Availability and use of non-oncology orphan medicines in Swedish healthcare

The 21 regions in Sweden are responsible for providing healthcare nationwide, with the ultimate goal of promoting good health and well-being for patients and residents, today and in the future. Equal access to safe, effective, and affordable medicines – in sustainable ways for the healthcare system – is essential for achieving this goal. Scientific and technological advancements create new opportunities for pharmaceutical development

The European orphan medicines legislation was introduced more than two decades ago to stimulate the development of medicines targeting rare and severe diseases – primarily for small patient populations – that were otherwise deemed commercially unviable. To incentivise the development of orphan medicines several benefits and market protection schemes exist in Europe as well as in other markets such as the United States and Japan. Investments have increased and the orphan market segment is today a lucrative one. Nonetheless, approximately 95 % of rare diseases still lack effective treatment. In this regard it is important to distinguish truly innovative orphan medicines from "regulatory innovation". Whereas the former addresses real unmet medical needs and often requires significant research and development, investments and risk-taking, the latter is primarily spurred by regulatory opportunities. The practice of so called "salami slicing" is an evident example of this. It is not uncommon that older, off patent and well-established medicines used for broader patient populations are subject to subdivision of indications into smaller patient subsets and narrower indications. Such repurposing allows companies to obtain orphan incentives such as data protection and market exclusivity for their repurposed product without addressing unmet medical needs in healthcare or adding clinical benefit to patients. These medicines are often reintroduced on the market with significantly higher pricing from the pharmaceutical companies.

In Sweden the public debate about patients' access to new medicines has increasingly emphasised the assumed poor access to orphan medicines in Swedish healthcare, in particular the non-oncology orphan medicines. This is a frequent message presented by the Swedish pharmaceutical industry association, Lif, based on the annual "WAIT report" presented by the European Federation of Pharmaceutical Industries and Associations (EFPIA).[1] Swedish healthcare representatives have opposed this view.[2] Other international comparisons present a more positive view on access to medicines in Sweden[3]. This briefing paper also provides a more nuanced perspective and is based on an in-depth analysis of the use of non-oncology orphan medicines in Swedish healthcare, as well as a greater understanding of processes for an orderly introduction and equal patient access to new medicines in Sweden. This is the second briefing paper of its kind.

