



Annexes

Early access to medicines in
Europe:

Compassionate use to
become a reality

A EURORDIS Position

Annexes

These annexes accompany the EURORDIS position paper [“Early access to medicines in Europe: Compassionate Use to become a reality”](#).

EURORDIS survey on Compassionate Use Programmes for orphan medicines

Survey description

In 2011, EURORDIS completed a retrospective survey on developers of orphan medicinal products, to learn from their experience in running compassionate use programmes. Sixty-four holders of a marketing authorisation for an orphan medicinal product were contacted (covering 2008-2011). Responses were obtained from 17 companies on 19 products. Valid data was obtained for 9 programmes in 42 European countries. Products and indications are shown in Table 1.

Product	Indication
Mozobil® (Genzyme)	Treatment to mobilise progenitor cells prior to stem cell transplantation
vandetanib (AstraZeneca)	Medullary thyroid carcinoma
inolimomab (Eusa Pharma)	Graft versus host disease
Kuvan® (Merck Serono)	Hyper-Phenyl-Alaninaemia in adults and paediatric patients
Carbaglu® (Orphan Europe)	NAGS deficiency, isovaleric, methylmalonic or propionic acidaemia
Yondelis® (Pharma Mar)	Soft Tissue Sarcoma
decitabine (Johnson & Johnson)	Myelo-Dysplasic Syndrome
Vpriv® (Shire Pharmaceuticals)	Gaucher type 1
Xyrem® (UCB)	Narcolepsy

Table 1: Compassionate Use Programmes, EURORDIS survey to Marketing Authorisation

Different companies had different practices regarding when to start a CUP in relation to the Orphan Drug designation, the completion of trials recruitment, and the marketing authorisation application.

The same applied to the termination of the programme, which continued for different times after a marketing authorisation had been granted. The European Regulation (EC) N° 726/2004 article 83-8 states:

When 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.

Examples of compassionate use programmes

In this first example below (Mozobil®), the trials to be submitted to authorities for the marketing authorisation (so-called pivotal trials) completed enrolment 38 months after the designation and the CUP started to enrol patients five months later. The CUP continued for more than a year after the marketing authorisation, filling the gap between authorisation and reimbursement/coverage decision.

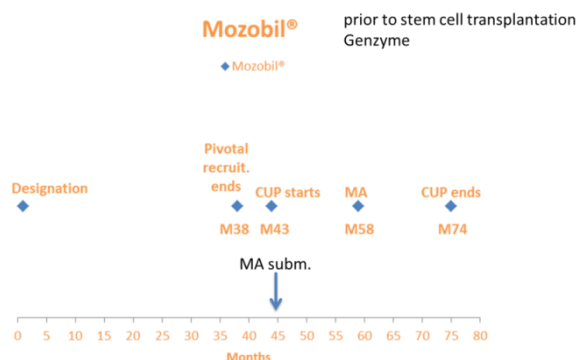


Figure 3: CUP for Mozobil® to prepare stem cell transplantation

For Xyrem®, the CUP started before the end of the recruitment in clinical trials and this did not prevent the trials from completing their objectives (below).

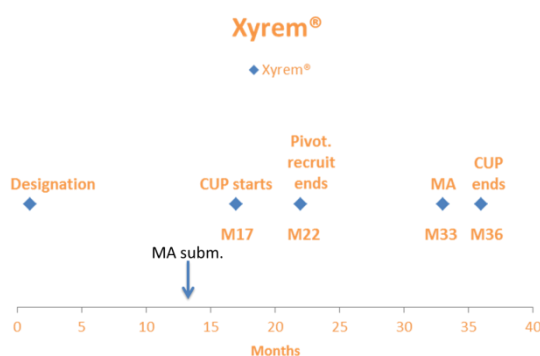


Figure 1: CUP for Xyrem® to treat narcolepsy

In this third example (Kuvan®), the CUP started well after the end of the trials' enrolment, and shortly before the marketing authorisation.

