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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON COMPASSIONATE USE OF MEDICINAL PRODUCTS, PURSUANT TO ARTICLE 83 OF REGULATION (EC) No 726/2004

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. INTRODUCTION

Article 6 of Directive 2001/83/EC[1] requires that medicinal products are authorised before they are marketed in the Community. Unauthorised medicinal products may be available through an approved clinical trial protocol. A treatment option for patients in the European Union suffering from a disease for which no satisfactory authorised alternative therapy exists or who cannot enter a clinical trial, may be the use of an unauthorised medicinal product in a compassionate use programme.

Compassionate use programmes are intended to facilitate the availability to patients of new treatment options under development.

National compassionate use programmes, making medicinal products available either on a named patient basis or to cohorts of patients, are governed by individual Member States (MS) legislation.

2. LEGAL BASIS AND PURPOSE

Recital 33 of Regulation (EC) No 726/2004[2] states that "In order to meet, in particular, the legitimate expectations of patients (…) a common approach should be followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under MS' legislation".

Article 83 (1) of Regulation (EC) No 726/2004 introduces the legal framework for the provision of compassionate use in the European Union for medicinal products that are eligible to be authorised *via* the Centralised Procedure, stating that "by way of exemption from Article 6 of Directive 2001/83/EC, MS may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and 3(2) of Regulation (EC) No 726/2004 available for compassionate use".

Compassionate use implementation remains the competence of a MS. Article 83 of Regulation (EC) No 726/2004 on compassionate use is complementary to national legislations and provides an option to MS who wish to receive a CHMP opinion regarding the conditions for compassionate use of a specific medicinal product which falls within the scope of Article 83(1) and 83(2).

The objectives of article 83 are to:

- Facilitate and improve the access of patients in the European Union to compassionate use programmes,
- Favour a common approach regarding the conditions of use, the conditions for distribution and the patients targeted for the compassionate use of unauthorised new medicinal products,
- Increase transparency between MSs in terms of treatment availability.

This document aims to provide guidance on the criteria and the procedure for using the possibility provided for in article 83 (1) of Regulation (EC) No 726/2004. It should be read in conjunction with article 5 of Directive 2001/83/EC, as well as the respective MS's legislation, as the case may be.

3. SCOPE AND GENERAL PRINCIPLES

The use of Article 83 is applicable to unauthorised medicinal products for human use falling within the scope[3] of articles 3(1) and 3(2) of Regulation (EC) No 726/2004, without prejudice to the subsequent marketing authorisation route as required or permitted by that Regulation.

In addition, as stated in Article 83 each of the following specific criteria should be fulfilled:

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

[2] OJ L 136, 30/4/2004 p. 1 – 33. 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.

[3] Guideline on Therapeutic areas within the mandatory scope of the Centralised Procedure for the evaluation for Marketing Authorisation Applications with reference to Article 3 and Point 3 of Annex of regulation (EC) No 726/2004 (EMEA/282954/2005).

- The medicinal product is to be made available to "*patients with a chronically or seriously debilitating disease, or a life threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product*" in the European Union,
- The compassionate use programme is intended for a "*group of patients*",
- 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 or elsewhere.

As a consequence, Article 83 is not applicable to:

- Medicinal products which are not eligible for the Centralised Procedures,
- Compassionate use on a named patient basis (as meant in Article 5 of Directive 2001/83/EC),
- 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. The recommendations for use of a medicinal product between a CHMP opinion for compassionate use and CHMP opinion for marketing authorisation, then between opinion for marketing authorisation and Commission Decision and its subsequent placing on the market, are described in chapter 6.

However, the existence of a Community authorisation for a medicinal product is without prejudice to any national legislation relating to compassionate use.

Compassionate use *versus* clinical trials

Article 83 (9) of Regulation (EC) No 726/2004 states that Article 83 "shall be without prejudice to Directive 2001/20/EC[4]". 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 programmes, such programmes cannot replace clinical trials for investigational purposes. Compassionate use is not a substitute for properly conducted trials. Compassionate use should therefore 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.

Patients should always be considered for inclusion in clinical trials before being offered compassionate use programmes.

Compassionate use *versus* off-label use

In this guideline, compassionate use does not refer to the use of an authorised medicinal product for an indication different from the one mentioned in section 4.1 of the summary of product characteristics (SPC), i.e. off-label use.

