Sustainable patient access to orphan medicines in Sweden

Core factors in the pharmaceutical system that enhances long-term sustainability in 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. In recent years, the European pharmaceutical industry's annual analysis of availability to medicines (the "WAIT report") has portrayed Sweden as a country of poor patient access, below EU average, particularly of orphan medicines for patients with rare and severe conditions. Swedish healthcare representatives do not share this view. The shortcoming of the methodology and non-comparable data used for the analysis as well as the conclusions drawn by industry representatives in Sweden have been questioned. The recent take from the Swedish Association of the Pharmaceutical Industry (Lif) is to link the use of medicine in healthcare to Sweden's economic growth, attractiveness to pharmaceutical research and investments, and the country's competitiveness in an international context. The view on the pharmaceutical system is thus shifting from traditional health policy to an industrial policy instrument. From a healthcare perspective, the purpose of the pharmaceutical system is first and foremost to contribute to equal and high-quality care and good health. This is also confirmed in Sweden's national pharmaceutical strategy.

Nonetheless, reforms of the pharmaceutical system* are inevitable in an era of rapid scientific and technological advancements, an evolving pharmaceutical market, and a changing regulatory landscape. Strategies and actions are needed to strengthen equal and fair accessibility, at costs that are sustainable and financially viable for the system. This is important to avoid unintended alternative costs and displacement of other essential health and medical care. For the healthcare system to be robust and resilient, access to both new and well-established medicines must be ensured. Therefore, pharmaceutical system reforms need to be founded in the healthcare perspective. Constructive partnerships between parties operating within the system, and joint and mutually beneficial efforts, will be necessary. This briefing paper is the fourth of its kind and focuses on key factors to consider for long-term sustainability when designing such reforms.

Key Messages

1. **Healthcare resources are and will remain limited. The pharmaceutical system can contribute to wise choices in clinical practice** and strengthen the conditions for ethical prioritisation in terms of medicine – ensuring patient access when clinical benefits and costs appear reasonable from medical, humanitarian, and socio-economic perspectives.
2. **The pharmaceutical system should contribute to sustainable and equal care and public health, today and in the future. This requires access to appropriate treatment options based on patient needs - in a timely and affordable manner.** New innovative therapies as well as older, well-established effective medicines are needed. The pharmaceutical system is closely linked to conditions and events in the pharmaceutical market, but the system itself should not be viewed as an industrial policy instrument.
3. **The pharmaceutical system in Sweden performs well in terms of making relevant orphan medicines available for patients in need of treatment,** even when these medicines are sometimes introduced with high prices and significant uncertainties regarding safety and efficacy. If a medicine is not deemed reasonable from a medical, humanitarian, and socio-economic point of view, this can hinder, delay, or sometimes prevent patients' access to medicines. Not all new medicines authorised for the European market will be relevant at the national level, for the Swedish health care system.
4. **The pharmaceutical system in Sweden can be strengthened by joint commitments to relevant, robust and affordable patient access by government actors, the regions, as well as the industry.** Sustainable financing and costs of medicines is a fundamental prerequisite for functioning healthcare and public health. A well-functioning system will have the capacity and resources for research, development and introduction of new therapies and technologies. This benefits the pharmaceutical industry and contributes to goals and ambitions of competitiveness in the global pharmaceutical market.

* Pharmaceutical system consists of structures, resources and processes that interact within the broader health care system and aim to ensure equitable and timely access to safe, effective, quality pharmaceutical products and related services that promote appropriate and cost-effective use to improve health outcomes. Pharmaceutical system reform refers to a process of identifying and implementing contextually relevant strategies and actions that achieve coordinated and sustainable improvements in the critical components of the pharmaceutical system – to make it more responsive and resilient and to enhance its performance for achieving better health outcomes.

Does the Swedish pharmaceutical system need a "makeover"?

The pharmaceutical industry's perspective on the Swedish pharmaceutical system

The European Federation of Pharmaceutical Industries and Associations (EFPIA) annually compiles the so-called WAIT report to analyse the degree of availability of new medicines from an industry perspective. For Sweden, this report is supplemented by Lif's national analyses for Sweden. In recent years, the conclusions have been that many new medicines are either unavailable or face delays in Sweden —particularly medicines for patients with rare diseases[1]. Sweden is presented in a relatively poor light compared to many other European countries – in contrasts with other international reports that describe Sweden as a country with fast market introduction and an early adopter of essential innovative medicines[2]. Healthcare representatives in Sweden have openly criticised the view presented in previous WAIT reports, in particular the methodological shortcomings and the discrepancy of collected data[3]. Similar concerns have also been raised in Norway.[4] The OECD emphasises that international comparisons and measurements of availability of medicines will always be problematic and influenced by the organisation and financing of national health care systems.[5]

In its 2024 analysis, Lif refers to statistics from the Swedish Dental and Pharmaceutical Benefits Agency (TLV) and the New Therapies Council (NT Council) of the regions. TLV granted reimbursement for 82% (50/61) of all applications that completed an evaluation process in 2022. This figure does not include cases where companies have chosen to withdraw their applications during an ongoing review. The NT Council issued positive recommendations for 66% (46/70) of the medicines that underwent the regions' joint introduction processes between May 2016 and April 2023. These figures exclude all pending recommendations. According to Lif this is a "relatively low proportion of clear decisions" for new medicines. The system is diffusely described as "complicated" and a system hampered by delays or complete absence of necessary decision making. Lif calls for a modernisation of the Swedish pharmaceutical system. Furthermore, Lif calls for enhanced industry policy perspectives and consideration to competitiveness in decisions on how medicines are reimbursed and used in the Swedish healthcare system.[6]

The concept of a "pharmaceutical system" from a healthcare perspective

The term "pharmaceutical system" can be defined as the structures, resources and processes that interact with the healthcare system to achieve equal access to high quality, safe, effective, affordable, and cost-effective medicines. These factors contribute to the overall goal of good public health. The pharmaceutical system is thus part of the broader healthcare system. From a healthcare perspective, a review of the pharmaceutical system is necessary, and reforms are needed for the system to align with the current trends and developments. This entails identifying and implementing strategies and measures to achieve sustainable improvements in the critical components of the pharmaceutical system – with the aim of enhancing patient access to appropriate treatments, at the right time, at a reasonable cost, and based on the truly unmet medical needs of patients.[7]

Sweden's National Pharmaceutical Strategy for 2024–2026 focuses on availability of new and already introduced and established medicines; effective pharmaceutical management; and development of new medicines and clinical trials. Appropriate use of medicines and costs that are reasonable in relation to effect and available resources is at the core of the strategy.[8]

The OECD emphasises that patient access is multidimensional and is influenced by many factors. Availability entails high quality, safe and effective medicines on the market, as well as a robust security of supply of medicines that have been introduced. Affordability is reasonably priced medicines and sustainable and manageable costs from a payer perspective (including patients and the public). Affordability can also reduce financial barriers and contribute to timely reimbursement decisions and introduction in healthcare. Acceptability of healthcare professionals and patients is critical for adoption. This includes trust in the pharmaceutical system. The OECD further points out that expectations of 100% accessibility to all new medicines is neither realistic nor necessary – not even from a patient perspective. Healthcare systems operate within resource constraints which call for prioritisation. This is key for the long-term sustainability of healthcare systems.[9]

[1] EFPIA (2024), EFPIA Patients W.A.I.T. Indicator 2023 Survey; Quantify (2024), Swedish national reimbursement of new medicines with EMA approval 2020-2022 (Lif's analysis for Sweden).

[2] See for example OECD (2024), OECD Health Working Papers No. 170 Access to oncology medicines in EU and OECD countries; IQVIA (2022), Defining Essential Innovative Medicines and Measuring their Use in Europe; Draghi, Mario (2024), The future of European competitiveness, Part B | In-depth analysis and recommendations, September 2024

[3] Region Västerbotten and Region Örebro County (2021), Kunskapsunderlag, Tillgänglighet till nya läkemedel för patienter i Sverige – utgångspunkter från svensk hälso- och sjukvård; Dagens Medicin, "Lif ger en missvisande bild av tillgången till läkemedel", published 2021-07-06

[4] Dagens Medisin, "Når har en pasient faktisk tilgang til en ny medisin?", published 2023-04-25

[5] OECD (2023), Exploring the feasibility of monitoring access to novel medicines: A pilot study in EU Member States

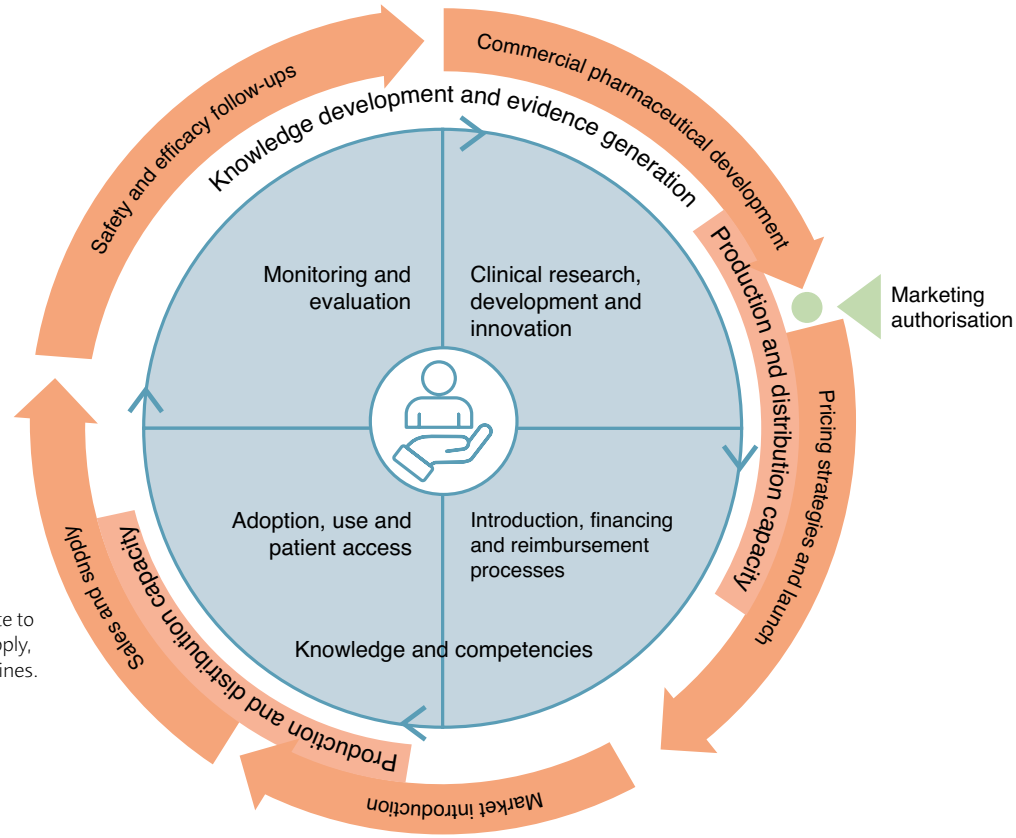
[6] Lif (2024), Handlingsplan för ett modernt läkemedelssystem

[7] Hafner, Tamara et al (2017), Defining pharmaceutical systems strengthening: Concepts to enable measuring, Health policy and planning, 32, 572-584. published 2017-05-01

[8] Regeringskansliet, Socialdepartementet, National pharmaceutical strategy 2024–2026

[9] OECD (2020), Addressing Challenges in Access to Oncology Medicines, Analytical Report och OECD (2023)

The current pharmaceutical system in Sweden and its relationship with the healthcare system



Generic illustration of the pharmaceutical system in Sweden and its key components from a healthcare perspective (blue fields). These include both reimbursed medicines (prescription medicines) and procured hospital-administered medicines (hospital medicines).

