# Expanded Access Programs (EAPs) in Europe

## Are they right for your therapy?

By Maximus Rex & Nicola Allen

Partners4Access
WWW.PARTNERS4ACCESS.COM

WHITEPAPER

# Introduction

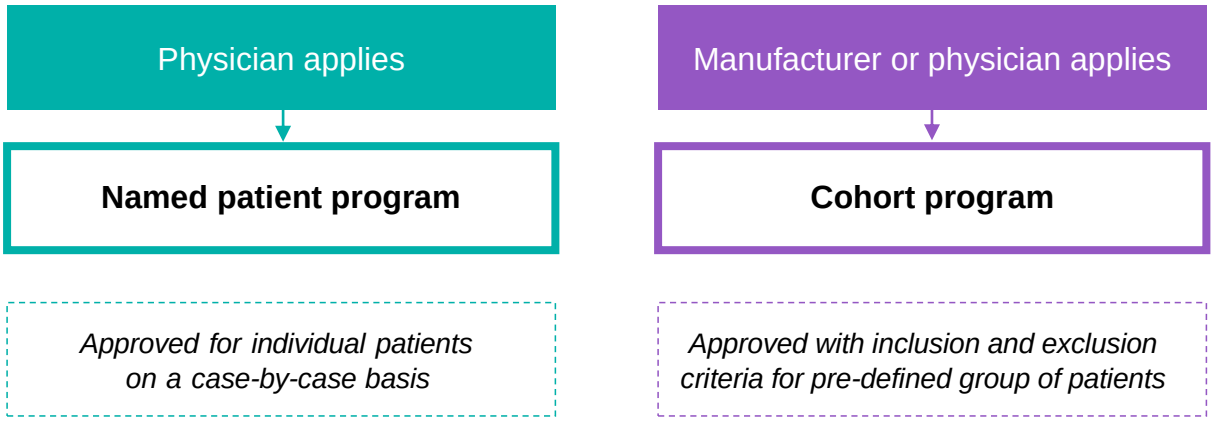
**Drug development is a long and costly process. It is not uncommon for a new drug candidate to take more than 13 years to progress from discovery to being commercially available, with costs often exceeding $1 billion for the manufacturer. For patients with severe conditions with no effective treatment options available, the prospect of waiting for more than a decade before being able to access a medicine that could potentially radically alter disease progression and their quality of life can be devastating. In order to speed up access to medicines that are still in clinical development, various expanded access pathways have been introduced since the first examples were introduced in late 1970s in the United States, and have subsequently been adopted by most major pharmaceutical markets.**

## Regulators in many major markets are now experienced with EAPs and have well-defined processes surrounding their use

**Expanded access programs (EAPs) allow patients to have access to medicines prior to being granted marketing authorization, outside of clinical trials. EAPs are known by a number of different names, including early access, compassionate use, managed access, and more.**

The standard pathway for patients to access a medicine prior to marketing authorization is via a clinical trial, not an EAP. However, there are many reasons why this may not be possible for some patients, such as a lack of a clinical trial site in their home country, or the patients may not meet the specific inclusion criteria. If enrolling in a clinical trial is a possibility for a patient, regulators will not consider an EAP, given that clinical trials are the gold standard for collecting evidence on the safety and efficacy of a new medicine. Although data can be collected through an EAP, this real-world evidence (RWE) is more susceptible to bias and inaccuracy than clinical trial data.

*Figure 1: Types of EAP pathways*




**EAPs can be subdivided into two main types: Named-patient programs (NPPs) and Cohort programs. NPPs are approved for individual patients on a case-by-case basis, whereas cohort programs are approved with inclusion and exclusion criteria for a pre-defined group of patients.**

