EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

STAMP 4/22

STAMP Commission Expert Group
10 March 2016

Subject: Compassionate use programmes

Agenda item 6

Compassionate use is a treatment option that allows the use of an unauthorised medicine for patients who have a disease with no satisfactory authorised therapies or who cannot enter a clinical trial**.** They are intended to facilitate the availability to patients of new treatment options under development.

Article 5(1) of Directive 2001/83/EC provides a legal basis to the Member States to supply unauthorised medicines in response to unsolicited requests for individual patients.

Regulation (EC) No 726/2004 recognises that in the field of medicinal products for human use, a common approach should also be followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under Member States' legislation. Under Article 83 the Regulation provides the possibility for Member States to make available for compassionate use medicinal products that are the subject of a marketing authorisation application or undergoing clinical trials.

In addition, the EU legislation requires under Article 83 of Regulation (EC) No 726/2004 that when a Member State makes use of this possibility they shall notify the European Medicines Agency (EMA) and provides the possibility for Member States to ask the EMA's Committee for Medicinal Products for Human Use (CHMP) to provide an opinion to all EU Member States on the conditions of use, the conditions for distribution and the patients targeted.

To facilitate the implementation of Article 83 of Regulation (EC) No 726/2004, EMA has developed a guideline on compassionate use of medicinal products[1].

For the purposes of the STAMP meeting, EMA has prepared an analysis annexed to this note on the experience of Article 83 compassionate use opinions at EMA.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf

The experience of EMA shows that that few Member States appear to notify the EMA about nationally implemented Compassionate Use Programmes (CUPs) intended for a group of patients. Furthermore, of those that notified to the Agency about CUPs, a CHMP Opinion on Compassionate Use was only requested 5 times[2].

EFPIA will present to the STAMP industry's experience with Article 83 of Regulation (EC) No 726/2004 in particular with daclatasvir and lessons learned.

A recent white paper authored by Bristol-Myers Squibb (BMS) and endorsed by EFPIA on the recent experience and learning of Article 83 implementation for daclatasvir discusses a number of measures which could improve the current use of CUPs in Europe. Several other papers (see references below) discuss the need for CUP and their implementation. The overall conclusion is that the intended common approach to CUP has not been achieved and that there are many differences in CUP among Member States.

The STAMP members are invited to reflect whether, within the existing legal framework and respecting the relevant national legislations, the use of compassionate use could be optimised in the EU for the interest of seriously ill patients who have no other treatment options. Based on the literature and input from EMA the following questions were identified to help structure the discussion of the group. Other questions or suggestions are welcome.

Points for discussion at STAMP	
1. Are MS aware of the obligation to notify the EMA about CUP at national level intended for a group of patients?	• Would a standardised template be useful for sending notifications to EMA by MS on CUPs (i.e. what information to send)
2. What are the constraints for the use of compassionate use programmes, at national and EU level?	• Which MS have a framework to support cohort CUPs and which are the difficulties in establishing one? • Would you consider it helpful to streamline the Article 83 application process by developing application standards, scientific guidelines and templates e.g. for submission and evaluation of compassionate use requests? • What are the main challenges for implementing CUP?
3. What are the benefits of CHMP compassionate use opinion?	• Does it facilitate patient 'access' in MSs and if so, how? • If yes to the above why is it not requested more often? • If no to the above, what other aspects of Article 83 could the CHMP consider to improve patient 'access' to CUP in your MS?