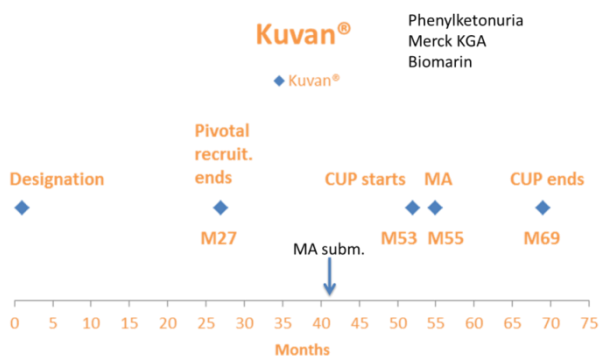


Figure 2: CUP for Kuvan® to treat phenylketonuria

In this fourth example (Vpriv®), the CUP started even before the orphan drug designation, and shortly before the marketing authorisation submission.

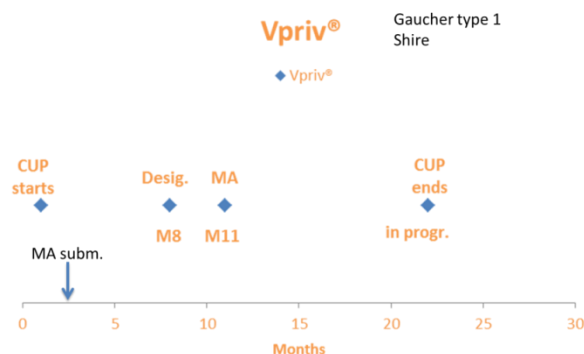


Figure 3: CUP for Vpriv® to treat Gaucher type 1

For Yondelis®, the CUP started well ahead of the designation and of the end of trials' recruitment, but ended shortly before the marketing authorisation.

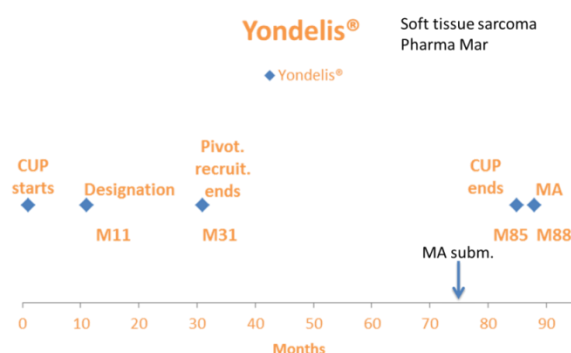


Figure 4: CUP for Yondelis® to treat soft tissue sarcoma

More recently, a new product was investigated to treat Batten's disease. When the first 9 patients in the phase I/II trial received treatment for more than six months, a press release was launched by the developer on "promising results, with 6 children who were stabilised" (BioMarin, 12 January 2015). These results were communicated without anticipation of the parents' reaction worldwide, who immediately asked for compassionate use for their own children. Batten's disease is characterised by a rapid loss of all cognitive functions once symptoms have started to occur.

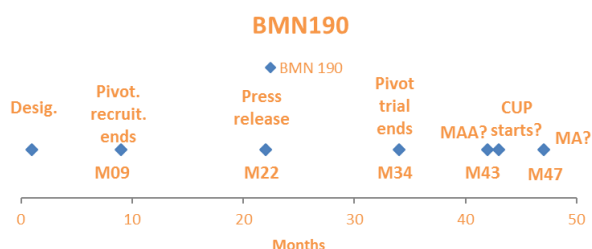


Figure 5: no CUP for Cerliponase-alpha (BMN 190) to treat Batten's disease

More than a year after this early communication, no compassionate use has started, and is not likely to start before 2Q-3Q/2016. For most children who had been expecting treatment since January 2015, this will be too late and the course of the disease will inevitably destroy the brain.