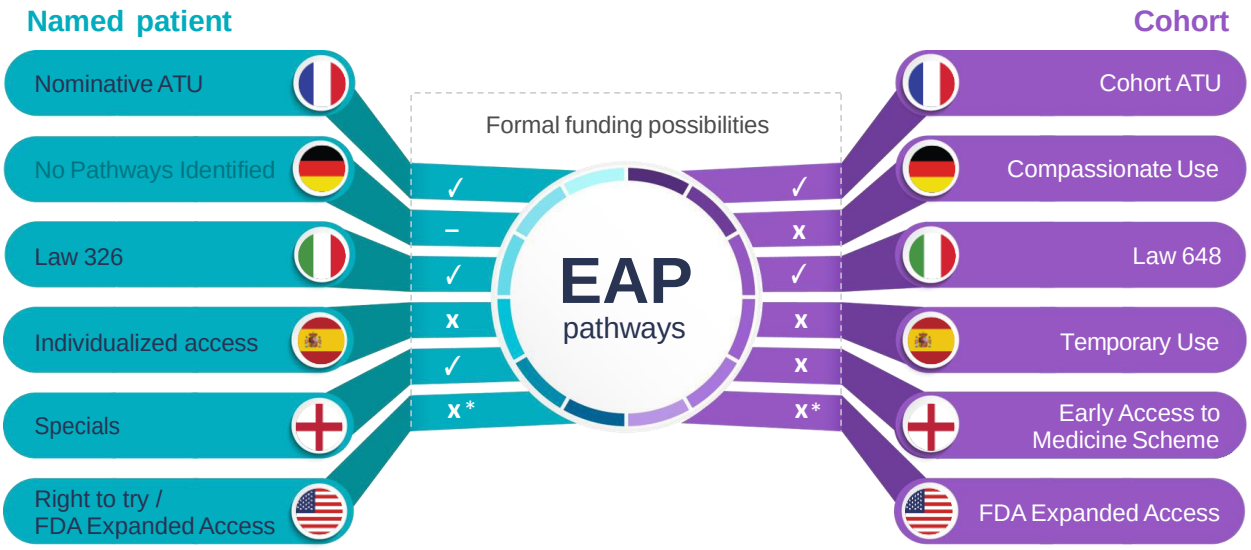
While there are over 7,000 currently identified rare diseases, there are only 169 approved orphan drugs (ODs) in Europe as of 2019. The European Medicines Agency (EMA) grants orphan designation for new products in diseases with a prevalence below 5 in 10,000 people that have no authorized treatment or if the new treatment offers a significant benefit over existing therapy. Many rare diseases are associated with significant mortality and morbidity, and patients are keen for any option to help control their disease. For this reason, ODs are often the most sought-after treatments for expanded access.

There are many potential benefits for manufacturers and patients associated with pursuing an EAP. In addition to the primary benefit of enabling patients to access the treatment prior to marketing authorization, EAPs allow clinicians increased opportunity to gain experience and familiarity with medicines. This experience can be vital in ensuring uptake of a drug after it is reimbursed, especially in countries where there may not be any clinical trial centers. Additionally, safety and efficacy data can be collected through EAPs, allowing manufacturers to build stronger data packages for reimbursement assessments. This can be particularly important in convincing payers of the utility of a drug in indications with small populations, where clinical trials are very limited in size.

# All EAPs in the US and major European markets share four major criteria for when an EAP is acceptable:

- **Lack of therapeutic alternative**
- **Serious, debilitating, or life-threatening disease**
- **Favorable efficacy/safety profile**
  Early clinical data must show the medicine is safe & likely to have positive efficacy
- **Monitoring requirements**
  Data must be obtained from all patients given a medicine in an EAP to monitor its safety

*Figure 2: Comparison of EAP pathways across EU5 and US*




**FDA allows manufacturers to charge for Expanded Access if certain criteria are met; however, insurers will rarely cover treatment costs*

Cohort programs are available in all 5 of the major European markets (EU5), whilst Germany is the only EU5 market where a formal pathway for named patient EAPs is not clearly defined. In most markets, manufacturers are not able to charge for a drug provided in an EAP, with two notable exceptions:

- **France: Nominative or Cohort ATU (Autorisations temporaires d'utilisation, or Temporary Authorization for Use)**
- **Italy: Law 325 (named patient) and Law 648 (cohort)**

Although it may be possible to charge for a drug through the Specials route in England, this is a very rare process and not a viable avenue for OD access.

In Germany, Spain and the UK, manufacturers are expected to provide the drug for free during the EAP. This does contribute to the already significant financial cost to pharmaceutical companies of running an EAP in most cases, and these costs may outweigh potential benefits. Therefore, it is critical that manufacturers carefully consider the opportunities and challenges of embarking on an EAP based on the unique aspects of their treatment, the target indication and subsequent commercialization plans.

> When considering an EAP, there are many potential factors that will impact whether it will be successful or not

The nature of different EAPs in various European countries is only one of many potential factors that manufacturers must consider when building their EAP strategy. It is vital to keep in mind that EAPs are only a short-term solution for patient access, and that patient access is best supported through optimizing the reimbursement strategy across Europe.

Every decision surrounding the use and implementation of EAPs must be considered in the context of the wider commercialization strategy. Although there are many similarities between EAPs in the different EU5 countries, it is possible that each situation will require solutions tailored to that specific market.