The illustration also highlights key components from a corporate perspective (orange fields).

The key components of the system interact with each other and contribute to pharmaceutical development and supply, which impact patient access to medicines.

The pharmaceutical system as an integral part of the healthcare system

The pharmaceutical system is an integral part of the healthcare system. The mandated government authorities and the 21 regions are responsible for different components within the system. The system also includes commercial actors that contribute to pharmaceutical development and supply. Commercial actors determine pricing strategies, launch and marketing of authorised medicines. Their production and delivery capacities are crucial for both sales and the supply of medicines on the market. This influences patients' access to medicines.

Sweden's pharmaceutical system includes medicines covered by the national pharmaceutical benefits scheme. Patients' costs of medicines over the high-cost protection threshold are then subsidised by the state. This is a benefit targeting patients (primarily for prescription medicines) and not a benefit or a right for pharmaceutical companies. The system also manages hospital medicines, which are procured and funded by the regions.[10] Hence, the financial responsibilities within the system are shared between the state and the regional level.

Patient access can be associated with various opportunities and challenges related to pricing, introduction, financing, and supply. Medicines that are introduced and used also require follow-up—both within the healthcare system and by pharmaceutical companies.

A more detailed description of the Swedish pharmaceutical system can be found in Appendix 1.

LONG-TERM SUSTAINABILITY IN SWEDISH HEALTH AND MEDICAL CARE

Life expectancy and overall health of the population in Sweden is above average, in comparison to most other countries in Europe. The quality of Swedish health and medical care is good and access to health and medical care is universal. The total costs of health and medical care, per capita, exceed the EU average, but individual patients' share of these costs is relatively low. This creates good conditions for equal care and health.[11] Safeguarding the sustainability of the healthcare system is therefore important for public health and the country's prosperity.

According to the National Board of Health and Welfare (Socialstyrelsen), long-term sustainability in health and medical care can be understood from social, economic and environmental perspectives.[12] The environmental perspectives consider the environmental footprint on humans and nature. The social and economic aspects are to be understood in terms of equal care and a coordinated and effective use of the public resources available in the system. This is derived from the Health and Medical Services Act and the three ethical principles of priority within the Swedish health care system: The human dignity principle, the needs and solidarity principle, and the cost-effectiveness principle. Furthermore, health and medical care should be based on good quality, scientific evidence and proven experience. The national pharmaceutical strategy for 2024-2026 further emphasises the correct use of medicines, and costs that are reasonable in relation to the effect of use and available resources in the short and long term.[13]

[10] See legislation on pharmaceutical benefits (2002:160) and public procurement (2016:1145)
[11] OECD/European Observatory on Health Systems and Policies (2023), State of Health in the EU State of Health in the EU: Sweden Country Health Profile 2023
[12] Derived from the report "Bästa möjliga hälsa och en hållbar hälso- och sjukvård - Med fokus på vården vid kroniska sjukdomar" (National Board of Health and Welfare, 2018)
[13] See the Health and Medical Services Act (2017:30), Municipal Act (2017:725), Patient Act (2014:821)

How does the Swedish pharmaceutical system perform in terms of patients' access to orphan medicines?

In international comparisons undertaken by the pharmaceutical industry, Sweden often ranks poorly. The 2024 WAIT report illustrates Sweden's overall availability of medicines as worse than in countries such as Luxembourg, Spain, and Denmark. For orphan medicines, Sweden ranks lower than Poland, Slovenia, Greece, and Bulgaria and is assumed to have slower access than for example North Macedonia and Serbia.[14] The report does not mention the major methodological shortcomings and inconsistent selection of entry data, and how this affects the comparison. Numerous other reviews and studies on the availability and reimbursement of medicines – not conducted by the pharmaceutical industry – provide a more nuanced picture of the performance of Sweden's pharmaceutical system. For example, the IQVIA Institute highlights Sweden as a leader in Europe when it comes to the use of essential innovative medicines, particularly medicines with new active substances. An OECD study on the availability of oncology medicines in Europe placed Sweden at the top in terms of reimbursement of high-clinical-value medicines and the share of indications covered. The time from a company's application to a reimbursement decision was among the fastest in the study. In Mario Draghi's report on Europe's future competitiveness Sweden is identified as one of the countries where medicines are first launched in Europe.[15]

Nonetheless, to draw meaningful conclusions about Sweden's pharmaceutical system, in-depth national analyses are required – including both quantitative and qualitative data.

Focus on orphan medicines authorised 2017– 2022

Between 2010 and 2022, approximately 1,200 medicines were granted European marketing authorisation by the European Medicines Agency (EMA). The proportion of orphan medicines has increased over time – from 2% during 2011–2013 to 19% in 2020–2022.[16] This in-depth analysis focuses on patient access to orphan medicines, as this is frequently described as one of the major shortcomings of the Swedish system. The selection includes orphan medicines approved in Europe between 1 January 2017 and 31 December 2022. The cut-off date for the review was set to June 30, 2024.[17] A total of 96 orphan medicines with European marketing authorisation were included.

Availability: Ensuring that effective and safe medicines are available on the European market

- **100% (96/96) of orphan medicines are available for use in Sweden,** based on the legislated "free prescription right". Prescribers can prescribe all medicines that are authorised regardless of official introduction or reimbursement status. Medicines that are not authorised for the European market can be prescribed with approval from the Swedish Medical Products Agency.
- 27% (26/96) of orphan medicines were approved with conditions or under special circumstances due to limited evidence. 13% of approved medicines (12/96) were advanced therapies (ATMPs).

Marketing and supply: Companies actively marketing and supplying medicines in Sweden

- **61.5% (59/96) of orphan medicines were actively marketed in Sweden** by pharmaceutical companies. This is not directly linked to reimbursement decisions or recommendations for use. Medicines not actively marketed in Sweden can still be imported when needed.
- Among the orphan medicines marketed in Sweden, the majority were used within healthcare. A small number had been used but were not yet formally marketed in Sweden.[18]

Accessibility: Patient access and use in healthcare

- **56% (54/96) of orphan medicines had been used within Swedish healthcare.** 67% of these (36/54) were introduced through national processes (17 prescription medicines, 19 hospital medicines). 33% (18/54) were introduced through regional processes.
- 44% (42/96) of the orphan medicines had not yet been used in Swedish healthcare. 90% (38/42) had not completed a national introduction process. 10% (4/42) had undergone a national process but received negative recommendations or reimbursement decisions. Some orphan medicines were in an ongoing process. In a few cases, companies had stated that launch in Sweden was not planned due to lack of relevant patient populations.

Public funding: Reimbursement and cost-coverage for medicines that are used in healthcare

- **67% (36/54) of the orphan medicines used in Sweden had received positive national reimbursement decisions** (TLV reimbursement for prescription medicines or positive recommendation for use from the NT Council). These medicines had undergone national introduction processes, with the majority receiving positive decisions following negotiations and agreements with the regions. More than half of these medicines had high uncertainties in their health economic evaluations.
- **33% (18/54) of the orphan medicines used in Sweden received positive regional reimbursement decisions**. These medicines were managed regionally. Individual reimbursement can be granted for patients, under exceptional circumstances and if they are deemed cost-effective at the individual level. Of the positive regional reimbursement decisions, approximately half had received negative national decisions. The remaining medicines had not completed the established national introduction processes.

[14] EFPIA (2024), EFPIA Patients W.A.I.T. Indicator 2023 Survey

[15] OECD (2024)/OECD Health Working Papers No. 170; IQVIA (2022); and Draghi (2024)

[16] Statistics from EMA, Medicines data table (medicines for human use), 2024-08-21. https://www.ema.europa.eu/en/medicines/download-medicine-data

[17] For ATMPs the cut-off date for sales (use) was 31 December 2023 due to data availability.

[18] Ebvallo, Filsuvez, Voxzogo and Vyxeos liposomal are registered as marketed in Sweden but have not yet been used. Libmeldy and Tavneos have been used but are not formally marketed by the companies. Libmeldy has a national recommendation for use (positive decision on reimbursement), after a joint Nordic negotiation process.

- **Only a small proportion of orphan medicines received negative national decisions or recommendations (14% or 13/96).** This also includes medicines that have not undergone the full national introduction processes or where companies have withdrawn their applications. When only measuring orphan medicines that have completed the national introduction process, the proportion is 27% (13/49).

Public expenditure: The cost of patient access and use of orphan medicines

- **The costs of the 54 orphan medicines varied,** depending on both the price of the medicine and the volume in terms of use (sales). For the period 1 January 2019 to 30 June 2024, the total medicine costs for these 54 orphan medicines amounted to approximately SEK 5.5 billion (gross sales, excluding potential rebates).
- Orphan medicines classified as ATMPs generated sales of approximately SEK 610 million (excluding potential rebates) for the period 1 January 2019 to 31 December 31. This included six recommended ATMP medicines: Kymriah, Yescarta, Zolgensma, Luxturna, Tecartus, and Libmedly. From their initial availability in 2019 through 2023, around 130 patients were treated with commercial ATMPs in Sweden, excluding patients treated in clinical trials or with non-commercial ATMPs under the hospital exemption. Over 80% of the total costs (around SEK 500 million) occurred in 2022–2023. More than half of the total sales volume was attributable to the CAR-T therapy Yescarta, while about one-third was for the gene therapy Zolgensma. Both medicines were global blockbusters in 2023, with total sales volumes of approximately USD 1.5 billion (Yescarta) and USD 1.2 billion (Zolgensma).
- **A few indications stood out in terms of total medicine costs.** Spinal muscular atrophy (SMA), Cystic fibrosis and hereditary transthyretin amyloidosis with polyneuropathy (hATTR, in Sweden referred to as the "Skelleftesjukan" due to its endemic nature). Tegsedi. The total sales for orphan medicines for these indications (authorised 2017-2022) amounted to approximately SEK 3.2 billion. In addition, sales for previously approved medicines for these indications accounted for another SEK 3 billion. These medicines are used for very limited patient populations.[19]

EVERY DAY COUNTS – TIME TO PATIENT ACCESS IS A JOINT RESPONSIBILITY

The time from European marketing authorisation to national reimbursement and use varies. Several actors influence how quickly, or slowly, actual patient access can take place – also the pharmaceutical companies have a responsibility.