Timelines summary

<i>Product</i>	<i>CUP started</i>	<i>MAA* submission</i>	<i>CUP started</i>
Mozobil®	15/05/2008	5/06/2008	21 days before submission
Xyrem®	01/07/2004	11/03/2004	112 days after submission
Kuvan®	01/09/2008	30/10/2007	307 days after submission
Vpriv®	01/10/2009	30/10/2009	29 days before submission
Yondelis®	30/06/2000	27/07/2006	2,218 days before submission
BMN 190	Pending	Pending	548 days after early press release on positive results

Table 2

*: Marketing Authorisation Application

MS disparities organising efficient compassionate use programmes

With 9 products and 42 countries, a maximum of 378 programmes could have been conducted if all countries in our surveys had authorised a compassionate use programme for each one of the 9 products. However, only 74 programmes were run, with marked differences among countries, as shown in table 3 below:

	EU/EEA	Non EU/EEA
Number of countries unable to run any programme	1	9
Number of countries able to run 1 or 2 programmes	21	2
Number of countries able to run 3 to 4 programmes	4	1
Number of countries able to run 5 to 6 programmes	3	0
Number of countries able to run 7 to 9 programmes	1	0
Total	30	12

Table 3

Of the 30 EU/EEA Member States, the vast majority (21) could only organise a compassionate use for 1 or 2 products of the 9 surveyed. Only one was successful in conducting a programme for all 9 products (France).

After France, other Member States that run CUPs for more than half of the products were Netherlands (5), Germany (5) and Spain (5).

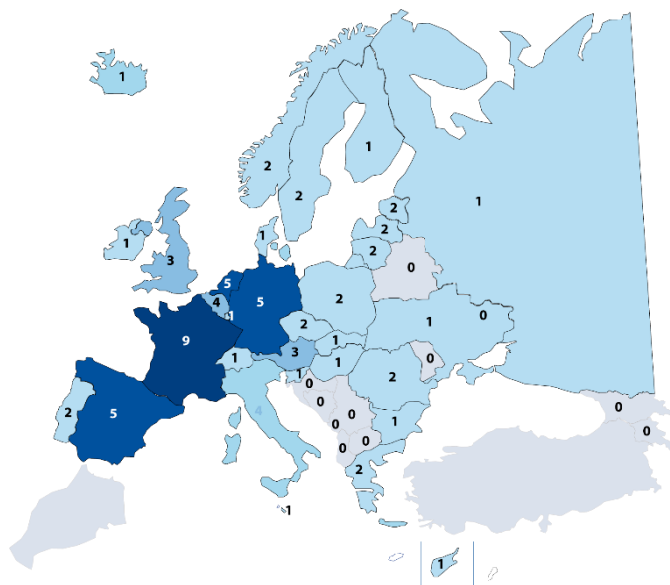


Figure 6

Difficulties for industry when undergoing compassionate use programmes¹

Companies have no legal obligation to offer access to experimental treatments; are often uncertain on how to respond to requests; and may be uncomfortable in determining how to respond fairly to requests from well-connected organisations or those using social media campaigns (Caplan, 2016).

These difficulties should not be underestimated:

- Differences in the local legislation across countries caused products to be available earlier in some Member States than in others
- The sites where the CUPs are run cannot be selected: any request needs to be honoured, for any patient that meets the criteria
- In emergencies, administrative constraints are difficult to manage; even in countries with sophisticated CUP schemes, emergencies remain difficult to respond to.

Administrative obstacles and lack of experience for some countries

Differences in local legislation across Member States can cause the product to be available earlier in some than in others solely based on the difference in speed of obtaining the local approval for the programme.

Labelling in local language information or obligation to use the commercial batches and not the pilot batches prepared for the clinical trials are examples of variations across Member States.

Lengthy and protracted negotiations on price and subsequently on reimbursement differences between MS are problematic from a budget impact on company's side: the exact duration of the compassionate use

¹ EURORDIS has listed information available on the contact points in national competent authorities:

<http://www.eurordis.org/content/links-national-authorities-websites>

programme can hardly be estimated. The programme has a cost for the company, and does not always generate revenues.