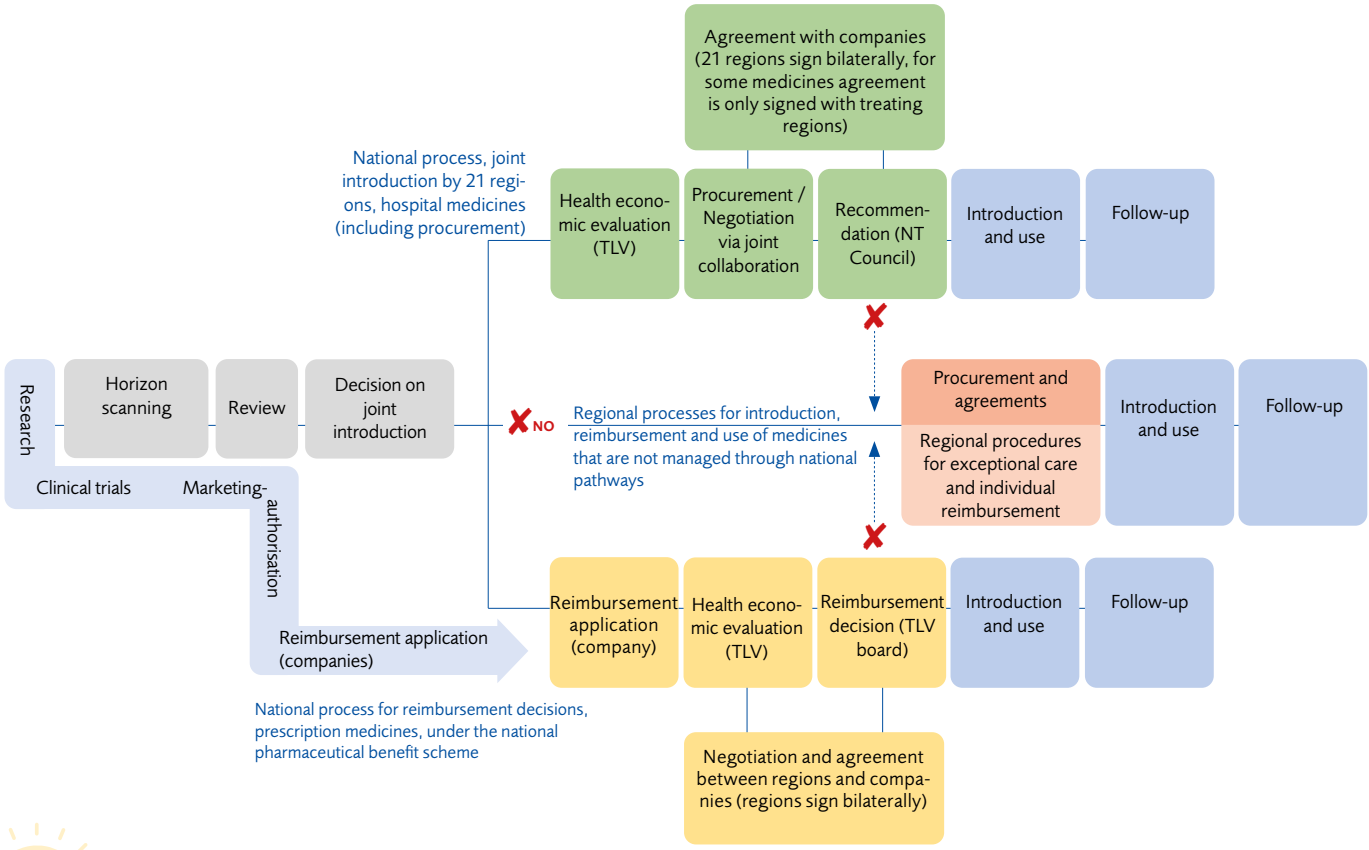
Key Messages

1. **The availability and actual use of orphan medicines must be understood in a broader context** context that considers patient populations, real unmet medical needs and access to other treatment options, the clinical benefit as well as relevance of a medicine.
2. **For orphan medicines it is important to distinguish the relevant medicines that represent true scientific advancements** from those that are "regulatorily innovative". Especially in cases where the authorisation of the latter risk undermining or compromising the access to well-established medicines and existing treatment options for patients.
3. **100% accessibility of authorised medicines is not a realistic expectation, neither is it always necessary from a patient perspective**. Patient access depends on multiple factors. It is therefore not possible to determine—based on statistics alone—whether it is right or wrong to use or not use a specific medicine, or to define what a "reasonable level" of use may be.
4. Swedish healthcare needs to **prioritise medicines that are effective and provide clinical benefits and represent safe and cost-effective treatment options**. Medicines are one of sometimes many treatment options to consider. Enhanced collaboration and **constructive partnerships among key stakeholders** are essential to ensuring that the development and use of truly innovative medicines remain sustainable in the long term—for all parties, and especially for patients.

1 See for example IQVIA (2021), EFPIA Patients W.A.I.T. Indicator 2020 Survey; Quantify (2021), Access to new medicines with EMA approval 2017–2019 in Sweden (as well as its Swedish version).
2 Dagens Medicin, "Bilden är formulerad utifrån ett företagsperspektiv " – Dagens Medicin, Published 20210706
3 OECD (2020), Addressing Challenges in Access to Oncology Medicines, Analytical Report

Highlights from the report

- **Availability of treatment options to use in Swedish healthcare**: Patients' access to treatment in Sweden is enabled in various ways. The Swedish healthcare system is based on the free prescription rights for qualified healthcare professionals. This enables a comprehensive access to various forms of treatment that are medically justified – based on the individual patient's needs as well as scientific evidence and clinical experience. Decisions on the use of medicines can include both products authorised for the European and Swedish market and products that lack such authorisation and/or are not (yet) commercial. Medicines that are not actively marketed in Sweden by the companies can be imported. Other treatment options such as surgery, radiation therapy, physiotherapy, psychotherapy, diet, and lifestyle treatments can also be considered relevant based on the patients needs and are key in addressing unmet medical needs and treatment gaps in the Swedish healthcare system. Sometimes it may be justified to apply a combination of several treatment options.
- **One pharmaceutical system – several introduction pathways for new medicines**: The introduction of new medicines is based on different pathways. Introduction can be managed in centralised national procedures as well as in decentralised regional procedures. This reflects the decentralised model of the Swedish healthcare system. Joint introduction processes and national coordination between the 21 regions are fundamental parts of the Swedish pharmaceutical system. *See figure below, illustrating the various introduction processes for new medicines - from research and development to patients' access.*