In the briefing paper from 2023, the time to access for orphan medicines in Sweden was analysed in more detail. The median time to the first national decision for hospital medicines was 320 days. About half of this time (156 days) was attributed to TLV's work on the health economic assessment. The remaining time was roughly evenly split between the pharmaceutical companies (submission of necessary documentation) and the regions (process for recommendation of use, including negotiation with companies). The 21 regions' decision to pursue regional collaboration and joint introduction of hospital medicine were generally made before the marketing authorisation date, providing companies with good foresight for their marketing in Sweden. For prescription medicines, the median time to the first national reimbursement decision was 526 days. Two-thirds of this time (360 days) accounts for the companies own processes for submission of a complete reimbursement applications. The remaining time covered TLV's processing of the application, including clock stop. In cases where confidential agreements or alternative payment models are negotiated, the regions and the pharmaceutical companies share the responsibility to reach a mutual agreement in a timely manner. Failure to do so is a failure on both sides.[20]

Lif sometimes emphasises that companies' marketing and supply in Sweden is fast, referring to a listing in the FASS registry. However, listing a medicine in FASS only indicates the availability of packaging information for approved medicines (median time: 16 days for medicines approved between 2020–2022). This is not the same as companies actively marketing and supplying medicines in Sweden. The actual time for this varies. According to statistics from the eHealth Agency's VARA database, the median time for marketing and supply of the orphan medicines studied in this report was 301 days.[21]

[19] For SMA, the therapies are Spinraza, Zolgensma, and Evrysdi (used for Type 1 SMA). For Cystic fibrosis, Symkevi and Kaftrio were approved after 2017. Kalydeco and Orkambi were approved before 2017 and the additional sales for these therapies during the period January 2019 to June 2024 totalled approximately SEK 1.9 billion. For hATTR/"Skelleftesjukan", the therapies Tegsedi, Onpattro, and Amvuttra were included in the analysis. Vyndaqel was approved before 2017 and was already included in the reimbursement system. Total sales for the period accounted for SEK 1.1 billion, some of which applies to wild-type transthyretin amyloidosis.

[20] Region Västerbotten, Region Skåne, Region Örebro County (2023), Tillgängliggörande av särläkemedel i svensk hälso- och sjukvård -Användning och tid till användning enligt införande¬processer för läkemedel i Sverige

[21] Date for marketing authorisation from EMA/Human medicines database; date for companies' submitted application/complete documentation as well as TLV's health economic evaluations from TLV; date for the regional collaboration processes and joint recommendations from the regions' joint coordination office for medicines. Complementary data on companies' marketing and supply in Sweden from the eHealth Agency's VARA database. Note that Lif's data on marketing and supply is based on listing in FASS and tracks registration of medicines in the eHealth Agency's LiiV database.

AVAILABILITY, SUPPLY AND ACCESS TO ORPHAN MEDICINES IN SWEDEN

Orphan medicines with European **marketing authorisation**, 2017–2022 (96)

Orphan medicines that are **available** for use in Swedish health care, according to prescription rights (96) — AVAILABLE 100%

SUPPLIED 61,5% — Orphan medicines that are **marketed and supplied by companies** on the Swedish market. Based on registry in the VARA database of the eHealth Agency, per 30 June 2024 (59)

Amvuttra, Arikayce liposomal, Aspaveli, Besponsa, Brineura, Bylvay, Cablivi, Crysvita, Cystadrops, Ebvallo, Enspryng, Epidyolex, Evrysdi, Filsuvez, Fintepla, Givlaari, Hepcludex, Idefirix, Inrebic, Isturisa, Jorveza, Kaftrio, Kimmtrak, Koselugo, Kymriah, Ledaga, Livtencity, Lunsumio, Lutathera, Luxturna, Minjuvi, Myalepta, Mylotarg, Namuscla, Natpar, Ngenla, Onpattro, Pemazyre, Poteligeo, Prevymis, Polivy, Qarziba, Reblozyl, Rydapt, Scemblix, Spinraza, Symkevi, Takhzyro, Tecartus, Tegsedi, Trecondi,Voraxaze, Voxzygo, Vyxeos liposomal, Xermelo, Xospata, Yescarta, Zejula, Zolgensma

NOT SUPPLIED 38,5% — Orphan medicines that are **not marketed and supplied by companies** on the Swedish market. Based on registry in the VARA database of the eHealth Agency, per 30 June 2024 (37)

Abecma, Amglidia, Alofisel, Artesunate Amivas, Ayvakyt, Carvykti, Chenodeoxy-cholic acid Lediant, Daurismo, Dovprela, Elzonris, Enjaymo, Imcivree, Kinpeygo, Lamzede, Livmarli, Libmeldy, Mepsevii, Mycapssa, Nulibry, Nyxthracis, Oxbryta, Oxervate, Oxlumo, Palynziq, Pyrukynd, Qinlock, Roctavian, Skytrofa, Sogroya, Tavneos, Trepulmix, Upstaza, Verkazia, Vyvgart, Waylivra, Xenpozyme, Zokinvy

USED 56% — Orphan medicines that have been **used in health care**. Based on sales statistics 1 Jan 2017 - 30 June 2024 (54)

Orphan medicines that have **not been used in health care**. Based on sales statistics 1 Jan 2017 - 30 June 2024 (42) — NOT USED 44%

67% — National introduction process, positive reimbursement via TLV (17)

Positive costeffectiveness (47%)
- Inrebic
- Jorveza
- Ledaga*
- Natpar
- Ngenla
- Prevymis
- Rydapt*
- Scemblix*

Agreement with the regions (53%)
- Amvuttra
- Givlaari
- Hepcludex
- Kaftrio
- Symkevi
- Takhzyro
- Xermelo
- Xospata*
- Zejula*

National introduction process, positive recommendation NT Council (19)

Positive costeffectiveness (16)
- Besponsa*
- Mylotarg
- Qarziba*

Agreement with the regions (84%)
- Cablivi
- Crysvita
- Evrysdi
- Idefirix
- Kymriah*/**
- Libmeldy**
- Lutathera*
- Luxturna**
- Onpattro
- Polivy*
- Poteligeo*
- Spinraza
- Tecartus*/**
- Tegsedi
- Yescarta*/**
- Zolgensma**

33% — Regional introduction process or individual reimbursement (18)

Negative decision TLV (33%)
- Aspaveli
- Bylvay
- Cystadrops
- Epidyolex
- Koselugo
- Livtencity

Negative NT recommendation (17%)
(• Kimmtrak*)
- Minjuvi
- Reblozyl

Ongoing national process (6%):
- Pemazyre*

Not completed national process (44%)
- Arikayce liposomal
- Brineura
- Namuscla
- Trecondi*
- Fintepla
- Enspryng*
- Tavneos
- Voraxaze

10% — National introduction process, negative reimbursement or recommendation via TLV/NT (4)

Negative TLV decision (50%)
- Imcivree
- Voxzogo

Negative NT recommendation (50%)
- Alofisel**
- Waylivra

90% — Not completed or ongoing national process and absence of positive regional decision (38)

Ongoing national process (18%)
- Abecma*/**
- Carvykti */**
- Enjaymo
- Ebvallo**
- Roctavian**
- Vyvgart
- Lunsumio*

Absence of completed process (74%)
- Amglidia
- Artesunate Amivas
- Ayvakyt*
- Chenodeoxycholic acid Leadiant
- Daurismo*
- Dovprela
- Elzonris*
- Filsuvez
- Isturisa
- Kinpeygo
- Lamzede
- Livmarli
- Mepsevii
- Myalepta
- Mycapssa
- Nulibry
- Nyxthracis
- Oxbryta
- Oxervate
- Palynziq
- Pyrukynd
- Qinlock*
- Skytrofa
- Sogroya
- Trepulmix
- Verkazia
- Vyxeos liposomal*
- Zokinvy

Company will not launch in Sweden (8%)
- Oxlumo
- Upstaza**
- Xenpozyme

* = Oncology orphan medicine

** = Advanced therapies, ATMP

( ) = Medicine with negative recommendation that is enrolled in a renewed and ongoing national process

The review illustrates the primary pathway for introduction of different medicines. Some medicines have been phased over from national to regional management.

Note: Active marketing and supply of authorised medicines by companies in Sweden is not directly linked to the introduction processes. Health care professionals are free to prescribe and use authorised medicines in health care.

An in-depth presentation of the orphan medicines in this illustration is found on pages 7-12.

56% Which Orphan Medicines Have Been Used in Sweden?

The ethical prioritisation platform adopted by the Swedish Parliament serves as the foundation for decision-making in healthcare. The application of these principles in the introduction of medicines involves a holistic assessment of factors such as the severity of the condition, the rarity of the disease, the actual treatment effect, and the reliability of clinical and health economic data. Sweden is allocating increasing resources to new orphan medicines. According to the need and solidarity principle it is justified to allocate more of healthcare resources for patients with greatest needs. However, as shown below, significant uncertainties often undermine informed decision making and complicate de facto prioritisation. At the same time, the system is increasingly faced with challenges of medicine shortages and vulnerabilities to patient access in terms of older, well-established, and often life-saving essential medicines that are equally necessary for a functioning healthcare system.