*Table 1: Factors that must be considered for EAPs*

| Factors | Questions |
|---|---|
| **Downstream impact on price and access** | • What are the downstream impacts of pursuing an EAP?<br>• How will EAP impact coverage, pricing & uptake once drug is EMA approved & launched? |
| **Investment required for EAP** | • What are the program set-up and ongoing support costs of providing the EAP, as well as the cost of the drug if not funded?<br>• What is the organizational set-up required to implement the EAP if the manufacturer has no pre-existing set-up in Europe?<br>• What are priorities in terms of return on investment (ROI) (financial & non-financial)? |
| **Drug pricing** | • If EAP is supplied via a funded route, how should the drug be priced?<br>• *The EAP price is likely to be the ceiling price for post-MA pricing negotiations, with a price reduction expected by payers* |
| **Drug supply / manufacturing** | • Will the EAP impact the supply of clinical trial patients? What is the level of certainty in demand?<br>• Once the EAP is active, will there be enough drug to supply the need?<br>• What are the logistical requirements (e.g. who can hold and store the drug) for pursuing the EAP? |
| **Data collection opportunities and risks** | • What data collection is mandatory in a particular market and what is optional?<br>• What is the risk of this data impacting the regulatory data package and chances of receiving a marketing authorization, as well as future HTA negotiations?<br>• Are the risks outweighed by the potential benefits of additional data collection? |
| **EAP inclusion / exclusion criteria** | • Is it appropriate to match the EAP inclusion criteria with the clinical trial population versus niching the population to a more severe subgroup, given the feasibility of regulatory approval for the EAP?<br>• What are the risks of the inclusion / exclusion criteria impacting downstream post-launch patient access? |
| **Use of Time caps** | • Is there a defined start and stop date for the EAP?<br>• Would the stop date be in line with expected reimbursement post-launch in the market?<br>• What is the strategy for transitioning EAP patients in case of delays in the post-launch processes? |
| **Use of Patient caps** | • What are the risks of the EAP showing more / less demand vs patient cap?<br>• *If demand is higher, potential public relations / KOL relationship risks*<br>• *If demand is lower, payers may perceive a lower unmet need in the indication, which could impact future reimbursement* |
| **Exit strategies** | • What are the available strategies to exit out of EAPs and when should these be activated?<br>• What are the downstream implications of each exit route? |

# Case Study

| | |
|---|---|
| Drug | Uptravi selexipag |
| Indication | Pulmonary Arterial Hypertension (PAH) in adult patients with WHO functional class (FC) II-III |
| Date of EMA Approval | May 2016 |
| Competitive Environment | 10 indicated, in-market competitors |
| OD Status | Originally granted OD status, but withdrawn at time of EMA approval |

## Uptravi in Pulmonary Arterial Hypertension (PAH)

Prior to gaining EMA approval for the long-term treatment of PAH in adult patients who were WHO Functional Class II or III, Uptravi was granted a cohort ATU program in France. After engaging with KOLs and the French regulators, a narrower population of only more severe WHO Class III patients who were insufficiently controlled on existing endothelin receptor antagonists (ERA) and/or phosphodiesterase type 5 (PDE-5) inhibitors were included. This subgroup of patients had no alternative therapeutic options and a severe medical need.

During the yearlong ATU, 80 patients were treated with Uptravi. Over the course of treatment, five patients died while many additional patients discontinued treatment due to severe adverse events. These results triggered a safety review by EMA almost a year after the original marketing authorization was granted, although no restrictions were ultimately put in place. However, the EMA safety review did result in delays to ongoing HTAs, as well as impacting how Uptravi was viewed by payers.

This was shown in France, where the Transparency Commission (TC) gave a 'Weak' medical benefit rating (SMR) and a 'no therapeutic improvement' added medical benefit rating (ASMR). This ultimately resulted in a 36% price reduction from the ATU price in France, and many other European countries aligned their reimbursed price to the French price. Additionally, only the more severe WHO class III was included in the positive decision, matching the ATU population.

# Key considerations for manufacturers considering EAPs

Since EAPs enable earlier access to drugs in diseases with high unmet needs, it is critical to have a thorough understanding of the post-launch patient access and pricing goals before embarking on such initiatives. This is particularly important for small OD manufacturers with few assets, where financial resources are generally limited, and the success of a single launch can fundamentally alter the future of the company. It is also key that companies pursue a collaborative approach to ensure positive outcomes for all stakeholders, from regulators to patient organizations.

