Tanner Pharma GROUP

Enabling Access to Medicines:

What Manufacturers and Patients Need to Know

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An introduction to access programs

Early Access Programs (EAPs), also commonly referred to as Compassionate Use, Managed Access Programs, or Expanded Access Programs among other names, are a pathway by which pharma and biopharmaceutical companies provide innovative drugs, some of which are still in development (INDs) or some that already have an approval somewhere in the world, to patients with serious conditions.

This white paper provides an overview of the key information drug developers and patients need to know about access programs and touches on the role Tanner Pharma Group plays in enabling global access to critical medicines.

Early access programs explained

Early Access Programs give patients with serious or life-threatening diseases the potential to receive access to a treatment that is not commercialized in their country, or access to an investigational medication outside of a clinical trial before the medication has received regulatory approval. In some cases, an Early Access Program might be a patient's final hope for treatment.

Early Access Programs can be uniquely designed and offer several compelling benefits to patients, physicians and manufacturers.

- Provide patients with no alternatives access to potentially life-improving or life-saving treatment
- Collection of real-world evidence and collection of safety data
- Provide continued access to treatment after clinical trials are complete
- Pre-launch physician and payor experience
- Greater product awareness
- Potential revenue generation

Patient Perspective

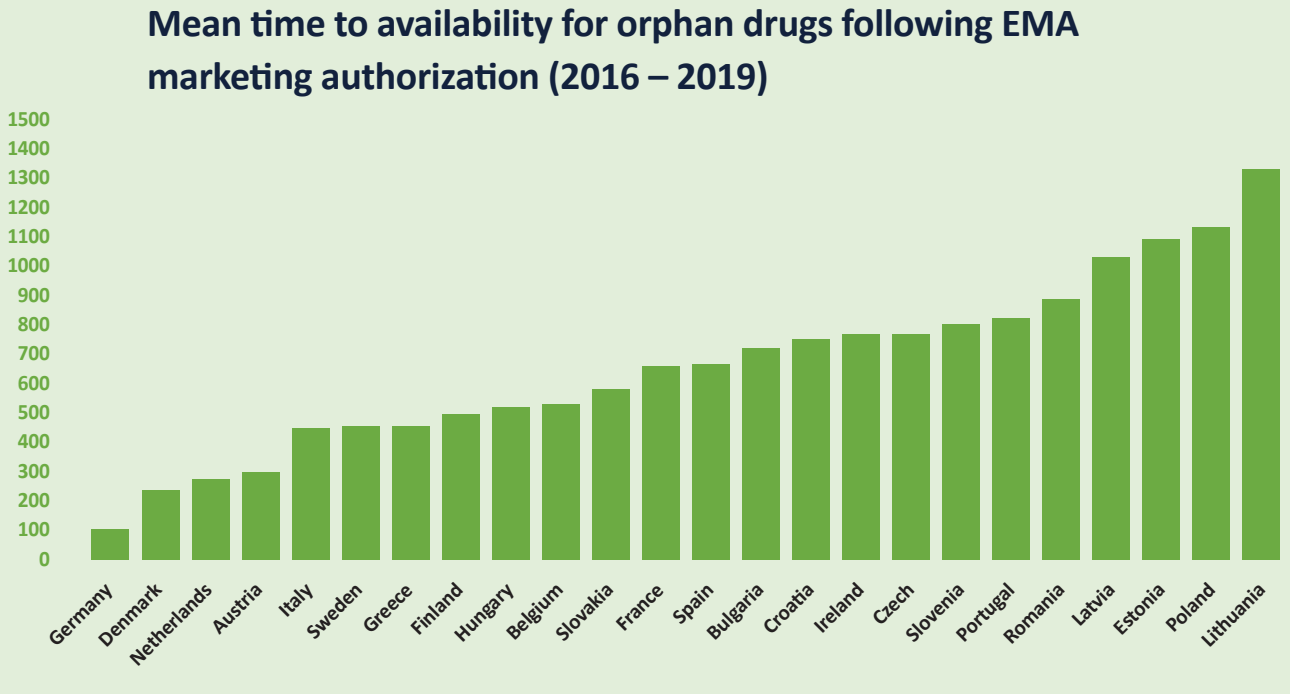
There are a number of reasons why patients may not have access to the critical, life-saving or life-improving therapies they need. Country-specific commercialization constraints, healthcare budgets, the type of healthcare available, differences in reimbursement and pricing systems, and other factors can inhibit access to treatment.