This is a deep dive into capabilities and challenges of the pharmaceutical system in providing patient access to orphan medicines in Sweden. As such, this section offers a transparent qualitative review of the studied orphan medicines used in Swedish healthcare.[22]

NATIONAL PROCESSES AND REIMBURSEMENT DECISIONS

Joint national negotiations enable patient access

Most orphan medicines that have been used in Sweden have received positive national reimbursement decisions or recommendations for use. Initially, most of these medicines were not deemed cost-effective, even with an increased willingness to pay. However, they were introduced after joint national negotiations that resulted in agreements with pharmaceutical companies. Examples include ATMP medicines such as **Kymriah, Libmeldy, Luxturna, Tecartus, Yescarta,** and **Zolgensma**. Since ATMP treatments often involve complex procedures and require standardised protocols, healthcare providers must, in some cases, undergo qualification processes before these therapies can be administered. Some treatments also target very small patient groups with rare and severe conditions which call for a geographical concentration of the treatment to one or a few university hospitals, with nationwide responsibility for all patients. For example, the gene therapy Zolgensma is administered at specialised centres in Region Stockholm and Region Västra Götaland. The gene therapy Libmeldy is administered at a Nordic treatment centre in Region Skåne.

The orphan medicines **Amvuttra, Givlaari, Kaftrio,** and **Takhzyro** (prescription medicines) as well as **Evrysdi, Onpattro,** and **Spinraza** (hospital medicines) have also been subject to joint national introduction processes and negotiations.

These are all important treatments but carry uncertainties regarding safety and efficacy and added clinical benefit. Their high costs also translate into uncertainties in the health economic evaluation. Many negotiations result in agreements, often involving a confidential rebate. Sometimes more complex payment models and agreements have been applied. For the ATMP Zolgensma, the initial ambition was to enter a performance-based payment model with individual patient follow-up. However, the approach proved incompatible with current legal restrictions on data use and sharing of sensitive data stemming from small patient groups. Availability of high-quality data was also limited. Instead, Zolgensma was introduced with a traditional rebate agreement. For the orphan medicine **Kaftrio**, several extended negotiations were needed before an alternative entry agreement with a population level expenditure cap was reached. This agreement covered all approved cystic fibrosis medicines – including Kalydeco, Symkevi, and Orkambi – and ensures broad patient access, although at a proportionally high cost in terms of the total public expenditure on medicines.

Uncertainties are accepted but can delay or complicate patient access

Among the orphan medicines that underwent health economic evaluations and were deemed cost-effective only after negotiations, about half were associated with very high uncertainty. Examples include **Crysvita, Evrysdi, Idefirix, Onpattro, Polivy, Spinraza** as well as the ATMP therapies **Libmeldy, Luxturna, Tecartus,** and **Zolgensma**. Identified uncertainties stem from the clinical studies, documented treatment effects, and the overall evaluation of the evidence base generated before market authorisation. Medicines such as Koselugo, Minjuvi, Pemazyre, Ebvallo, Tecartus, and Zolgensma were approved based on open-label, single-arm studies with very limited number of patients and only indirect comparisons. Koselugo and Minjuvi received negative national reimbursement decisions (not only in Sweden but in several countries) due to these uncertainties. Despite this, decentralised regional processes and the possibility to apply individual patient-based reimbursement have allowed their use under exceptional circumstances.

In TLV's health economic assessments of orphan medicines, there is significant variation in cost per quality-adjusted life year (QALY). In sensitivity analyses, this variation is even greater. Crysvita is an example where the cost per QALY was estimated at SEK 3 million in the base scenario of the company. In the TLV scenario the same estimate was SEK 12 million per QALY. The adopted time horizon, assumptions about conventional treatment effects, and quality-of-life weightings had a major impact on the final valuation in this case.[23]

For ATMPs, which are often assumed to be one-time treatments, the primary uncertainty stems from questions regarding long-term effects and side effects. A one-time treatment does not necessarily mean cure. Combined with high prices, this uncer-

[22] Information on each medicine is gathered from EMA (https://www.ema.europa.eu/); TLV (https://www. tlv.se/); and the regions' joint coordination office for medicines (https://samverkanlakemedel.se/) – complemented by qualified medical and pharmacological assessments.

[23] Reference tlv.se for the health economic evaluations as well as TLV (2023), Uppdrag att analysera och föreslå hur patienternas tillgång till läkemedel för behandling av sällsynta sjukdomar kan stärkas. Delredovisning av regeringsuppdrag

tainty creates significant challenges to patient access. As a result, some medicines undergo repeated reassessments and renegotiations based on updated or new documentation on safety and efficacy before reimbursement and use can be recommended. Examples of this include Luxturna and Tecartus.[24]

High prices and high costs pose threats to patient access and sustainability

Zolgensma and **Libmeldy** are examples of ATMP one-time treatments both launched under the label "the world's most expensive medicines." At the time of their health economic assessment in Sweden, the officially stated prices were approximately SEK 20 to 31 million per patient treated. Libmeldy, used for the treatment of metachromatic leukodystrophy, was introduced without relevant treatment alternatives for patients—other than best supportive care. Zolgensma was the first gene therapy for SMA, but an alternative treatment had already been established in Sweden: **Spinraza**, a continuous treatment with a medicine cost of approximately SEK 4.8 million in the first year and then about SEK 2.4 million annually (excluding potential rebates). For the third medicine introduced for SMA, **Evrysdi**, the estimated annual medicine cost was on par with Spinraza's yearly cost. The medicines **Amvuttra**, **Givlaari**, and **Oxlumo**[25] are three medicines with similar mechanisms but approved for different rare conditions: hATTR/"Skelleftesjukan", acute hepatic porphyria, and primary hyperoxaluria type 1. All three medicines are marketed by the company Alnylam and stem from the same platform technology. The officially stated prices for Amvuttra and Givlaari varied at the time of introduction in Sweden between SEK 4.5 to 5.9/11.8 million per patient per year.[26]

Nonetheless, the official prices do not tell the full story. As all these medicines are subject to agreements with confidential prices, it is not possible to determine the actual cost of treatment per patient—after potential rebates—in specific cases. Rebates cannot be equated with cost savings but are rather a necessary reduction of the officially stated price for the medicines to be considered cost-effective given current practices. Moreover, rebate levels vary, and the medicines remain costly for the public despite rebates.

Prices, combined with the total number of patients treated (volume), equals the overall budget impact. Extremely high prices, despite relatively small patient groups, can still result in significant budgetary impact and pose risks of displacing other healthcare services that lead to subsequent net health loss. The medicines for cystic fibrosis are illustrating examples of this dilemma. All four authorised orphan medicines are covered by the pharmaceutical benefits scheme in Sweden. Total costs between 1 January 2019 and 30 June 2024 amounted to approximately SEK 2.9 billion, excluding rebates. These orphan medicines are marketed by the same pharmaceutical company, Vertex, which holds a market monopoly in the cystic fibrosis indication. The ability for the buyer, i.e. payer, to influence and reduce prices in a market with no competition is generally low. It is therefore not a surprise that public expenditure for cystic fibrosis medicines is high, as are company sales, not only in Sweden. All authorised medicines have, at some point, been so called "blockbusters" – selling more than USD 1 billion per year. For the orphan medicine Kaftrio (also known as Trikafta), sales on the global market, amounted to USD 8.9 billion in 2023; USD 7.7 billion in 2022; and USD 5.7 billion in 2021.[27]

For conditions of endemic nature, with (uneven) geographical concentration of the patient population, the budget impact on different healthcare providers and payers can also differ. One example is the cost of medicines for hATTR/"Skelleftesjukan", which is concentrated in the northern regions of Sweden. The pharmaceutical budgets of regions Norrbotten and Västerbotten have thus been significantly impacted as the orphan medicines Onpattro and Tegsedi were introduced. With the negotiated rebate for the prescription medicine Amvuttra and the subsequent TLV reimbursement decision in 2023, the treatment regime is now shifting away from the hospital-administered treatment options (Onpattro and Tegsedi). Consequently, the payer responsibility and costs have also shifted from the regional level to the national pharmaceutical benefit system. The reverse occurs when prescription medicine use is replaced by hospital medicines.

REGIONAL PROCESSES AND DECISIONS

Regional processes and individual reimbursement scheme also enable patient access

For medicines that have been rejected for national reimbursement or lack national decisions or recommendations, patient access can still be enabled through regional processes in place. Examples of this include **Epidyolex**, **Koselugo**, and **Minjuvi** (which received negative national decisions or recommendations) and **Namuscla**, **Enspryng**, and **Tavneos** (which have not yet started or completed national introduction processes). The degree of medical urgency and necessity dictate individual-level use and reimbursement in exceptional circumstances.

Several orphan medicines can be categorised as "repurposed" medicines, many of which have originally been approved, established and used as treatment for other indications – before receiving market authorisation as an orphan medicine. For these medicines, it is difficult in the analysis to determine whether their use in Swedish healthcare is based on the original indication or the narrower orphan medicine indication. Namuscla and Epidyolex are examples of such repurposed medicines. **Namuscla** (mexiletine) was originally approved as a cardiology medicine for patients with severe cardiac arrhythmias. This indication is no longer valid under the current European approval, which instead covers the orphan indication for patients with dystrophic myotonia. **Epidyolex** (cannabidiol) was initially es-

[24] Abuloha, Sumaya et al (2024), A Review of the Cost-Effectiveness Evidence for FDA-Approved Cell and Gene Therapies, Human Gene Therapy, vol. 35 (ed. 11-12), s 365-37. published 2024-06-01.

[25] Oxlumo is not marketed in Sweden. See section "Which orphan medicines have not yet been used in Sweden?"

[26] For Givlaari the price varies between SEK 5.9 and 11.8 million depending on the patient's weight. For Evrysdi official prices are sourced internationally, e.g. via Canadian Journal of Health Technologies, Aug 2021, Volume 1, Issue 8, CADTH Reimbursement Recommendation Risdiplam (Evrysdi)

[27] Vertex https://investors.vrtx.com/news-releases/news-release-details/vertex-reports-fourth-quarter-and-full-year-2023-financial och https://investors.vrtx.com/news-releases/news-release-details/vertex-reports-fourth-quarter-and-full-year-financial-2022

tablished as an anti-epileptic medicine. Its orphan designation applies to Lennox-Gastaut syndrome and Dravet syndrome. Similarly, **Fintepla** is approved for specific childhood epilepsy forms, mainly for symptom relief, often in combination with other epilepsy medicines. Fintepla can also be considered a repurposed medicine, as its original substance, fenfluramine, was previously used in weight-loss medications. It was withdrawn in Sweden in the 1980s due to severe side effects and heart-related issues.

Other examples of repurposed medicines include **Arikayce liposoma**l, **Cystadrops**, and **Jorveza**.

A common feature of repurposed medicines is that the patent for the original indication has often expired, and production costs are typically very low.

PRICE TRANSPARENCY – IS IT A CITIZENS' RIGHT?