*Table 3: Key considerations for manufacturers considering EAPs*

| **Ensure organizational alignment on the reasons to pursue an EAP** | **Create a Region Europe policy tailored to individual market situations** |
|---|---|
| • Different groups in a company may target different goals<br>• Aligning on whether the aim is for early revenue generation, building relationships with KOLs / treatment centers etc. is vital for building a cohesive strategy | • Each market is very different with specific requirements<br>• Requires a regional team to provide guidance on homogeneity of approach in Europe<br>• Country teams can tailor EAP offering based on local needs<br>• Focus resources on priority markets where EAPs could be most useful |
| **When making decisions around the design of the EAP program (e.g. patient caps, price charged, data captured), ensure a downstream view with a thorough risk assessment of impact on final commercialization outcomes** | **Engage early with regulators, clinicians, treatment centers and patient associations to ensure EAP approval and uptake success** |
| • There are risks associated with EAPs<br>• Can be very costly, both financially in the short-term as well as to the long-term outlook for a drug<br>• All decisions must be made in the context of what will ultimately help commercialization prospects | • Partnering with KOLs / centers is crucial for understanding demand amongst patients, as well as agreeing on potential data collection<br>• These partnerships will allow useful data to be collected and will increase the chance of KOLs providing this data for the manufacturer |

Partners4Access will be at the World Orphan Drug Congress USA from 24th – 27th August 2020. We will be discussing how EAPs can be used to support successful OD launches in Europe and the challenges faced by all stakeholders during "Roundtable 1: Expanded Access Programs (EAPs) in Europe: Are they right for your therapy?" at 14:10 EST on Wednesday 26th August.

## Please join us for this discussion

## References


1. DiMasi, J. (2016) Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics, (47), pp. 20-33
2. Jarow, J. (2017) Overview of FDA's Expanded Access Program for Investigational Drugs. Therapeutic Innovation & Regulatory Science, 51(2), pp. 177–179
3. EMA (2019) Orphan Medicines Figures 2000-2019 [Online] Available at: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2019_en.pdf
4. NSM (2015) Notice to applicants for marketing for Temporary Authorisation for Use (ATU) [Online] Available at: https://ansm.sante.fr/var/ansm_site/storage/original/application/cadfbcf9594614d59c8915670853a28b.pdf
5. BfArm (2019) Guideline for Notification of a Compassionate Use Programme [Online] Available at: https://www.bfarm.de/SharedDocs/Downloads/EN/Drugs/licensing/clinicalTrials/compUse/Guideline_for_Notification.html
6. AIFA (2003) Law 326 [Online] Available at: http://www.agenziafarmaco.gov.it/wscs_render_attachment_by_id/111.42553.11466446734191bc6.pdf
7. AIFA (2019) Law 648 [Online] Available at: http://www.agenziafarmaco.gov.it/content/legge-64896
8. MHRA (2020) Early Access to Medicines Scheme [Online] Available at: https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams
9. AEMPS (2013) Spanish routes for making available medicines to patients before authorisation [Online] Available at: https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_stamp_agenda_point_4_es_aemps_en.pdf
10. EMA (2016) European public assessment report (EPAR) for Uptravi [Online] Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/uptravi
11. ANSM (2017) Uptravi ATU information [Online] Available at: https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-arretees/Liste-des-ATU-arretees/UPTRAVI
12. HAS (2017) Transparency Commission Uptravi Evaluation [Online] Available at: https://www.has-sante.fr/upload/docs/evamed/CT-16185_UPTRAVI_PIC_INS_Avis3_CT16185.pdf
13. ANSM (2020) ATU price [Online] Available at: https://solidarites-sante.gouv.fr/ministere/acteurs/instances-rattachees/article/atu-autorisations-temporaires-d-utilisation
14. L'Assurance Maladie (2020) French drug prices [Online] Available at: http://www.codage.ext.cnamts.fr/codif/bdm_it/
15. EMA (2017) EMA Safety Review of Uptravi [Online] Available at: https://www.ema.europa.eu/en/news/ema-concludes-safety-review-uptravi
16. ANSM (2018) Crysvita ATU information [Online] Available at: https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-arretees/Liste-des-ATU-arretees/CRYSVITA-10-mg-solution-injectable
17. HAS (2017) Transparency Commission Crysvita Evaluation [Online] Available at: https://www.has-sante.fr/jcms/c_2900188/fr/crysvita-burosumab-medicament-agissant-sur-la-mineralisation-dans-le-traitement-de-l-hypophosphatemie-liee-a-l-x


At Partners4Access, we believe in striking an equilibrium in the orphan drug, cell and gene therapy world. That means helping drive access to the most appropriate treatments for patients and physicians, a fair return on investment for manufacturers at an affordable proposition for payers.


**Web: www.partners4access.com**
**Twitter: @Partners4A**
**Email: contact@partners4access.com**
**Phone: +44 (0) 2071507351**