[2] see EMA website on Compassionate Use:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac058007e691

4. Is there scope for more systematic data gathering and information sharing on safety and efficacy between national regulatory authorities and EMA?	• Would an agreed mechanism for collection of data (safety and efficacy) be useful?
5. Is there a need to increase transparency on compassionate use on EU level?	• Understand the MS requirements of setting up CUP (named patient use and/or cohort of patients) • Support availability of key information on compassionate use requirements (e.g. naming conventions, ethics, informed consent, reporting, review times, etc) in MS (e.g. comparative table) published on EMA website with links to NCA? • Proposal to publish which MSs have implemented CUPs (with or without CHMP Opinion)
6. Need for dialogue on CUP amongst sponsors, regulators, prescribers and patients?	• Opportunity to discuss pan-European experience of CUPs to identify areas for further improvement, by involving all stakeholders
7. Could compassionate use be combined with other regulatory tools and schemes to facilitate timely access for patients with unmet medical needs?	• Could, for example, an investigational medicinal products meeting PRIME criteria be considered for compassionate use? or • Could Article 83 and accelerated assessment be combined since both tools concern medicines for patients with a chronically or seriously debilitating disease, or a life threatening disease, for which there is no alternative treatment available in the EU?

Additional information

Brizmohun N. Five Times In 10 Years: EMA Investigates Poor Uptake Of Compassionate Use Scheme. Scrip Regulatory Affairs, 25 Nov 2015 (published on http://www.rajpharma.com/home/)

Ericson M, Akers C. Named patient and other compassionate use schemes in Europe: far from a single market. Scrip Regulatory Affairs, 27 April 2012 (published on http://www.rajpharma.com/home/)

Hyry H I *et al*. Compassionate use of orphan drugs; Orphanet J. of Rare Dis 2015, Aug 21;10:100 (http://ojrd.biomedcentral.com/articles/10.1186/s13023-015-0306-x)

Rahbari M, Rahbari NN. Compassionate use of medicinal products in Europe: current status and perspectives. Bull World Health Organ. 2011 Mar 1;89(3):163 (http://www.who.int/bulletin/volumes/89/3/10-085712/en/)

Sou H. EU Compassionate Use Programmes (CUPs). Regulatory Framework and Points to Consider before CUP Implementation. Pharm Med. 2010, Aug 24;4:223-229 (http://voisinconsulting.com/sites/default/files/2010_Pharma%20Medecine%20Journal_Helene%20Sou.pdf)

Whitfield K *et al*. Compassionate use of interventions: results of a European Clinical Research Infrastuctures Network (ECRIN) survey of ten European countries; Trials 2010, Nov 9;11:104 (http://www.trialsjournal.com/content/11/1/104)

European Medicines Agency webpage on compassionate use accessed 29 February 2016: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp

Non-published references

Rupalla K, Iglesias-Langer V. White paper on Article 83 on compassionate use of Regulation (EC) No 726/2004. Recent Bristol-Myers Squibb (BMS) experience and learning's from daclatasvir.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annex
STAMP 4/22

1 March 2016
EMA/166084/2016
Human Medicines Research and Development Support Division

Analysis on the experience of Article 83 compassionate use opinions at EMA

Introduction

Compassionate use is a mechanism that enables health care professionals in a European Member State (MS) to provide access to investigational products to patients with serious or life-threatening conditions who have no satisfactory alternative treatment options outside clinical trial setting, i.e. investigational products that have not yet been authorised by regulatory authorities.

Regulatory and Legal Framework

The European legal framework foresees two situations of exceptional application of a non-licensed medicinal product to patients. Those applicable for a cohort (group) of patients and "Named Patient Use" (also referred to as Named Patient Programme, NPP).

According to Article 6 of directive 2001/83/EC, a medicinal product may not be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State or an authorisation has been granted through a centralized procedure.

Article 5 of Directive 2001/83/EC defines an exception to this requirement under defined circumstances.

Article 83 of Regulation (EC) No 726/2004 provides the possibility for a MS to make a medicinal product for human use belonging to the categories referred to in Article 3 paragraphs 1 and 2 of Regulation (EC) No 726/2004 available for compassionate use to a group of patients and for the CHMP to adopt opinions on the conditions for use, conditions for distribution and the patients targeted. The use of Article 83 is applicable to unauthorised medicinal products for human use and which are either the subject of an application for marketing authorisation via the centralised procedure or undergoing clinical trials. Article 83 is not applicable to compassionate use on a named patient basis.

If a Member State makes use of the possibility for compassionate Use for product subject to the Regulation (EC) No 726/2004, it is requested to notify the EMA.