The programme may deprive the Member States of a “real incentive” to conclude the pricing and reimbursement decision, given that the patients receive the treatment (when free programme).

In general, the sites cannot be selected: any request needs to be honoured, for any patient that meets the criteria for use of the product. One approach could be to restrict the compassionate use programme to Centres of Expertise for Rare Diseases, however the concept of Centre of Expertise not established in all Member States.

Developer’s variable experience with compassionate use

Often, the company that develops the investigational product considers that the product has not yet reached a stage where a CUP may be envisioned. This could be solved by seeking early scientific advice with regulators and external experts, for example in the frame of the EMA PRIME initiative (EMA, 2016). Scientific advice can be requested at any time, to discuss and anticipate these aspects.

Many recently created pharmaceutical companies are confronted for the first time with compassionate use requests and do not necessarily have the in-house resources to deal with many different and complex national procedures. This is again a reason to advocate for a more elaborate European scheme.

The bewilderment of many companies when receiving a request for a compassionate use is obvious when they respond negatively, objecting that the programmes will be discussed once efficacy has been demonstrated, which usually means towards the end of the phase III / confirmatory trials and not at the end of the phase II/ proof of concept trials.

Requests come sometimes from very prominent people and they can get around the official legal way, but this is obviously not possible for the majority—this is then an ethical issue to handle as well.

Scientific and medical difficulties

It is not always possible to distinguish between two groups of patients: one eligible for clinical trials, and one who is not. When no distinction can be proposed, there is a risk that patients who are in a clinical trial leave the trial to benefit from the product in the compassionate use programme (in particular when the clinical trial is comparative and the comparator is a placebo or no treatment).

This is one more reason to ask for scientific advice to expand the discussion on those eligible for the clinical trial and the compassionate use programme with regulators, clinicians, patients’ representatives.

The prospective collection of data in a structured way is not possible, unless a huge effort to standardise the data is made before the programme starts. Different sites may use different lab tests, imaging devices or health status scales, and this would make the aggregated results difficult to analyse.

Where to find information on compassionate use programmes (public domain)?

Web site of the Heads of Medicines Agencies (HMA)

HMA is a coordination of national regulatory authorities. They share common projects, including the improvement of the transparency of their activities.

Recently the HMAs published a list that contains information on compassionate use in many, but not all, Member States:

http://www.hma.eu/fileadmin/dateien/HMA_joint/02-HMA_Strategy_Annual_Reports/08_HMA_Publications/2016_05_HMA_Compassionate_use_program.pdf

It is positive a step forward towards more transparency on compassionate use programmes, which supports the need of developers of pharmaceuticals, clinicians and patients to have access to detailed information on how these programmes can be run in each Member State.

However, this does not respond to all of the information needs. Patients and clinicians would welcome information on specific authorised compassionate use programmes with the aim of ensuring fairness and equity in accessing these programmes designed for unmet needs in life-threatening diseases.

European Medicines Agency

On this page, you can find information on the role of the agency, on how Member States can request an opinion to the EMA for a given compassionate use, and a register of such EMA opinions already given.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac05809f843c

There are also links to an Answers & Questions document on the on the compassionate use of medicines in the European Union ([here](#)) and guidelines ([here](#)).

For any query to the EMA on this matter, use this email address: compassionateuse@ema.europa.eu

European Register of Clinical Trials


Compassionate use programmes are not clinical trials, however in Member States that do not have a regulatory scheme for compassionate use, open label trials can serve to provide a product available on a compassionate basis. Use keywords such as “compassionate” or “open label” to find them. The site URL is: <https://www.clinicaltrialsregister.eu>

For example, when entering the words “compassionate use” in the search area, 110 such programmes for adults and 28 for children can be found in August 2016:

X Search

Examples: Cancer AND drug name. Pneumonia AND sponsor name.

[How to search \[pdf\]](#)

Advanced Search: [Search tools](#) 

Trials with a EudraCT protocol (110)

Paediatric studies in scope of Art45 of the Paediatric Regulation (28)

110 result(s) found for: compassionate. Displaying page 1 of 6.