Other principles and definitions

- "*Group of patients*" can be interpreted as any set (i.e. more than one) of individual patients that would benefit from a treatment for a specific condition. The terms "*cohort*", "*collective use*", "*patient group prescription*" or "*special treatment programme*" used in some MSs, in accordance with national legislations, may correspond with this concept. The possibility of using an unauthorised medicinal product for compassionate use on a named patient basis (Article 5 of Directive 2001/83/EC) does not fall under the scope of Article 83.
- "*Chronically or seriously debilitating disease or whose disease is considered to be life threatening":* The severity of the disease, i.e., its chronically or seriously debilitating, or life-threatening nature needs to be justified, based on objective and quantifiable medical or epidemiologic data. Whereas a life-threatening condition is relatively easily recognisable, definitions of what conditions are chronic and seriously debilitating should consider aspects as

[4] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

regards the condition is associated with morbidity that has substantial impact on patients' day-to-day functioning and will progress if left untreated. Typical examples are cancer, HIV/AIDS, neurodegenerative disorders and auto-immune diseases. Chronic or serious debilitation, or fatal outcome should be a prevalent feature of the target disease.

- "*An authorised medicinal product*", as used in Article 83 (2), means a product authorised nationally (national, decentralised or mutual recognition procedures) or by the Community (Centralised Procedure), in the MS(s) where compassionate use is envisaged.
- "*Patients who cannot be treated satisfactorily*", as used in Article 83 (2), means patients left without treatment options or patients whose disease does not respond or relapses to available treatments, or for whom the treatments are contraindicated or inadequate. Whether patients can be treated satisfactorily or not, will be assessed by the CHMP based on the review of diagnostic, preventive or therapeutic medicinal products authorised, and on the justifications as to why the medicinal products reviewed are not considered satisfactory for the treatment of the patients' disease.
- In this guideline, the term "company" should be understood as meaning "*the manufacturer or the applicant*" as referred to in paragraph 4 of Article 83 of Regulation (EC) No 726/2004 and denotes the person responsible for providing the scientific file to the CHMP for assessment of the compassionate use of a medicinal product under article 83 of the Regulation. This person is either "*a marketing authorisation applicant*" if a centralised marketing authorisation is being submitted, or "*a manufacturer*" if the medicinal product concerned is not the subject of an application for a centralised marketing authorisation.
- "*Conditions for distribution*" are not defined in the pharmaceutical legislation and are therefore understood as the conditions or restrictions regarding the supply and use of the medicinal product, as provided for in Article 9(4)(b) and Article 14(10) of Regulation (EC) No 726/2004. The conditions specify whether or not the medicinal product is subject to medical prescription, or whether it is subject to special or restricted medical prescription.

  The conditions for distribution do not cover the strategy for supplying the medicinal product in the MSs (e.g. quantity of product, choice of MSs).
- "*Patients targeted*" is the restricted population (including age groups), as identified by the CHMP, that would benefit from the treatment for compassionate use.
- "*Conditions for use*" are recommendations for health professionals on how to administer and to use the medicinal product safely and effectively. These recommendations include relevant information on the clinical, pharmacological, pharmaceutical properties of the medicinal product and on the conditions for patient monitoring.

4. INITIATION AND REQUEST OF CHMP OPINION

When a MS envisages the need to make a medicinal product, as defined in paragraph (1) and (2) of Article 83, available for compassionate use, the Competent Authority of that MS must notify the EMEA.

For medicinal products belonging to the categories referred to in Article 3(2) of Regulation (EC) No 726/2004 (the so-called "optional scope"), the EMEA shall only be notified when the eligibility to the Centralised Procedure has been already confirmed by the CHMP.

When notifying the EMEA, MSs may indicate whether they consider that a CHMP opinion on the conditions for compassionate use would be of interest.

Companies should not directly contact the EMEA to request a CHMP opinion. However, companies may, at their own initiative, inform the EMEA of compassionate use applications in MS(s), or of an ongoing procedure for compassionate use at national level. The EMEA may then contact the relevant MS(s) for information only.

5. CHMP OPINION FOR COMPASSIONATE USE

Further to notification (and possible request) by MS(s), the CHMP may adopt an opinion on the conditions for use, the conditions for distribution and the patients targeted for compassionate use in a given therapeutic indication. CHMP opinions are not binding on MSs, however, MSs shall take account of any available opinions.

Adopted opinions are applicable to any subsequent notifications from another MS concerning the same programme.

Grounds for assessing a request for compassionate use

The grounds for triggering a CHMP assessment are based on the principle laid down in Recital 33 of Regulation (EC) No 726/2004, where a *common approach* should be followed whenever possible, as regards the criteria and the conditions for compassionate use. In this context, to consider assessing, the CHMP will check the following:

- The criteria listed in paragraphs 1 and 2 of Article 83 are met,
- A MS has notified the EMEA and requested a CHMP opinion, or,
- If more than one MS have notified the EMEA of their use of Article 83 for the same compassionate use programme, without an explicit request for a CHMP opinion, the CHMP will consider whether, in the interest of patients, there is a need to provide an opinion.