Often, the treatments that will be most impactful to improving patient lives are investigational products that are in various phases of clinical trials that are not taking place in a patient's country. Furthermore, if the studies were taking place in a patient's home region, the likelihood of inclusion into a trial may be limited due to very tight inclusion and exclusion criteria. What's more, there is no guarantee a treatment that has been approved in a major market will ever be commercialized in a patient's country, thus further preventing access, especially in low and middle-income countries or countries with small patient populations. It is with cases like these, and others, that an Early Access Program would be of particular benefit.

Rare Disease Community

Early Access Programs can also be of benefit to the rare disease community. At present, there are between 6,000 to 8,000 rare diseases that have been identified, with only roughly 5% having approved treatments. Innovative therapies have made headway in recent years providing rare disease patients with more options, but these novel treatments are not widely available, and are especially inaccessible to those in low-resource countries. In some cases, an orphan drug may receive market authorization in a patient's country, but even then, availability may be pending for several months or even years.

That is the case in Europe where a centralized approval by the European Medicines Agency (EMA) does not mean that a product will be made commercially available widely across Europe. The following chart shows the mean time to commercial access for orphan drugs following a centralized approval. A patient in Germany must wait on average 106 days compared to a patient in Lithuania that waits on average 1,313 days. This means that depending on where you live in Europe, you may still have to wait several years to get access to a life-changing or life-saving medicine.



Source: EFPIA Patients W.A.I.T. Indicator 2020 Survey, IQVIA, April 2021

Early Access Program Eligibility

It is important to note the requirements that must be met for individual patients who desire to access an unapproved medicine through an Early Access Program.

- The patient typically must have a life-threatening, chronic, or severely debilitating condition
- No approved therapies can be available to effectively treat the disease or condition, or the patient has tried these approved therapies and failed
- The patient cannot be currently enrolled in an ongoing clinical trial
- The therapy must be going through clinical trials, have started the application process for marketing authorization, or obtained a marketing authorization somewhere in the world

Manufacturer Perspective

Driven by the level of unmet medical need, early access requests may come at any point during clinical development, even as early as Phase I with data availability. Publications or study results can also cause an increase in early access requests, especially for rare diseases. Drug developers should consider Early Access Programs as part of their initial market strategy as there are a number of valuable benefits.

Early Access Program Pathways

It is less well known that many countries already have early access pathways in place under compassionate use or named patient terms. These pathway specifications include:

1 Country-specific legislation that allows for named patient supply
2 Legislation that allows companies to respond to unsolicited medication requests that are not commercially available in that country
3 Legislation that requires doctors to get permission from their local health authority to treat a "named" patient if no alternative therapy is available

In addition to enabling patient access, Early Access Programs can provide manufacturers with several advantages.

Collection of Real-World Evidence

Regulators, physicians, payors, and patients are realizing that medicines should not just work in controlled clinical trials, but that they should also work while patients live their normal lives. This changing attitude is driving demand to test whether medicines work in the real world. More and more drug developers and regulators are incorporating data collected outside clinical trials in their decision making. Real-world data capture from global Early Access Programs are increasingly accepted by regulators as supportive evidence for safety and effectiveness – especially with small patient populations.