As the pharmaceutical market in Europe and internationally is characterised by price discrimination and parallel pricing systems—official prices and confidential prices—the question of price transparency has emerged. According to an OECD study, increased transparency and shared information on actual prices are desirable from a payer perspective and for a functioning market with sound competition. However, conditions for transparency vary between countries, as does the perception of risks and potential consequences of increased price transparency on companies' pricing strategies and the ability to introduce medicines at reasonable prices in each country. Sweden is one of the few European countries that apply value-based pricing. The prevalence of agreements with confidential costs and prices for new medicines is increasing.[28]

In Spain, the issue of price transparency has recently been raised from a citizen and taxpayer perspective, leading to the disclosure of net prices for some orphan medicines. This initiative was driven by the civil society organisation Fundación Civio. The decision to disclose "net prices" (prices after rebates) was made by Spain's transparency council, "El Consejo de Transparencia y Buen Gobierno." This decision acknowledged that it is of public interest – and a right – to know how public healthcare resources are spent. This overrode the risks of the potential commercial harms to the pharmaceutical companies, particularly as the disclosed net prices covered medicines with limited competition in the foreseeable future.

The net prices of the following medicines have been disclosed.[29] All are ATMP gene therapies.

- Kymriah: Spanish net price approximately EURO 307,000 (SEK 3.5 million).
- Yescarta: Spanish net price approximately EURO 314,000 (SEK 3.5 million).
- Luxturna: Spanish net price approximately EURO 221,000 (SEK 2.5 million).
- Zolgensma: Spanish net price approximately EURO 1,340,000 (SEK 15.1 million).

The difference between official prices and rebated net prices in Spain varied from about 5% for Kymriah and Yescarta (CAR-T for oncology) to about 35% for Luxturna and Zolgensma (non-oncology orphan medicines). It is important to note that these prices apply to the Spanish context and do not indicate corresponding net prices or agreements in Sweden.

[28] OECD (2024), Exploring the feasibility of sharing information on medicine prices across countries

[29] See e.g. Fundación Civio: https://civio.es/medicamentalia/2019/10/29/car-t-kymriah-yescarta-precios-novartis-gilead/ och https://civio.es/medicamentalia/2023/04/11/precio-zolgensma-luxturna-novartis/ Note that prices are exclusive of VAT. The information is derived based on agreements signed between the companies and different hospitals in Spain. All prices are states per single treatment. For Luxturna, a treatment for a rare eye disease, the price is per single treatment, per eye. Corresponding net prices in SEK are based on the EURO/SEK exchange rate of 11.3, per 30 June 2024. Differences in exchange rate can thus occur for signed agreements.

44% Which orphan medicines have not yet been used in Sweden?

The reasons why certain orphan medicines have not been used in Sweden can vary. It is likely a combination of factors. First and foremost, with a few exceptions, these medicines are not introduced, marketed and made available by the companies on the Swedish market. According to Lif, this may be explained by small patient populations, a lack of company representation in the Nordic region – resulting in limited knowledge of the Swedish pharmaceutical system – or an assumption that the likelihood of a positive reimbursement decision is low for the specific medicine.[30]

From a healthcare perspective, the relevant question is how this affects the availability of safe, effective and cost-effective medicines for health care providers and what the consequences are for patients' access to relevant treatment options.

This is a deep dive into orphan medicines that have not been made available in Sweden, including a transparent qualitative review of each of these medicines.[31]

COMPLETED NATIONAL PROCESSES AND NEGATIVE DECISIONS

For **Alofisel**, **Imcivree**, **Voxzogo**, and **Waylivra**, there are negative national decisions or recommendations. In the TLV assessment of the ATMP cell therapy Alofisel the high level of uncertainty, particularly concerning long-term effects is highlighted. The submitted documentation was deemed to lack "sufficiently robust evidence to extrapolate the results over a longer time horizon". Imcivree is targeting genetically caused obesity and intended to help control hunger. The health economic evaluation found costs higher than TLV's usual acceptance level. TLV concluded that "even though a higher cost per QALY can be accepted for very rare and severe diseases, any cost is not justifiable." For Voxzogo a joint Nordic health economic assessment concluded that "the cost of using Voxzogo does not match the benefit." Uncertainty was deemed very high, primarily due to a lack of evidence. Waylivra was also associated with multiple uncertainties and a very high cost per QALY.

ONGOING NATIONAL PROCESSES (AS OF 30 JUNE 2024)

Abecma, **Carvykti**, and **Ebvallo** are all ATMP medicines where the regions have decided to enter into a joint national process for introduction. While waiting for the health economic evaluation, the regions are advised to abstain from use. The same applies to **Enjyamo**. For **Lunsumio**, **Roctavian**, and **Vyvgart** the health economic evaluations or negotiations where ongoing at the time of the cut-off date for this review. In August 2024, Biomarin that is marketing Roctavian announced a shift in its strategic focus. Aiming to cut costs and improve profitability by 2025 the company is concentrating its commercial operations to three markets (U.S., Germany, and Italy).[32]

NO COMPLETED PROCESS FOR MARKETING, INTRODUCTION AND REIMBURSEMENT IN SWEDEN

Medicines with existing treatment alternatives

Orphan designation or orphan status for an authorised medicine does not necessarily mean that a real unmet medical need exists for the patient population. It can also imply lack or limited availability of other authorised commercial medicines within the specific indication and the assumed benefits to patients' treatment. In the Swedish context, many such medicines lack decisions on joint introduction.

Ayvakyt is a targeted oncology medicine for gastrointestinal stromal tumors (GIST). Primary treatment in Sweden is surgery and tyrosine kinase inhibitors. Ayvakyt has conditional approval and requires further data to confirm safety and efficacy.

Qinlock is authorised as a fourth-line oncology treatment, also for GIST and only after treatment with three or more kinase inhibitors. In current national guidelines, other effective treatment options have been established and Qinlock is not included in these. In cases where Qinlock would still be deemed medically appropriate it is possible to grant access to the medicine and approve an individual reimbursement through the regional processes – under exceptional circumstances.

Daurismo is an oncology medicine for acute myeloid leukaemia (AML) in patients that do not qualify for chemotherapy. Standard treatment includes intensive combination therapy with chemotherapy and other medicines.

Filsuvez is a treatment for two types of the hereditary skin disease epidermolysis bullosa. The active substance is birch bark extract. The medicine has not been used commercially but a few patients in Sweden have accessed it through a compassionate use program (CUP). However, the medicine did not meet the efficacy expectations. Other treatment options for symptom relief are available, but the need for an effective treatment still exists. The gene therapy Vujuvek was recently approved by the Food and Drug Administration (FDA) for the American market.[33]

Isturisa is an anti-cortisol medicine for Cushing's syndrome in adult patients. In Sweden, surgery and/or radiation are standard treatments, with other medicinal therapies also available. Isturisa would in this case be considered as treatment option if other medicines fail.

Oxervate is intended as treatment for the rare eye disease neurotrophic keratitis, for adults with moderate or severe disease. Alternative treatments exist.

[30] Life-time, Nya läkemedel, var god dröj (published 2024-09-24). https://www.life-time.se/ledare/nya-lakemedel-vad-god-droj/

[31] Information on each medicine is gathered from EMA (https://www.ema.europa.eu/); TLV (https://www. tlv.se/); and the regions' joint coordination office for medicines (https://samverkanlakemedel.se/) – complemented by qualified medical and pharmacological assessments.

[32] Biomarin, news published 2024-08-04: https://investors.biomarin.com/news/news-details/2024/BioMarin-Announces-Updated-Strategy-for-ROCTAVIAN-to-Fo-cus-on-U.S.-Germany-and-Italy/default.aspx

[33] US Food & Drug Administration, FDA, Vujuvek. https://www.fda.gov/vaccines-blood-biologics/vyjuvek

Palynziq is a treatment for phenylketonuria (PKU), supplementing diet therapy. The condition is rare. Only about five new cases occur per year in Sweden, diagnosed through PKU screening. The condition can also be treated with the medicine Kuvan. The market authorisation holder initiated a reimbursement process in Sweden but later withdrew its application. No formal decision on Palynziq was thus made.

Pyrukynd is a treatment for pyruvate kinase deficiency (PKD), an inherited disease that cause the excessive breakdown of red blood cells (haemolytic anaemia). Existing standard treatment in Sweden exist and generally works well.

Skytrofa and **Sogroya** are both growth hormone deficiency (GHD) treatments. The active substances lonapegsomatropin and somapacitan are similar. Several similar treatment options exist.

Livmarli is a medicine for treatment of rare genetic liver diseases causing severe itching, caused by Alagille syndrome. Livmarli has an exceptional circumstances market authorisation. Standard treatment for the patient population includes other medicines that are used off-label, surgery, or liver transplant. Livmarli is similar to the medicine Bylvay which was denied national reimbursement due to its high price. Bylvay has been used regionally under the provision of exceptional circumstances.

Oxbryta is indicated for symptomatic treatment of sickle cell disease. Other treatments exist, and in some cases, stem cell transplantation may be considered. Ongoing gene therapy research aims to develop curative treatments. At the time of Oxbryta's approval, there was uncertainty regarding improvement in clinical symptoms and patient quality of life, but since the observed side effects appeared limited and manageable, EMA granted a standard marketing authorisation. In September 2024, Pfizer announced the worldwide withdrawal of Oxbryta – including clinical trials, compassionate use and early access programmes – following new information about potential serious side effects and deaths. EMA and its scientific expert committee CHMP also announced that the information raises serious safety concerns for the medicine and recommended to suspend the marketing authorisation. The medicine is currently under evaluation.[34]

New areas of use for repurposed and hybrid medicines

Repurposed medicines are existing medicines with already approved active substances, often lacking patent protection, with new areas of use/indications. Hybrid medicines are variations of reference medicines containing the same active substance but with a difference in the strength, indication or pharmaceutical form. In some cases, the regulatory system for orphan medicines and its incentives can be utilised for approval of anti-competitive protection mechanisms such as market exclusivity, as well as higher pricing potential or willingness to pay, for already well-established treatments. A type of "regulatory innovation" from the industry. Most medicines in this section have not been selected for regional collaboration on introduction.

Kinpeygo is a medicine for primary immunoglobulin A nephropathy (IgAN), a condition that gradually deteriorates and lead to kidney failure. The medicine is based on the active substance budesonide, initially patented in 1973, and has extensive and well-established use globally. Budesonide has been used for a long time for the treatment of asthma and allergies. It is available in various combinations. Budesonide is available as oral treatment for ulcerative colitis and microscopic colitis, as well as rectal treatment for ulcerative colitis and proctitis. Kinpeygo is classified as a hybrid medicine. Kinpeygo's reference medicine is Entocort, which was approved in Europe in 1992.