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Glossary

ACCESS (ACCESSIBILITY)

The patient's ability to obtain medical care and a measure of the proportion of a population that reaches appropriate health services. The ease of access is determined by such components as the availability of medical services and their acceptability to the patient, the location of health care facilities, transportation, hours of operation and cost of care. Barriers to access can be financial (insufficient monetary resources), geographic (distance to providers), organisational (lack of available providers) and sociological (e.g., discrimination, language barriers). Efforts to improve access often focus on providing/improving health coverage. [Source: WHO. A Glossary of Terms for Community Health Care and Services for Older Persons]

ACCESS WITH EVIDENCE DEVELOPMENT (AED)

Initiative in which a payer provides temporary or interim funding for a particular technology or service to facilitate the collection of information needed to reduce specific uncertainties around a coverage decision. [Source: Stafinski T, McCabe C, Menon D: Funding the unfundable – mechanisms for managing uncertainty in decisions on the introduction of new and innovative technologies into healthcare systems. *Pharmacoeconomics* 2010; 28:113-42.] See also: managed entry agreements

AFFORDABILITY

The extent to which medicines and further health care products are available to the people who need them at a price they / their health system can pay. [Source: adapted from WHO. A model quality assurance system for procurement agencies]

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.

BRAND NAME (INNOVATOR'S NAME, PROPRIETARY PRODUCT NAME, MEDICINE SPECIALITY PRODUCT NAME, MEDICINAL SPECIALITY PRODUCT NAME)

Name given for marketing purposes to any ready-prepared medicine placed on the market under a special name and in a special pack. A brand name may be a protected trademark.

BUDGET IMPACT

A budget is an estimate of revenue and expenditure for a specified period. Budget impact refers to the total costs that pharmaceutical reimbursement and use entail with respect to one part of the health care system, pharmaceutical care, or to the entire health care system, taking into account the possible reallocation of resources across budgets or sectors of the health care system.

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 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.

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).

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.

CO-PAYMENT

Insured patient's contribution towards the cost of a medical service covered by the insurer. Can be expressed as a percentage of the total cost of the service or as a fixed amount. [Source: OECD – Pharmaceutical Pricing Policies in a Global Market] See also: out-of-pocket payments

COMMUNITY PHARMACY

Health care facility dispensing medicines (POM and OTC, reimbursable and non-reimbursable medicines) to out-patients. Pharmacies are subject to pharmacy legislation (e.g. national legislation regarding establishment and ownership of pharmacies). In many countries, community pharmacies are private facilities, but public pharmacies (i.e. in public ownership) also exist. Pharmaceutical provision for inpatients is provided for by hospital pharmacies or pharmaceutical depots; in some

cases, hospital pharmacies also act as community pharmacies. [Source: adapted from PPRI Glossary]
See also: hospital pharmacy

Good Manufacturing Practices (ISPE, 2016)

Is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

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.

HEALTH TECHNOLOGY ASSESSMENT (HTA)

Health technology is the application of scientific knowledge in health care and prevention. Health technology assessment (HTA) is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. [Source: EUnetHTA]

HOSPITAL-ONLY MEDICINES (HOM)

Medicines that may only be administered in hospitals [Source: PPRI Glossary]

Patients targeted

Is the restricted population (including age groups), as identified by the CHMP, that would benefit from the treatment for compassionate use.

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.

PAY-BACK

A financial mechanism that requires manufacturers to refund a part of their revenue to a payer (i.e. third party payer) if sales exceed a previously determined or agreed target-budget.

RISK-BENEFIT BALANCE

An evaluation of the positive therapeutic effects of the medicinal product in relation to its risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment.) [Source: 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]

TRANSPARENCY DIRECTIVE

Directive 89/105/EEC (of 21 December 1988) relates to the transparency of measures regulating the pricing of medicines for human use and their inclusion in the scope of national third party payers. [Source: PPRI Glossary]

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