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Are There Any Common Denominators for Early Access Programs in Europe?

Objectives

Early access to medicinal products prior to marketing authorization (MA) addresses a patient need and can be a relevant strategy for successful market access. An EU legal framework for the provision of early access in the form of compassionate use (CU) for investigational products undergoing clinical trials or subject to marketing authorization application (MAA) has been set by the Article 83 of EU Regulation 726/2004 and the conditions described therein.
This analysis sets out to explore if and which common denominators exist for early access programs (EAP) including CU within the EU and what are the potential implications for market access.

Methods

For this analysis, current state of EAP regulation, design and conditions of EAP and number of medicinal products included under EAP for Spain, Italy, France, Germany, and Austria have been researched and reported by respective country experts, as of September 25, 2023. Focus of this analysis is on cohort programs, while programs on a named patient basis (nominative) have been excluded.

Of note, the term "early access" does not naturally occur in all jurisdictions (e.g. compassionate use as the term preferentially used in German or Austrian law) but is used here as an umbrella term for all kinds of pre-authorization drug use.

Results

Germany

In Germany, early access to medicines is possible under CU (Arzneimittel-Härtefall) free of charge under the conditions specified in Article 83 of Regulation (EC) No. 726/2004 for a cohort of patients with a seriously debilitating or life-threatening disease and a lack of authorized alternatives. Sufficient evidence of the efficacy and safety of the drug must be available and either a clinical trial being conducted, or a MAA being submitted. As of 25/09/2023, a total of 24 CU programs (CUP) were listed as ongoing on the webpage of BfArM.

France

After the reform in 2021 early access to medicines is possible under either the early access (AAP: "autorisation d'accès précoce") or the compassionate access. AAP is reserved for medicinal products whose efficacy and safety are strongly presumed for a serious, rare or disabling disease, without appropriate treatment and for which they are presumed to be innovative. The manufacturer must commit to submit an MAA within a specified period of two years. APP is possible for drugs without any previous MA (before 1st MA or after MA but before coverage under ordinary law) or with a MA in another indication. Medicinal product use in AAP is 100 % reimbursed with either price set by manufacturer (however, annual rebates depending on the turnover apply, and any difference to the price ultimately negotiated with the national payer must be compensated) or existing price (for medication with a previous MA). As of 25/09/2023, AAP includes 17 medicinal products in 20 indications in the pre-MA phase and 58 active substances in 78 indications in post-MA early access.
Under the compassionate prescription framework (CPC), compassionate access for established off-label prescriptions of medicinal products authorized for another indication is possible, which is compensated depending on the reimbursed price in the other indication. As of 09/2023, 5 active substances in 13 indications are CPC listed. Nominative programs that are possible under the compassionate access are not discussed here.

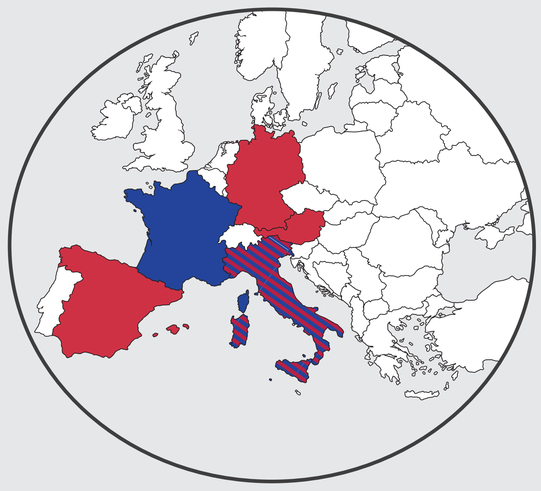

Figure 1: EAP/CUP availability and type per country

- only CUP available (paid by manufacturer; Spain: case-by-case decision)
- reimbursed EAP available
- both EAP (reimbursed) and CUP (paid by manufacturer) available
- not part of this analysis

Austria

Austria has implemented a CU program as an agency-approved program for a defined group of patients, which is similar in design to its German counterpart and is also based on the principles defined in Article 83 of Regulation (EC) No. 726/2004 . Currently, the Austrian authorization authority BASG listed 3 CU programs as ongoing in Austria.