Mycapssa[35] (hybrid medicine), intended for the treatment of acromegaly, overproduction of growth hormone. Mycapssa is similar to the reference medicine Sandostatin IR, which is administered via injection or infusion. Mycapssa is given orally. Treatment alternatives exist, and for some patients, surgery may also be suitable.

Trepulmix (hybrid medicine) is approved for the treatment of conditions linked with high blood pressure in the lungs caused by blood clots. Treatment options exist. Trepulmix's reference medicine is Remodulin.

Vyxeos liposomal is a cancer medicine used to treat adults with newly diagnosed acute myeloid leukaemia. The active substances daunorubicin and cytarabine have been used together for many years in the treatment of leukaemia and other types of cancer. Other treatments are available for this patient group.

Amglidia is an older, now deregistered, diabetes medicine with the active substance glibenclamide. The reference medicine Daonil is given as tablets. Amglidia is liquid (oral suspension) and used to treat newborns and children with neonatal diabetes. The condition is rare but can be satisfactorily treated by simply crushing newer and effective diabetes medicines.

Chenodeoxycholic acid Leadiant is a hybrid medicine and emanates from an older form of treatment developed in the 1970s, for bile duct diseases. The reference medicine is Xenbilox. Chenodeoxycholic acid Leadiant is intended for the rarer form cerebrotendinous xanthomatosis. The patient population is very limited in Sweden. Approximately ten patients have been diagnosed in the Nordics in the past 30 years.

Verkazia contains the already known substance ciclosporin in a new formulation as eye drops for vernal keratoconjunctivitis. The condition is rare but can be satisfactorily treated with the medicine Ikervis, also ciclosporin, which is included in the pharmaceutical benefits scheme. Ikervis has previously had a broader indication and is marketed by the same company that sells Verkazia.

[34] See EMA, EMA recommends suspension of sickle cell disease medicine Oxbryta, https://www.ema.europa.eu/en/news/ema-recommends-suspension-sickle-cell-disease-medicine-oxbryta (published 2024-09-26)

[35] Update per 25 March 2025: Mycapssa's marketing authorisation for Europe was withdrawn in February 2025.

Limited or no patient population in Sweden

Not all medicines approved for the European market will be relevant for Sweden. Sometimes there is a lack of patient population, especially for orphan medicines intended for very rare conditions. Examples are numerous. Most medicines in this section have not been selected for regional collaboration on introduction.

Elzonris is approved as a treatment for blastic plasmacytoid dendritic cell neoplasm, a very rare form of blood cancer. The patient population in Sweden is limited.

Lamzede is an enzyme replacement therapy used as symptomatic treatment for patients with mild to moderate alpha-mannosidosis. The condition is rare and exists in three forms. In Sweden, only a few known patients exist.

Mepsevii is a treatment for mucopolysaccharidosis type VII. The condition is rare. In 2018, according to Socialstyrelsen, there were no known patients in Sweden or the other Nordic countries.

Myalepta is a medicine used in addition to diet to treat lipodystrophy. It is a recombinant version of the hormone leptin and is injected subcutaneously. The condition is rare, and the patient population in Sweden is unknown.

Nulibry is a medicine for a very rare form of congenital metabolic disorder (MoCD type A), with an estimated incidence of fewer than 1 patient per year in Sweden.

Artesunate Amivas is a medicine for severe malaria. Since malaria does not occur in Sweden, the incidence will be sporadic. The low incidence in Europe has also enabled the granting of orphan medicine designation. The medicine has the classification "new active substance" even though the medicine has been available and used in Europe under special licence since 2007 (not formally authorised for the European market). The medicine could technically be characterised as a repurposed medicine, but since the medicine does not hold previous approval in Europe, this "old" molecule is classified as a new substance, and the repurpose classification is omitted.

Zokinvy is a medicine for the treatment of the very rare Hutchinson-Gilford syndrome, patients with premature aging, or rare metabolic conditions. The prevalence is estimated to be 1/20 million with a patient population of only 400 patients worldwide. Research and clinical studies have largely been funded by the Progeria Research Foundation. The collaboration with biotech companies Eiger BioPharmaceuticals resulted in the market authorisation of the medicine. In connection with Eiger's bankruptcy in 2024, Sentynl Therapeutics acquired the rights to Zokinvy, including manufacturing and commercialisation.

Nyxthracis was approved as a treatment for the severe and life-threatening condition inhalation anthrax, often associated with accidents or terrorist attacks. The condition is rare, and the need is limited and random. Therefore, the medicine has not been possible to study in humans. In September 2024, the medicine was deregistered from the European market. The marketing authorisation is withdrawn.

COMPANIES ACTIVELY CHOOSING NOT TO LAUNCH IN SWEDEN

Companies can also choose not to launch their medicines in Sweden. This is often due to a lack of patients to treat. Three examples have been identified in this review.

Oxlumo is a medicine for primary hyperoxaluria type 1, a severe rare kidney disease. Prevalence is less than three cases per million inhabitants.

Upstaza is a gene therapy for a very rare neurological disease (AADC deficiency), with a severe phenotype. Only 265 known cases have been identified worldwide, and so far, no children have been diagnosed in Sweden.

Xenpozyme is intended for treatment of acid sphingomyelinase deficiency (ASMD), a genetic condition historically known as Niemann-Pick disease. Socialstyrelsen estimates that fewer than 1 person per 120,000 births develops the disease each year (fewer than one person per year).

The review shows that most new orphan medicines with high scientific and technological innovation—targeting patients with rare and severe diseases who currently lack relevant pharmaceutical treatment—are made available in Sweden. A significantly increased willingness to pay is often accepted for these medicines. However, for many medicines, there are significant uncertainties regarding safety and efficacy in both the short and long term. In some cases, limited data may result in delays in introduction, reimbursement and use, while awaiting additional information and documentation from the companies.

Most of these medicines are initially assessed as not being cost-effective. As a rule, they should not be used in or funded by the healthcare system, which limits patient access. Under exceptional circumstances, these medicines may still be made accessible to patients and individual reimbursement can be granted. New orphan medicines for which there are no patients in Sweden or where other relevant and more cost-effective treatments are available naturally have a lower degree of patient access.

THE ORPHAN MEDICINE MARKET

Unmet medical needs

Given that there are between 6,000 and 8,000 known rare health conditions, and approximately 95% are estimated to lack pharmaceutical treatment, there are endless unmet medical needs of varying nature and scale. The EU has introduced extensive incentives to strengthen the orphan medicine market. This is positive if patients with rare and severe health conditions gain access to effective treatments. However, documentation requirements for a medicine's efficacy are often low, making it difficult to predict real-world effects in advance. The availability of orphan medicines further depends on how the orphan medicine market is structured and operates. With significant relative advantages compared to the broader pharmaceutical market, this is a market expected to grow.

Growth

The pharmaceutical market is generally profitable and exhibits strong growth. In 2023, the global pharmaceutical market was valued at approximately USD 1.6 trillion. The expected compound annual growth rate (CAGR) between 2024 and 2033 is around 6%. The market segments for advanced therapies (ATMP) and orphan medicines (rare diseases) are expected to grow even more in the coming years. In 2022, the global orphan medicine market was valued at approximately USD 154 billion, with an expected CAGR of about 12%. By 2032, the orphan medicine market is projected to reach approximately USD 484 billion. More and more companies are investing in orphan medicines within their product portfolios.[36] The ATMP market is also a highly lucrative segment with strong relative growth, a trend expected to continue globally and in Sweden. Between 2023 and 2030, the expected CAGR for this segment is 16.8%.[37]

One market – with multiple submarkets

The pharmaceutical market consists of several segments. The product market includes commercial medicines approved for various health conditions (categorised by indications). Each indication can be seen as a market segment where pharmaceuticals and other treatment options compete. Historically, the focus has been on indications with large patient populations, making these markets large enough to support multiple players and fostering healthy competition. In the orphan medicine segment, pharmaceutical products are approved for more specific indications with fewer patients. Orphan medicines also often receive market exclusivity for a period. This results in fewer market players and, in many cases, companies holding monopolistic positions. The conditions for competition within these therapeutic areas are often limited.

The global pharmaceutical market is also divided into multiple geographic submarkets. Europe is one such market, but within it, each country represents a separate "price market" since the EU does not have authority over member states' pharmaceutical pricing and reimbursement policies. This leads to pricing variations between countries. Companies increasingly apply parallel pricing strategies, using both officially listed prices and confidential prices, enabling price discrimination and maximisation of prices within national markets.

In countries like Sweden, where most prescription and hospital medicines are subsidised for patients and publicly funded, companies do not need to consider individual patients' willingness or ability to pay. Medicines that address real unmet medical needs for a small number of patients are often associated with significantly lower price sensitivity. Demand for the medicine is therefore not necessarily affected by high prices or price changes. This is particularly true for first-in-class medicines within a therapeutic area and for situations where competition is limited, and companies hold dominant market positions (such as monopolies). Additionally, subsequent market competition does not always lead to automatic price reductions. For similar medicines, multiple competing treatment options are often required before the price is affected.[38]

Market failures and inefficiencies

Beyond the existence of concentrated market power in various therapeutic areas and the potential for price discrimination across markets, the pharmaceutical market suffers from several inherent inefficiencies and a lack of competition—phenomena described in economic terms as "market failures". For example, it can be challenging for payers to estimate how many patients will be eligible for treatment and which patients will respond to therapy. Expectations regarding medicine efficacy (and its duration) may differ between pharmaceutical companies and payers. Similarly, expectations regarding a medicine's relative effectiveness compared to other treatment options may vary. Many times, comparative studies have not been conducted. These factors complicate pricing negotiations between companies and payers, which can hamper optimal patient access.[39]

[36] See e.g. market institutes and databases Presedence Research, Orphan Drugs Market Size, Share, and Trends 2024 to 2034; Vision Research Report, Pharmaceutical Market - Global Industry Analysis, Size, Share, Growth, Trends, Revenue, Regional Outlook and Forecast 2024-2033; Statista, Leading pharmaceutical companies by orphan drug revenue worldwide in 2023.