The EU legislation also allows for the option of a Member State to ask the Committee for Medicinal Products for Human Use (CHMP) to provide an opinion on the conditions for use, conditions for distribution, as well as the target patient population. CHMP opinions are not binding on MSs, however, MSs shall take account of any available opinions.

Analysis of experience to date

Since the introduction of Article 83 with Regulation (EC) No 726/2004, the CHMP adopted scientific opinions (5 in total) for compassionate use opinion for two conditions (hepatitis C and influenza) as shown in Table 1.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5510
Send a question via our website www.ema.europa.eu/contact

Table 1.

INN Dose	Request by Target population	Date of CHMP Opinion on CU Date of MA
ledipasvir, sofosbuvir 90 / 400 mg film-coated tablets	Ireland Ledipasvir/sofosbuvir fixed dose combination (with or without ribavirin), when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C genotype 1 virus, with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated	20/02/2014 17/11/2014
Daclatasvir 30 and 60 mg film-coated tablets	Sweden Daclatasvir for the use in combination with sofosbuvir +/- ribavirin, for genotype 1 patients that are above 18 years of age and at a high risk of decompensation or death within 12 months if left untreated	21/11/2013 22/08/2014
Sofosbuvir 400 mg film-coated tablets	Sweden Sofosbuvir Gilead, when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C who are also: • Actively on the waiting list for liver transplantation (documented) and require treatment to prevent graft reinfection with hepatitis C virus, or • Who have undergone liver transplantation and have aggressive, recurrent hepatitis C infection resulting in progressive and worsening liver disease, and are at a high risk of death or decompensation within 12 months if left untreated.	24/10/2013 16/01/2014
Zanamivir 10 mg/ml solution for infusion	Sweden Compassionate Use IV zanamivir should be considered only to treat critically ill adults and children having a life-threatening condition due to suspected or confirmed pandemic influenza virus infection or infection due to seasonal influenza A or B virus and answering to the following criteria: • Patients not responding to either oral or inhaled authorised antiviral medicinal products, or • Patients for whom drug delivery by a route other than IV (e.g. oral oseltamivir or inhaledzanamivir) is not expected to be dependable or is not feasible, or • Patients infected with documented influenza virus resistant to other antiviral agents and notsuitable for therapy with inhaled zanamivir	18/02/2010 N/A
Oseltamivir phosphate 100 mg Powder for solution for infusion	Finland Compassionate Use Tamiflu IV should be considered only to treat critically ill adults and children older than 1 year of age having a life-threatening condition due to suspected or confirmed pandemic (H1N1) infection or infection due to	18/02/2010 N/A

INN Dose	Request by Target population	Date of CHMP Opinion on CU Date of MA
	seasonal influenza A or B virus and answering to the following criteria: • patients not responding to either oral or inhaled authorised antiviral medicinal products, or • patients for whom drug delivery by a route other than IV (e.g. oral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible. For infants below 1 year of age, no recommendation can be given at this stage due to the absence of pharmacokinetic and safety data on the use of Tamiflu IV in this very young population. Should a physician decide to treat an infant below 1 year of age, the decision should be taken based on the assessment of the benefit and risk for the individual.	

Notifications of nationally approved compassionate use programmes (CUPs) received from MS in line with Art 83(3) of the Regulation are the only source of information that the EMA has in terms of the Compassionate use programs available at MS level. Member states are required to notify the EMA about initiated CUPs; however, there is no specific procedure to notify the EMA about initiated compassionate use programmes following the CHMP opinion or the alignment of conditions of the compassionate use with the recommendations included in the CHMP opinion.

Furthermore, as there is no harmonisation on how the notifications are sent to the EMA, at times the notifications are sent in the language of the MS.

Figure 1 shows the distribution of received notifications for newly initiated CUPs from MS by EMA on national CUPs from 2006 (pre-2010) to end of 2015. The graph only depicts new notifications of investigational products received per year and does not include any renewals or end of CUPs notifications.

