use programs that apply to a group/cohort of patients, named patient use, as the name implies, refers to a single individual. Named patient use in Austria does not require agency notification or approval and lies in the sole responsibility of the treating physician.

For additional information see the website (L_I236_Information about Named Patient Use in Austria_en_01.pdf at <https://www.basg.gv.at/en/companies/medicinal-products/compassionate-use-1>)

12.2. Compassionate Use versus Clinical Trials

From a methodological point of view, clinical trials are practically the only means of obtaining reliable and interpretable efficacy and safety data for a medicinal product. Although safety data may be collected during compassionate use programs, such programs cannot replace clinical trials for investigational purposes.

Therefore compassionate use should not slow down the implementation or continuation of clinical trials intended to provide essential information relative to the benefit/risk balance of a medicinal product.



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Patients should always be considered for inclusion in clinical trials before being offered CUPs.

Compassionate use cannot be considered as the means to extend treatment of patients whose therapy was initiated in the context of a clinical trial, if systematic data collection on efficacy is envisaged. The evidence level of data obtained in a CUP framework is not equal to that of systematically collected data in the Good Clinical Practice Framework of clinical trials. In the described scenario, the applicant should therefore first consider extending the given clinical trial by a substantial amendment.

However, if patient treatment rather than data collection is the primary focus, the options of named patient use (§ 8 Art. 1 (2) AMG) or a CUP can be considered.

13. References

BASG/AGES

www.basg.gv.at

www.ages.at

Relevant legal documents

<https://www.basg.gv.at/en/about-us/legal-basis>

Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz

<https://www.sozialministerium.at/>

European Medicines Agency

www.ema.europa.eu

International Conference on Harmonisation (ICH)

www.ich.org