One system - several introduction processes: Research, development, and clinical studies are conducted both publicly and privately. For commercial pharmaceutical products, marketing authorisation is required. Through horizon scanning, the development on the pharmaceutical market is monitored and the regions can work proactively to identify new medicines 1-2 years before expected approval and make decisions on the most suitable pathway for introduction. For hospital medicines, the national procedure involves a health economic evaluation by the Dental and Pharmaceutical Benefits Agency (TLV), followed by procurement – sometimes including negotiations and agreements with companies. Following a joint recommendation on use, issued by the Council for New Therapies (NT Council), the medicine is then jointly introduced - orderly and equitably - and available for use in healthcare. For prescription medicines the national process is initiated after the companies apply for pricing and reimbursement under the national pharmaceutical benefit scheme. TLV evaluates the medicines and make the formal decision. In some cases, additional negotiations on pricing are necessary. These negotiations and subsequent agreements are managed by the regions and companies, as the contractual parties. The decentralised regional procedures can also apply, particularly for medicines where the overall budget impact is assessed to be limited and where there are regional processes that can ensure an equitable use of medicines. Individual reimbursement can also be granted regionally, under exceptional circumstances and provided that the medicine is considered cost-effective at the individual level. This considers the urgency of the medical need in the specific case and the availability of clinically relevant treatment options, as well as the condition that the medicine must be considered included in the public health and medical care commitment.

- **Non-comparable data in the WAIT report**: A review of the underlying data of the WAIT report confirms that key concepts such as availability, reimbursement and accessibility are defined by different parameters for different countries. For Sweden, mainly medicines that successfully completed national procedures and were granted national reimbursement and recommendation for use were included. Regionally introduced and reimbursed medicines - through decentralised procedures - were excluded. In countries such as Denmark, Finland, Germany and Austria, however, medicines available for individual reimbursement were included. Hence, the comparisons made in the WAIT report are misleading.
- **Country context is key for the comparison:** The comparisons between countries in the WAIT report does not account for differences in country context and national healthcare systems. In the Swedish context, all new medicines are available for use and companies can set prices freely. What is measured for Sweden in the WAIT report is only the formal national reimbursement decisions - through centralised procedures - for new medicines. This requires a health economic evaluation and sometimes negotiations with companies on price reductions. Value-based pricing applies. Germany also has a system that allows for early introduction and free pricing of all newly approved medicines, but systematic evaluations and price regulations apply only later. Price adjustments can be made retroactively. Medicines can also be withdrawn from the market. For orphan medicines, the timing of the evaluation is linked to the total annual costs of use. This means that the initial availability of medicines on the market, measured in the WAIT report, can be higher than the availability 12-24 months after market introduction.
- **Different perspective on availability, reimbursement and use of orphan medicines in Sweden:** During the period 2017-2019, a total of 40 orphan medicines were authorised by EMA. 27 of these were non-oncological products.[4] 100 % of new medicines are always available in Sweden and can be used in Swedish healthcare, based on the regulation of prescription rights for qualified healthcare professionals. For the review period applied for this briefing paper, 1 January 2017 to 30 June 2021, 56 % had been used in healthcare. Approximately half of these (47 %) had been introduced through national procedures, while the remaining medicines (53 %) had been managed regionally. This is significantly higher figures than the 26 % reported in the WAIT report and the corresponding Swedish analysis commissioned by Lif.
- **Factors influencing the use of orphan medicines:** Potential factors affecting the use of orphan medicines include the size of the patient population, the occurrence of various health conditions in Sweden (incidence, prevalence, and geographical distribution or geographical concentration of conditions). A disease may also have different levels of severity or phenotypic expressions, which means that the choice of relevant treatment must be based on individual needs and conditions - for more precision. Other possible treatment options must also be considered in the evaluation of the individual patient as well as the relative clinical benefit of different treatments. Equitable access to healthcare, does not mean that a specific medicine should be applied equally across the entire patient population.
- **Evidence is key. Access to relevant and robust evidence at the time of marketing authorisation facilitates introduction processes and informed decision making on pricing, reimbursement and use.** Study design, selection and size of the study population, the outcomes that have been studied (and if and how comparisons have been made), as well as the length of the follow-up period all affect the validity of the results. The same applies to assumptions about how study results can be transferred to actual safety and efficacy in clinical practice. For example, some medicines have been approved only based on registry data or have not been able to demonstrate any significant clinical benefit. Higher degree of uncertainty creates higher degree of risk for healthcare providers and payers as well as for patients.
- **Unintended limitations in patients' access to treatment and/or other healthcare interventions:** Limited evidence that is coupled with high prices is a challenge for the Swedish healthcare system and raises questions about the sustainability of the development. Difficulties to make informed decisions, the unintended inefficient use of resources or significant budgetary impacts from medicine use may result in unintended displacement effects. For example, the discontinuation of other healthcare services or limitations in access to treatment or interventions for other patient groups. Patients' out-of-pocket cost for healthcare services may also increase over time.