Real-world data capture from Early Access Programs can provide:

- Supportive or even primary data in regulatory submissions
- Demonstration of product safety and value in support of Health Technology Assessments to facilitate initial product pricing and market access
- Potential publications from use in a real-world setting
- Help to corroborate results from controlled trials

While not common, data from Early Access Programs can provide additional evidence for approval, particularly in the case of medicines being developed for rare diseases. The following table presents 13 medicines where data coming from early access were used in support of regulatory approvals with both the US FDA and EMA. In the case of rare diseases, companies may have limited data coming from their clinical trials and should consider the capture of supplemental data coming from early access.

Generic Name	Indication	FDA	EMA	Studies
Amphotericin B	Fungal Infections	1997	N	10CT (n=2038), 1 EA (n=133)
Anagrelide	Essential thrombocythemia	1997	2004	2 SACT (n=35 + 254), 1 EA (n=245)
Cholic Acid	Inborn errors of bile acid metabolism	2015	2015	2 EA (n=63 + 22)
Clarithromycin	Mycobavterium avium complex	1993	N	1 RCT (n=154), 1 SACT (n=25), 1 EA (n=469)
Dinutuximab β	Neuroblastoma	N	2017	1 RCT (n=370), 1 SACT (n=44), 1 EA (n=54)
Fish Oil Triglycerides	Parenteral nutrition-associated cholestasis	2018	N	1 SACT (n=144), 1 EA (n=37)
Glucarpidase	Elevated metrotrexate levels	2012	W	1 SACT (n=147), 1 EA (n=22)
Lutetium Oxodotreotide	Neuroendocrine tumours	2018	2017	1 RCT (n=229), 1 EA (n=558)
Nitisinone	Tyrosinemia	2002	2005	1 EA (n=207)
Sodium Phenylaccetate/benzoate	Acute hyperammonaemia in urea cycle disorders	2005	N	1 EA (n=316)
Uridine Triacetate	Fluorouracil or Capecitabine overdose	2015	N	2 EA (n=75+60)
Velmanase α	Alpha-mannosidosis	N	2018	1 RCT (n=25), 1 EA (n=35)
Vestronidase α	Mucopolysaccharidosis vII	2017	2018	2 SACT (n=3+12), 1 EA (n=2)

Source: Polak TB, van Rosmalen J, Uyl-de Groot CA. Expanded Access as a Source of Real-World Data: An Overview of FDA and EMA Approvals. Br J Clin Pharmacol. 2020;10.1111/bcp.14284. doi:10.1111/bcp.14284

Continued Access to Clinical Trial Patients

The US FDA has encouraged manufacturers to consider post-trial access through Expanded Access Programs stating, "If the purpose is primarily to provide the drug to patients who continue to need it, an Expanded Access Program may be used for either moderately sized populations (Intermediate Size Expanded Access) or large size populations (Treatment Protocol), often when most studies in support of approval have been completed.

"Expanded access is generally available when clinical trial results show that the drug is effective in the studied population. However, sometimes drugs that have not shown benefit across the overall study population may still be providing benefit for individual patients."

This means that when companies have a responsibility to continue providing a medicine for responders in trials where the medicine failed, use of an Expanded Access Program in the US can be an appropriate mechanism to continue providing access for patients that were receiving benefit from the investigational medicine.

Additionally, Expanded / Early Access Programs can provide continued access to treatment in place of using an Open-Label Extension (OLE) once a clinical trial closes. This can ultimately help reduce costs (e.g., investigator payments, CRO costs, etc.) associated with continuing to manage these patients like they are in a clinical trial.

Increased Physician Experience

Commercial performance in the first year following launch sets the tone for long-term product outlook. 70% of products that miss expectations at launch continue to do so in subsequent years and 80% of products that meet or beat expectations in year 1 continue to do so in subsequent years. Early access pathways allow healthcare providers to become more familiar with innovative medicines during the treatment process. This enhances physician experience in markets where commercialization is already planned, providing an advantage at launch. Additionally, with greater product awareness there is the opportunity for higher sales at launch with revenue generation that could ultimately help to offset development costs.