[37] Grand View Research, https://www.grandviewresearch.com/industry-analysis/advanced-therapy-medicinal-products-market

[38] See e.g. Gronde Tvd, Uyl-de Groot CA, Pieters T (2017); Addressing the challenge of high-priced prescription drugs in the era of precision medicine: A systematic review of drug life cycles, therapeutic drug markets and regulatory frameworks. PLoS ONE 12(8): published 2017-08-16; Berdud, et al. (2020), Establishing a reasonable price for an orphan drug, Cost Effectiveness and Resource Allocation vol 18, Art 31, published 2020-09-04; Parziale, Andrea (2017), Orphan drugs under EU Competition Law: The Price is not Right, Orphan Drugs under EU Competition Law: The Price is not Right, i Opinio Juris in Comparatione, 2017, 1; Morgan, Steven et al (2022) Pricing of pharmaceuticals is becoming a major challenge for health systems, published 2020-01-13; Perloff, Jeffrey M (2012), Microeconomics, Sixth Edition, Pearson.

[39] Hlávka, Jakub P et al (2021), The economics of alternative payment models for pharmaceuticals, The European Journal of Health Economics, Vol 22, published 2021-03-16.

Current observations in the orphan medicine market – with examples

This section presents current observations related to the orphan medicine market that may be relevant to consider in the development of the Swedish pharmaceutical system and its broader impact on healthcare.

Successful clinical research and efficient medicine development are interconnected

Medicine development has traditionally been associated with prolonged processes of research and development, including quality-assured product development and extensive preclinical and clinical studies. The likelihood of reaching full market approval for a medicine is often described as low, and the risks for companies engaged in medicine development are considered high. The relatively high profitability of the pharmaceutical market has been explained and justified by the extensive historical investments and costs associated with the many failed attempts required to develop a successful medicine.

However, an increasingly lucrative and less risky orphan medicine segment is emerging. Compared to the overall pharmaceutical market, there are indications of a rising success rate in orphan medicine development. This can be partly explained by scientific and technological advancements, such as precision medicine, which has contributed to a deeper understanding of diseases and led to new diagnostic methods and more targeted medicine development.[40] Additionally, strategies for repurposing are also driving further advancements. Between 2010 and 2022, repurposed medicines accounted for approximately 17% of all approved orphan medicines in Europe. New uses for existing substances can now be identified using available datasets and computational approaches, making parts of the medicine development process more efficient. This makes repurposing a less risky and costly path to market, particularly for orphan medicines. A higher success rate translates into shorter development timelines and reduced development costs.[41]

Basic and clinical research—largely funded through public investment—also plays a crucial role in the development of orphan medicines. In Sweden, for example, research on hATTR/"Skelleftesjukan" and clinical trials conducted within the Swedish healthcare system have contributed to several new treatment options for patients. Another key area is the development of CAR-T therapies, where Swedish academia and healthcare have been instrumental in driving new commercial treatments. Clinical trials for CAR-T therapies have been conducted in Sweden for medicines such as Kymriah, Yescarta, Tecartus, and Carvykti.[42]

Furthermore, there are economic and regulatory incentives, as well as various forms of support, to facilitate research and development of orphan medicines for rare conditions. These include development grants, protocol assistance, scientific advice, accelerated assessments, reduced fees, and other benefits. In Europe, these incentives are largely regulated by European legislation, but similar measures exist in other markets as well.

70 YEARS OF RESEARCH IN SWEDEN
THE DEVELOPMENT OF TREATMENTS FOR hATTR

To illustrate groundbreaking basic research within academia can create the foundation for successful and effective medicine development, the research history of hATTR/"Skelleftesjukan" serves as a good example. The condition was first described in the 1950s, after which its genetic causes were mapped. In Sweden, a geographical concentration of the condition was found in regions Norrbotten and Västerbotten. This laid the groundwork for further knowledge development regarding the disease's mechanisms. The primary cause of the disease was traced to a hereditary mutation in the transthyretin protein, which is mainly produced in the liver. During the 1980s, preclinical and clinical research gained momentum, largely driven by research at Umeå University Hospital.

In 1990, the first successful treatment—a liver transplant—was performed in Stockholm. Later, some medicines were also found to have positive stabilising effects on the disease. This led to the introduction of the licensed medicine diflunisal as the standard treatment, used outside its original indication (off-label). The clinical efficacy of diflunisal has been confirmed in academic studies. Since the 2000s, the development of targeted medicines has accelerated. This began with similar stabilising yet better-tolerated medicines such as Vyndaqel. The development of the Nobel Prize-winning RNA interference (RNAi) technology has also contributed to new substances, including the biological medicines Onpattro, Tegsedi, and, most recently, Amvuttra. Onpattro was the first RNA-based medicine and was named one of the world's greatest scientific breakthroughs in 2018. Several of the academic studies and clinical trials for the now-approved medicines have been conducted at Umeå University Hospital. When these medicines were approved for the specific indication behind hATTR/"Skelleftesjukan" , the possibility of obtaining licenses for the off-label use of diflunisal was restricted, even for patients who had previously responded well to the medicine. In 2022, a process was initiated to reintroduce diflunisal as an extemporaneous formulation in Europe, and a medicine candidate has since been granted orphan medicine status for the indication of hATTR/"Skelleftesjukan" .

In 2012, the Nobel Prize-winning gene-editing tool CRISPR-Cas9 was discovered at Umeå University. Less than a decade later, one of the world's first in human clinical trials using CRISPR-Cas genome editing technology *in vivo* was initiated—at Umeå University Hospital, for patients with hATTR/"Skelleftesjukan".

[40] Gronde Tvd, Uyl-de Groot CA, Pieters T (2017)

[41] Dhir, Neha et al (2020), Drug repurposing and orphan disease therapeutics, från Drug Repurposing - Hypothesis, Molecular Aspects and Therapeutic Applications, published 2020¬04-23; Bouwman et al (2024) Trends in orphan medicinal products approvals in the European Union between 2010–2022, Orphanet J Rare Disease. published 2024-02-27.

[42] ATMP Sweden, Clinical Trials list, September 2024, https://atmpsweden.se/wp-content/uploads/2024/09/Clinical-Trials-ATMP-Sweden-sept-2024.pdf

Medicine development through acquisitions affects the level of risk-taking of the pharmaceutical industry

In addition to opportunities for more cost-effective medicine development, there are also signs of a shift in risk-taking within the pharmaceutical industry. In recent years, larger pharmaceutical companies have increasingly acquired smaller research-driven firms with promising late-stage medicine candidates or technology platforms. This has become an attractive strategy for expanding into advanced therapies, rare diseases, and orphan medicines. Licensing and commercialisation agreements for late-stage medicine candidates are also common. This trend shifts the risks associated with potential failures in medicine development, from large companies to smaller firms and their original investors.[43] This shift is reflected in the types of companies commercialising orphan medicines in Europe. Between 2010 and 2022, only about 14% of the companies applying for European marketing authorisation for orphan medicines were small or medium-sized enterprises (SMEs).[44]

There are many recent examples of orphan medicine companies being acquired. The CAR-T platform that eventually became Yescarta and Tecartus was initially developed by Kite Pharma and was acquired by Gilead in 2017 for USD 11.9 billion.[45] Yescarta received FDA approval in the U.S. in 2017 and EMA approval in Europe in 2018, with both medicines now available in Sweden. Yescarta has been the top-selling product among them. Similarly, the medicine candidate that later became Zolgensma was originally developed by AveXis, which was acquired by Novartis in 2018 for USD 8.7 billion. This acquisition included a broader gene therapy platform for treating central nervous system-related conditions.[46] Luxturna was initially developed by Spark Therapeutics, which entered a USD 170 million licensing and supply agreement with Novartis in 2018 for sales rights outside the U.S. Spark Therapeutics was later acquired by Roche in 2019 for USD 4.8 billion.[47] Beyond the acquisition of specific portfolios, larger strategic acquisitions, research collaborations, and philanthropic partnerships (so-called "venture philanthropy") are also taking place. Collaborations with patient organisations have led to the development of some of the new medicines now available on the market. One example is the partnership between the San Raffaele-Telethon Institute for Gene Therapy and Orchard Therapeutics, which resulted in the approval of the ATMP medicine Libmeldy in 2020.[48]

The high acquisition costs illustrate the expected revenues, returns, and profitability that justify these types of investments and acquisitions in the orphan medicine market.

Earlier approvals and changing evidence requirements extend revenue periods under patent protection

The European regulatory system aims to ensure the quality, safety, and efficacy of new medicines intended for human use. Marketing authorisation is granted to medicines that meet the criteria. Over the past decade, the possibility of exceptions to standard requirements has increased, allowing for more flexibility and the acceptance of more limited evidence at the time of approval. This "regulatory efficiency" creates conditions for a higher success rate in medicine development and potentially lower costs for companies. Additionally, profitability is further enhanced when medicines can be commercialised earlier, allowing companies to benefit from extended periods of market exclusivity under patent protection.[49] This also applies to the European orphan medicine market.

The prevalence of conditional approvals or approvals under exceptional circumstances has increased over time. Between 2010 and 2012, 26% of orphan medicines received such approvals; by 2020–2022, this share had risen to 40%. Examples of orphan medicines with positive national decisions or recommendations in Sweden that have been approved under conditional or exceptional circumstances include Idefirix, Qarziba, Tecartus, and Zolgensma. Some medicines are also processed under accelerated assessment. Bylvay, Koselugo, Minjuvi, and Voraxaze have all received negative recommendations but have still been used in healthcare to meet urgent needs for individual patients through regional processes. Pemazyre, Roctavian, and Carvykti were undergoing health economic assessments or negotiations at the time of this report, while Evrysdi, Jorveza, Onpattro, Spinraza, and Takhzyro have all received approval through expedited pathways.[50]

Regulatory streamlining has led to changes in the structure of clinical trials undertaken before a market authorisation. Among orphan medicines approved between 2010 and 2022, 76% were based on one or none pivotal efficacy study. About half of these studies were randomised, double-blinded clinical trials (compared to 60% between 2000 and 2010), and 81% of these included a placebo control (compared to 49% in the 2000–2010 period). Around one-third of studies were open-label, single-arm trials.[51] While this trend is often seen as a natural consequence of orphan medicines targeting rare and/or severe conditions, it can impact the reliability and validity of study results. Greater flexibility in study design is intended to facilitate medicine development and speed up market authorisation, but it also carries risks such as overestimating treatment efficacy and failing to detect or underestimating rare adverse effects. From a regulatory standpoint, this is not necessarily a problem if the benefits for patients outweigh the risks. However, for de facto introduction and use in healthcare, clinical trials, documented efficacy, and real-world experience with a medicine are all crucial factors for health economic evaluations, which inform reimbursement

[43] Se bl a Gronde Tvd, Uyl-de Groot CA, Pieters T (2017) och Berdud, et al. (2020)

[44] Bouwman et al (2024). Note that the proportion of SMEs is measured in September 2023.