  Marketing authorisation of new medicines can also result in so called "regulatory displacement" of well-established clinical practice and medicines that were previously available for use in the Swedish healthcare system. For example, safe and effective medicines authorised for other markets - outside of Europe - or medicines used outside of their intended indication (off label), that have previously been available and used in the treatment of patients - with the approval of the Swedish Medical Products Agency (Läkemedelsverket). This also applies to non-commercial hospital-produced advanced therapy medicinal products (ATMPs approved under the provision of "hospital exemption"). Hence, **orphan medicine incentives and anti-competitive protection mechanisms that delay or limit the development of, and availability to, substitutive medicines may negatively influence patient access.** Without sound competition, there is also a risk of continued excessive pricing on the orphan medicine market and an unsustainable development of the pharmaceutical costs in healthcare.

4 The analysis included the orphan medicines Amglidia, Alofisel, Brineura, Cablivi, Chenodeozycholic acid Lediant, Cystadrops, Epidyolex, Jorveza, Lamzede, Luxturna, Mepsevii, Myalepta, Namuscla, Natpar, Onpattro, Oxervate, Palynziq, Prevymis, Spinraza, Symkevi, Takhzyro, Tegsedi, Verkazia, Xermelo, Waylivra and Zynteglo.

This is an English abstract of the original briefing paper, published in Swedish 2022. The review illustrates that patients' access to non-oncology orphan medicines is not as limited as the pharmaceutical industry has previously concluded. A deeper understanding of introduction processes and pathways for patient access is key for all stakeholders within the pharmaceutical system. National processes and centralised procedures serve as effectuve ways of coordinating introduction, pricing and reimbursement as well as procurement and recommendations for use of new medicines. However, in a decentralised healthcare system there will arguably also be medicines that are deemed better suited for decentralised procedures. In Sweden, this means regional introduction. Reviewing the conditions for introduction, pricing and reimbursement as well as factors for prioritisation of medicines for use in Swedish healthcare raise several questions. Are all orphan medicines marketed in Europe automatically relevant treatment options and is it reasonable to assume that they automatically provide an added clinical benefit to patients? Are the companies' current price expectations for orphan medicines realistic and how can the industry help lower the barriers to sustainable patient access? How can collaboration be strengthened between different stakeholders?

The scientific and technological advancements, and especially the development of precision medicine, bring new opportunities and prospects for early detection, diagnosis and targeted treatment of rare and severe health conditions. This is a desired development that is important to support—from research, development, and marketing authorisation all the way to the very patients with truly unmet medical needs. The prerequisite of sustainability for healthcare systems all over Europe can however not be ignored. It is key for the functioning of healthcare systems, the availability of good quality care and for the public health and well-being of European patients and residents. This will also strengthen the conditions for long-term profitability of pharmaceutical companies with relevant and safe, effective - reasonably priced - and cost-effective medicines. All of this is fundamental to Europe's competitiveness in the global arena.

ORPHAN MEDICINAL PRODUCTS[5]

The regulatory framework for orphan medicinal products is governed by Regulation (EC) No 141/2000 of the European Parliament and of the Council. The original purpose was to address a gap in the pharmaceutical market and stimulate the research and development of medicines "intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the Community" or for conditions that "occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions". The regulatory framework also introduced the possibility of granting orphan medicines special access to financial incentives and other benefits such as market exclusivity for approved indications. The intention of the orphan legislation was to address unmet medical needs and treatment gaps for rare diseases, where there were no satisfactory treatment alternatives, and to promote medicines that were deemed to provide a significant benefit to patients. The regulatory changes in Europe, combined with research successes in e.g. molecular genetics and the shift towards precision medicine, have led to an increase in the proportion of authorised orphan medicines in Europe. From five percent for the period 2010-2012 to 13.6 percent for the period 2017-2019. The orphan market has also grown in monetary terms and constitutes a lucrative market segment within the pharmaceutical field.

[5] Regulation (EC) No 141/2000 of the European Parliament and of the Council, on orphan medicinal products

*** How was the review conducted?** An analysis of non-oncology orphan medicines authorised for the European market for the period 2017-2019, according to statistics from EMA's database. The review focused on the use of these medicines in Swedish healthcare, based on sales statistics in the Concise database of the Swedish eHealth Agency (total period 1 January 2017 to 30 June 2021). Pathways for introduction was established by reviewing TLV's reimbursement decisions and the NT Council's recommendations for use. Medicines with registered sales but an absence of positive TLV decisions or NT Council recommendations was deducted as regionally processed and introduced. Complementary qualitative assessment of the medicinal products was conducted by medical and pharmacological experts from Swedish healthcare, in addition to the review of referenced literature. The briefing paper was prepared by Region Västerbotten and Region Örebro County, in cooperation with Region Stockholm, Region Skåne, Swedish Association of Local Authorities and Regions (SALAR/SKR), and TLV.

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Layout: Leena Hortell, Ord & Co. Accessibility: WCAG Networks
Date: Original version 2022-02-24 (English abstract version 2025-04-12)