Figure 1.

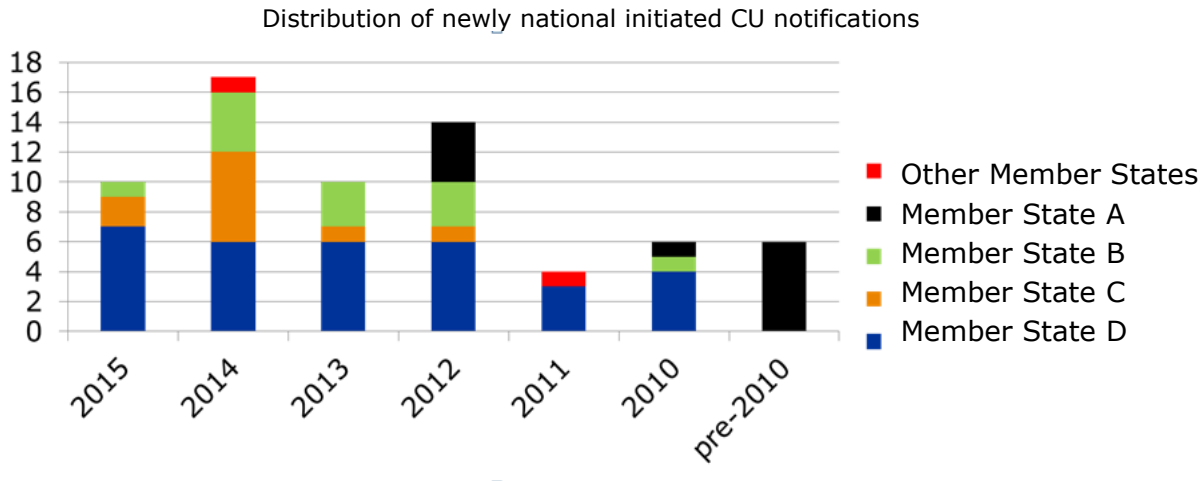

Figure 1 shows new notifications of investigational medicinal products received by EMA per year and does not include any renewals or end of CUPs notifications.

For completeness, table 2 shows the notifications received for investigational products for the same condition by more than one MS. Of note, national CUPs were predominantly in the oncology

therapeutic area. The products highlighted in yellow received a CHMP adopted scientific opinions for compassionate use in accordance with Article 83 with Regulation (EC) No 726/2004.

Table 2.

Products	Disease/Indication
Regorafenib	Gastrointestinal Stromal Tumors
Enzalutumide	Castration resistant prostate cancer
Bedaquiline	(MTB) Pulmonary Infection
Teriflunomide	Multiple Sclerosis
Dolutegravir	HIV-1
Zanamivir	Life-threatening influenza infection
Abirateron-acetate	Castration resistant prostate cancer
Ibrutinib*	CLL and/or SLL and Relapsed or Refractory Mantle Cell Lymphoma
Daclatasvir	Hepatitis C
Ramiricumab	Gastric or gastroesophageal adenocarcinoma
Ceritinib	ALK-positive NSCLC
Alectinib	ALK+ NSCLC
Cobimetinib	Unresectable locally advanced stage IIIC or IV metastatic melanoma

Summary

The analysis of the experience to date for CUP at EU level reveals that few member states appear to follow the requirements to notify the EMA about nationally implemented CUPs intended for a group of patients. Furthermore, of those that notified the Agency about CUP, a CHMP Opinion on Compassionate Use was only requested 5 times (see EMA website on Compassionate Use: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac058007e691).

As per the EMA guidance on compassionate use pursuant to Article 83 of Regulation (EC) No 726/2004, compassionate use programmes are intended to facilitate the availability to patients of new treatment options under development. However, the experience thus far on the European level shows that only few MS have made use of this provision and though notifications of nationally implemented compassionate use programmes in more than one member state have been received by the EMA, only two of those have resulted in a scientific opinion adopted by the CHMP on compassionate use.