Patient Connection

Engaging with patient advocacy groups can build relationships between pharmaceutical companies and patients. By engaging with patient advocacy groups, pharmaceutical companies have the opportunity to learn more from patients' key quality of life indicators, which can contribute to the collection of important real-world data from Early Access Programs. Companies can also work with patient advocacy groups to provide educational information to patients who are seeking information on access programs and investigational treatments.

Supply Chain Insight

In addition to real-world patient data, access programs allow drug developers the opportunity to collect real-world supply chain data. Early distribution studies can help identify favourable transit channels, determine ideal shipment conditions, evaluate in-country regulations and requirements, and discover any potential risks in countries that are commercial targets.

Other considerations in supply chain:

- Understanding the required lead time for providing treatment once an early access request is received
- Ensuring adequate stock without impacting clinical studies
- Confirming treatment sites have necessary storage facilities (i.e.-20˚C freezer)
- Reviewing labelling requirements and capabilities to support, if needed

The difference between early access programs and clinical trials

There are some key differences between Early Access Programs and clinical trials, but both can work in tandem to prove the safety and efficacy of medical treatments. In fact, an Early Access Program can be viewed as an extension of and complement to a clinical trial.

The globalization of clinical trials has increased significantly over the last decade, bringing studies into new regions. Through this process, the number of clinical trials has increased in emerging markets such as Asia Pacific, Central and Eastern Europe, Latin America, and the Middle East. These regions are a focus for clinical trials in that they can offer reduced costs, availability of a large number of patients, faster subject recruitment and often less burdensome regulatory requirements. However, these markets are not always an ideal commercial target for manufacturers, so Early Access Programs can serve as a beneficial alternative.

When a biopharmaceutical company wants to get a new medicine approved, it must conduct clinical trials to prove the safety and efficacy of the treatment before widespread use. In turn, select patients can obtain the medicine in a controlled setting. To take part in a clinical trial, patients must meet certain eligibility criteria that might include age, gender, type and stage of disease, previous therapies, and other medical conditions. Often patients who are too sick

do not qualify based on the strict requirements.

An Early Access Program often has fewer inclusion/exclusion restrictions compared to a clinical trial since the primary purpose is to provide urgent treatment for patients with limited options.

Clinical trials cover a narrow population of patients to prove the safety and efficacy of the medical product to treat a specific disease. Data collection is extensive to support the aims and endpoints of a study. The number of patients in a clinical trial is strictly determined, as are the locations where treatment takes place. Source document verification rate is 100% in clinical trials with risk-based monitoring taking place, as well as further assessments from onsite visits.

Whereas Early Access Programs exist solely to provide treatment to a designated patient, much less data is collected across fewer individuals. Yet real-world safety and efficacy data collected from early access treatments can supplement clinical trial data and support the product gaining regulatory approval. However, the numbers of patients and locations in an Early Access Program are often unknown. Monitoring (if needed) takes place centrally and remotely.

Experience is another line of contrast. In a clinical trial, staff are often highly experienced in running the processes. While in an Early Access Program, it is not uncommon for a physician and site staff to have minimal initial experience with the medical products they are using in the program. However, training is provided to the physician as needed, which ultimately contributes to local physician knowledge if the treatment is eventually commercialized in that area.

	Clinical Trials	Early Access
Goal	Research	Treatment
Data Collection	Extensive & controlled	Ad hoc real-world and safety data
Site Staff	Experience running clinical trials	Physician and or staff may have limited experience
Eligibility	Strict based on protocols	Flexible as it is sponsor dependent
No. of Patients	Defined enrolment	Unknown
Site Contracts	Required	Program dependent

Looking at US expanded access initiation and protocols

Different countries have different requirements when it comes to access initiation processes, and different types of Early Access Programs exist. In the US, Expanded Access Programs are typically split into two categories. They are either run for an individual patient or performed as part of a cohort program for a group of patients. Below, we explain these terms.