Italy

In Italy, medicinal products are eligible for early access under the 648/1996 Law, if they are foreign innovative medicines without MA in Italy, not yet authorized but in clinical trials or are used off-label. Originally, only products without a viable alternative were eligible. Since 2014 medicinal products with a therapeutic alternative can be included under the same law based on economical considerations. Prices for drugs to be included in the L648 List are to be negotiated with AIFA. For orphan drugs, reimbursement is also possible under the 326/2003 Law on an individual basis (Fondo AIFA 5%, not discussed here). Italy has also implemented a CU pathway under the 07/09/2017 ministerial decree, which by design is comparable to CU implemented in Germany and Austria. As of 25/09/2023, 118 active substances in 146 indications were included in the L648 List, while 31 CU programs were ongoing.

Spain

In Spain, there are no early access schemes available for innovative products. However, access to a medicine before completion of MA and pricing & reimbursement (P&R) process is possible under the process called "Medicines in Special Situations (MSE)". The Spanish Medicines Agency (AEMPS) may authorize the use of investigative medicines through compassionate use programs, regulated by the Royal Decree 1015/2009, or foreign medicines without a suitable alternative in Spain. There is no public information about which products (and under which conditions) have been accepted in Spain for CU neither on foreign medication, as their use is accepted on a case-by-case basis.

Table 1: Comparison of early/compassionate access programs per country

Early access pathway	**Compassionate use**	**Compassionate use**	**early access authorization ("AAP")**	**compassionate prescription framework ("CPC")**	**648/1996 Law**	**Compassionate Use (2017 Min. Decree)**	**Medicines in Special Situations**
Initiator	Manufacturer	Manufacturer	Manufacturer	ANSM	Prescriber	Manufacturer	Hospital
Agency	BfArM or PEI	BASG	HAS, ANSM	ANSM	AIFA	AIFA	AEMPS
Evidence requirements	confirmatory clinical tria results	Phase III RCT, phase II, if safety is given	pivotal RCT, except for severe / rare diseases	Well established off-label prescriptions	Phase II	Phase III, phase I/II for rare / life-threat. conditions	Abibliography or data supporting use
Duration	1 year, max. until MA	until market availability in Austria	Until regular reimbursement, provisions on supply of drug	3 years, renewable	until MA	until MA	until MA and marketing in Spain
Payment by manufacturer	yes	yes	no	no	no	yes	no
Price	Free of charge	Free of charge	Free pricing minus annual discounts and refunds or existing price (if previous MA)	Price in other indication minus discounts	Price negotiated with AIFA	Free of charge	Free of charge or price agreed with manufacturer

Commonalities and differences

- Most countries place specific requirements in terms of evidence availability (usually at least positive results from phase II studies), which are less strict for severe or rare diseases. Additionally, access to most EAPs obliges the manufacturer to collect real world evidence.
- In Germany, Austria, and Italy, CU can be initiated by the manufacturer, but treatment is not compensated. The French EAP (AAP) is also initiated by the manufacturer but is fully reimbursed by the social health insurance. Notably, Italian EAPs under the 648/1996 law are reimbursed, but cannot be initiated by the manufacturer directly. Italy and France employ different mechanisms for setting prices (price negotiation vs. free pricing with annual discounts and refunds). In Spain, decisions on compensation of CU and its amount are made on a case-by-case basis.
- Currently, the number of medicinal products under CU in Germany is higher than in Austria (24 vs. 3). The Italian CU offers a similar number of CUPs (n=31) as Germany.
- Most medicinal products under AAP in France (n=58) are at post-MA stage. In contrast, early access in other countries usually ends by MA and/or placing on the market of the medicinal product (in line with the requirements of the Regulation (EC) No 726/2004). This indicates that AAP is not only a pre-MA access pathway, but to an even greater extent, a tool for seamless reimbursement after MA and prior to inclusion in the full reimbursement list. The greater number of medicinal products in reimbursed early access under 648/1996 Law (n=118) in Italy is rather indicative of a broader range of medicinal products to be included which are not necessarily innovative (e.g. off-label use and more economic alternatives).

Conclusions

- The interpretation of what constitutes early access depends heavily on the country-specific context.
- Free provision of medicinal products by the manufacturer to a defined group of patients under CU is an early access scheme possible in Germany, Austria and in part in Italy.
- The specific conditions of CU in Spain are not clearly defined.
- France and Italy have distinct early access pathways, providing reimbursement for early access. This can serve an additional purpose in the country-specific context, such as to bridge the time from market entry to full reimbursement (French AAP) or to promote the prescription of more economic alternatives (Italian L648 List).
- In most countries the initiation of EAP is the responsibility of the manufacturer, or sometimes of the service provider, and specific evidence requirements need to be met.
- Despite a common legal foundation by European law, countries follow different approaches towards EAP. At present, there is no such concept as a common EU EAP strategy.

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