Information to the company

Whenever the CHMP considers that there is a need to provide a CHMP opinion on compassionate use, the EMEA will inform the company.

Documentation to be supplied

When they notify the EMEA, MS(s) may have already collected and assessed data following a request for compassionate use. In other situations, MS(s) may have notified the EMEA and asked for a CHMP opinion in accordance with Article 83, without having yet collected or assessed data. If a CHMP opinion is to be adopted, the CHMP should use any relevant data provided by the MS(s) or available in the public domain, and any existing MS(s)' assessment(s) on the quality, safety and efficacy of the medicinal product, the comprehensiveness of which will depend of the stage of development of the product. After consulting the company, the CHMP may request additional data.

Detailed justifications should be provided to support the claim that the medicinal product meets the criteria listed in Article 83(2), in accordance with the definitions provided in this guideline.

The scientific data submitted should allow evaluation of the conditions for use of the medicinal product, for the intended target population, in the context of compassionate use. In terms of efficacy, the assumptions for compassionate use may be based on mature randomised phase III trials (e.g. in case of parallel assessment of compassionate use and application for marketing authorisation). However, acceptable assumptions may rely on promising early data observed in exploratory trials (e.g. uncontrolled phase II trials). In terms of safety, submission of all available data, which may contribute to refinement of the conditions for use defined in the opinion, is encouraged.

Pharmacovigilance

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 24(1) and 25 of the Regulation referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted.

Update of opinions

The legislation requires the Agency to update CHMP opinions on compassionate use on a regular basis. Updates of CHMP opinions may be triggered by MS(s) on their request, or whenever considered appropriate by the Committee based on available data or data provided by the MS(s) or companies (e.g. new safety data).

The CHMP shall coordinate multiple MS(s) requests, if appropriate, in order to avoid excessive numbers of CHMP opinion updates.

Following a CHMP opinion on compassionate use, the company may provide further information or request a hearing with the CHMP to provide new information or express disagreement with the terms of the CHMP opinion.

6. FROM OPINIONS ON CONDITIONS OF COMPASSIONATE USE TO OPINIONS ON MARKETING AUTHORISATIONS

Once a medicinal product for which a CHMP opinion on the conditions for compassionate use exists, has received a CHMP opinion for a marketing authorisation, its opinion for compassionate use may be updated taking into account the marketing authorisation opinion, where appropriate (e.g. safety recommendations). Once a medicinal product has been authorised, updates of compassionate use opinions are no longer required and reference is made to the relevant information published on the EMEA website about the authorised product.

Where a compassionate use programme has been set up in a MS, the company shall ensure that patients taking part in the programme have access to the medicinal product during the period between the granting of the centralised marketing authorisation and its placing on the market.

7. TRANSPARENCY

In accordance with Article 83 (6) of Regulation (EC) No 726/2004, the EMEA is responsible for keeping an up-to-date list of the opinions adopted on a public register available on the EMEA website.

The information available on the register includes:

- MS(s) having notified the EMEA

- the name of the medicinal product for compassionate use,

- the active substance,

- dosage(s) and pharmaceutical form(s),

- the conditions of use,

- the conditions for distribution,

- the target population,

- the name and contact details of the company,

- the date of the CHMP opinion for compassionate use,

- the date of the CHMP opinion and Commission decision on marketing authorisation, where relevant,

When relevant, each product is electronically hyperlinked to the following information:

- Before an opinion for marketing authorisation is given:
  - the summary of CHMP opinion on compassionate use
- After an opinion or a decision for marketing authorisation is given:
  - the relevant documents published on the EMEA website for medicinal products authorised according to the Centralised Procedure (e.g. EPAR).

8. FEES FOR COMPASSIONATE USE

The fee payable for an opinion on a medicinal product for compassionate use shall be deducted from the fee payable to the EMEA for an application for a marketing authorisation for the same medicinal product, where such application is submitted by the same company (see Council Regulation No 297/95 as amended on the fees payable to the European Medicines Agency and Rules of implementation and other measures- EMEA/MB/356866/2005).

Companies that have been assigned small and medium enterprise (SME) status by the Agency are eligible for a 90% reduction in the scientific service fee (which includes opinions on medicinal products for compassionate use), see Commission Regulation (EC) No 2049/2005 which lays down the rules regarding the payment of fees to, and the receipt of administrative assistance from, the EMEA by SMEs. See also the specific provision in Article 7.1(c) of this Regulation.