Single Patient IND for an Individual Patient

A physician may seek access for an individual patient through direct application to the FDA. The physician often has responsibility for the trial as the sponsor and holder of the investigational new drug (IND). Physicians must also determine that the potential risk to the patient from taking the medication is not greater than the potential benefits. When treatment concludes, a written summary must be provided for the results of the individual expanded access case, including any adverse effects.

Intermediate Size

For intermediate-sized Expanded Access Programs, patient numbers are typically small at between ten and 100 patients. For this type, the pharmaceutical company is normally the sponsor. When the FDA receives a significant number of single patient IND requests for the same use, it may ask the sponsor to consolidate access. In addition, a sponsor may choose to run an intermediate program up front.

Treatment Protocol

Larger-sized Expanded Access Programs may involve more than 100 patients and the pharmaceutical company is usually the sponsor. Should enrolment increase in an intermediate size Expanded Access Program, the FDA may request the sponsor submits documentation under a treatment protocol. The sponsor may also opt to begin with a treatment protocol up front. For this type of program, sufficient safety and efficacy evidence is often needed to support use in a larger patient population.

Funding

Patients typically receive medication from an Early Access Program free of charge prior to any global approvals, but there are different rules for different countries. For example, US FDA guidelines allow companies to charge for the medications if the FDA has approved them to do so. However, companies can typically only charge for direct costs, such as manufacturing and shipping, and costs associated with administering the Early Access program.

Outside the US, it is common for companies to provide a medicine free of charge via early access prior to approval in a major market like the US or Europe. Thereafter, it is very common for a company to charge for the medicine provided under early access. Smaller companies generally can’t afford to provide their treatments free-of-charge and must often wait until they receive US FDA approval and charge the US price.

How Tanner Pharma Group can help

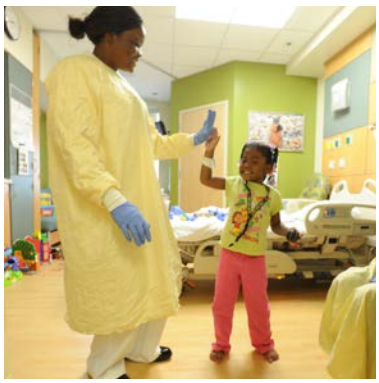
Developing an access program is an intricate process that relies on harmonized efforts from multiple stakeholders.

These programs can be an opportunity to prepare for a medication's market launch and build relationships with key opinion leaders, physicians, and patient advocacy groups, while also offering an opportunity for more patients to benefit from treatment. There can also be supplementary benefits from real-world data collection.

When planning an Early Access Program, there are several complex pieces that require detailed oversight. Drug approval timelines, supply availability, safety data, resourcing, stakeholder alignment, training, data collection, costs – these are just a few of the program elements that need consideration.

Tanner Pharma Group is a US-based pharma services company that provides specialized access solutions in international markets. Over more than two decades, Tanner has developed a portfolio of services driven by the determination to improve global access to medicines for patients. Part of the organization's focus is advocating for the rare disease community and offering solutions that can cross borders.

Tanner operates as a liaison between pharmaceutical companies, physicians, patients, and health authorities to expedite access and deliver therapies for unmet medical needs.



Tanner's comprehensive services ensure the delivery of a successful access program for industry partners, which don't have to allocate internal resources or expertise towards designing, setting up, and managing an Early Access Program.

"Part of our mission is the fact that we're able to benefit both ends of the supply chain, not only to a pharmaceutical company that wants to increase access in international markets, but also to patients that want to increase their access to medicines that aren't available," explains Steve Scalia, president of Tanner Pharma Group.

"We've set ourselves up from the beginning to be a turnkey solution to improve access. We can handle everything. If we can collect the product from the back warehouse door of a pharma company, they don't need to do anything except receive the data on where the product went and see the success that we've had."

"We've always looked at it from the perspective of the sponsor and trying to make it as easy on them as possible. We try to be a single point of contact that can provide everything."

To learn more about Tanner Pharma Group and its role in supporting patient access, please visit **www.tannerpharma.com**

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