[45] Gilead: https://www.gilead.com/news/news-details/2017/gilead-sciences-to-acquire-kite-pharma-for-119-billion

[46] Novartis: https://www.novartis.com/investors/financial-data/product-sales

[47] Fierce Pharma, Spark, Novartis tie up in gene therapy licensing deal worth up to $170M (published 2018-01-25); https://www.fiercepharma.com/pharma/spark-novartis-tie-up-gene-therapy-licensing-deal-worth-up-to-170m; and https://pharmaphorum.com/news/roche-to-buy-spark-therapeutics

[48] San Raffaele-Telethon Institute for Gene Therapy https://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy.html

[49] Van den Berg, Sibren, et al (2021), Drug repurposing for Rare Diseases: A role for Academia, Frontiers in Pharmacology 12:746987, published 2021-10-20.

[50] See EMA/human medicines database and Bouwman et al (2024)

[51] Bouwman et al (2024)

decisions and adoption in healthcare practices. Uncertainties in these data can lead to delays or rejections of new treatments, misallocation of healthcare resources, and unmet treatment expectations.[52]

Pricing of orphan medicines – What is a fair price?

Understanding medicine pricing requires an awareness of how the pharmaceutical market operates. The limited competition in the orphan medicine sector partly explains pricing strategies and the increasing costs of these therapies. Official medicine prices are generally set based on global market conditions, with companies using price discrimination strategies across different geographic markets to maximise revenues according to each country's willingness and ability to pay.

It is not always high absolute prices that stand out. In cases where older substances or well-established medicines are repurposed for new indications, multiple price hikes are not uncommon. The case of Namuscla (mexiletine) is an example of this. Originally introduced in the 1980s for severe cardiac arrhythmias, mexiletine was later used off-label for patients with dystrophic myotonia. In the 2000s, the original medicine was deregistered in Europe, but it continued to be prescribed through importation from markets like the U.S. During the 2010s, mexiletine's efficacy for dystrophic myotonia was confirmed, largely through academic clinical research. Lupin Europe GmbH supplemented this with a clinical trial involving 25 patients, leading to orphan medicine designation, market approval, and the reintroduction of mexiletine in Europe under the brand name Namuscla—this time with a significantly higher price, impacting patient access to treatment.

It is difficult to determine what pricing levels are necessary to ensure a reasonable return on investment for the pharmaceutical industry. High prices are often justified as a prerequisite for continued investment in research and development. However, when high prices are combined with increased success rates in medicine development, streamlined regulatory processes, and earlier market entry, the conditions for profitability become exceptionally strong.

The relationship between profitability and investments in research and medicine development, however, is not straightforward. How companies utilise their profits likely varies. Historical reviews of the more successful companies show that a large portion of profits are sometimes used for share buybacks or dividends to shareholders. It is reasonable to assume that the profitability conditions in the orphan medicine market and the actual profits generated would allow for both reasonable pricing and dividends to shareholders, as well as necessary reinvestments in research and development of medicines for high-priority diseases that currently lack treatment.[53]

The World Health Organisation (WHO) has also raised the issue of fair pricing and "reasonable profit", as a key prerequisite for the long-term sustainability of patient access to medicines. Research in this area is ongoing in several countries, including Sweden.[54]

CLINICAL STUDIES ON ZOLGENSMA AT THE TIME OF MARKETING AUTHORISATION

Zolgensma was approved as a treatment for patients with spinal muscular atrophy (SMA) in 2020. At the time of approval in Europe, clinical studies existed that documented efficacy for symptomatic patients with SMA type 1 and two copies of the SMN2 gene, up to and including 6 months of age (22 and 33 study patients), and presymptomatic newborn patients with genetically diagnosed SMA with two or three copies of the SMN2 gene (14 and 15 study patients). The studies were open-label single-arm studies. In addition, results from phase I studies and ongoing follow-up programs were available. Zolgensma had not been studied in older patients, patients in advanced stages of the disease, or patients with only one copy of the SMN2 gene. For patients with three copies, there was no data to support the benefit, but the medical need for these patients was considered high. Zolgensma was granted conditional marketing authorisation for a broader patient population, with a postponement from the obligation to submit results of studies in one or more subgroups. The approved indication included patients with a clinical diagnosis of SMA type 1 or patients with "biallelic mutation in the SMN1 gene and 1-3 copies of the SMN2 gene."[55]

Zolgensma was introduced to the European market in 2020 (2019 in the US) and was at the time referred to as "the world's most expensive medicine." There was limited experience of treatment in patients 2 years and older or with a body weight over 13.5 kg. Safety and efficacy for these patients had not been established. Long-term effects were unknown. Similarly, the need for other medical interventions to maintain the effects of treatment over time. In 2022, Zolgensma was recommended for use in Swedish healthcare, based on the approved indication and the studied patient population from the clinical trials. Newborn screening for SMA was introduced in 2023 to enable early detection and early treatment.

[52] Van den Berg, Sibren, et al (2021)

[53] See e.g. Lazonick, William et al (2017) US Pharma's Financialized Business Model, Institute for New Economic Thinking, Working Paper No. 60, published 2017-07-13.

[54] Paulden, Mike (2024), A framework for the fair pricing of medicines. Pharmacoeconomics 42(2):145–164, published 2023-12-08.

[55] See EMA's available information on Zolgensma; https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma; as well as information from the Swedish regions' joint collaboration on Zolgensma: Genterapin Zolgensma rekommenderas till små barn med SMA, https://samverkanlakemedel.se/lakemedel---ordnat-inforande/nyheter/nyheter/2022-02-01-genterapin-zolgensma-rekommenderas-till-sma-barn-med-sma (published 2022-02-01, sourced 2024-10-30).

WILLINGNESS TO PAY AND UNCERTAINTY FOR PUBLICLY FUNDED MEDICINES – THEORY OR PRACTICE?

A company's pricing is only one part of the economic equation. Prices do not indicate whether a medicine is cost-effective or whether the costs associated with its use are reasonable, justified, or manageable. Determining what constitutes a reasonable price from a value-based perspective is complex. From a patient perspective, some medicines are undoubtedly "priceless," particularly for severe conditions where effective treatment options do not exist. There are also theoretical frameworks suggesting that a wider dimension of value should be considered when assessing a medicine's actual societal value and willingness to pay. This would subsequently justify higher prices despite demands for cost-effectiveness.[56] However, this does not mean that infinitely high prices can be accepted in practice. The actual costs must still be managed by the payers responsible for financing medicine use. In a value-based pricing system there is no consideration to the extent and underlying costs of medicine development. There is therefore no differentiation in willingness to pay between highly innovative new medicines and, for example, repurposed or hybrid medicines with low levels of innovation and limited additional research.

The issue of affordability is emerging as a contentious issue in many European countries, not just in Sweden. In the US, traditionally associated with the world's highest medicine prices, certain price regulations have been introduced with the Inflation Reduction Act.[57] In Sweden, TLV has proposed models for increased societal willingness to pay for certain particularly urgent medicines for rare conditions with high severity where no alternative treatments exist. A prerequisite for TLV's proposals is that it cannot result in higher overall medicine costs for the state (central level). TLV concludes that different cost-containment measures such as re-evaluations, price reductions for older medicines, and proposals for lower willingness to pay for medicines with high expected sales volumes will be key.[58]

If the documented effect is limited at the time of approval, uncertainties arise in the evaluation, reimbursement and pricing of the medicine. TLV has elaborated on such uncertainties.[59] Difficulties in assessing total costs and actual cost-effectiveness are also influenced by uncertainties regarding medicine usage, such as whether the treatment will be applied to a broader and more heterogeneous patient group than the studied population. Uncertainty regarding actual efficacy and risks of serious side effects also influences patients' assumed need for other healthcare services. From a payer's perspective, there is also uncertainty regarding companies' pricing strategies over time, including the risk of future price increases for treatments that have been introduced and that are continuous – sometimes lifelong – and the availability of other relevant treatment options that would enable price competition. This factor is particularly relevant for orphan medicines, which often receive a period of market exclusivity. These types of uncertainties are increasingly proposed to be managed through agreements with pharmaceutical companies.

Both TLV and Lif have emphasised the need for a strengthened national function for pricing and negotiations. This function for negotiation already exists within the established model for regional collaboration for joint national introduction on hospital medicines (procured by the regions). The same function is used for negotiations on prescription medicines. The regions are the contractual parties with pharmaceutical companies. A regional initiative has been commissioned by the board of the Swedish Association of Local Authorities and Regions (SALAR/"SKR") to develop a framework for alternative, feasible, payment models and agreements.[60] This also requires pharmaceutical companies to have both an interest in, and a mandate from global headquarters, to explore new payment models and agreements in the Swedish context. Like other European countries, various types of alternative agreements have been tested on a small scale. While alternative payment models have the potential to address some of the identified challenges, they also introduce greater uncertainties, leading to more complex agreements and the need for strengthened capabilities to monitor medicines, agreements, and costs. Among the Nordic countries, Denmark is in the forefront of enhancing conditions for alternative payment models, yet only a few alternative models have been implemented.[61]

Acceptance of higher prices and greater uncertainties also need to consider potential negative consequences for research. If reasonable prices are not demanded by payers, there is a risk that this will reduce company incentives for efficiency in pharmaceutical development and affordability of medicinal products from a payer perspective ("product-market-price fit"). For CAR-T therapies, which were initially introduced with high prices and resource-intensive qualification, manufacturing, and administration processes, ongoing development aims to achieve more efficient production, treatment, and logistics. This could allow for lower prices in the future and enable both broader and more targeted patient access. At the same time, another outcome is also possible if acceptance of higher prices prevails among the payer community, that such efficiency gains will solely benefit companies in the form of higher profits. Similarly, a higher degree of accepted uncertainty risks undermining incentives for companies to conduct well-designed clinical studies and provide robust evidence of clinical effects. Lower willingness to pay and price reductions for older and well-established medicines could also lead to the deregistration or complete withdrawal of medicines currently in use within the healthcare system.

[56] Persson U, Olofsson S. ISPOR:s "Värdeblomma" för in ny kunskap om individers preferenser för hälso- och sjukvård. En litteraturgenomgång av skattningar av potentiellt nya värde¬attribut. IHE Rapport 2022:8, IHE: Lund. Note that the study was financed by Janssen-Cilag AB and Pfizer AB.

[57] See e.g. European Social Insurance Platform (ESIP) and Medicine Evaluation Committee (MEDEV), review "Trends in Pharmaceutical Expenditure" from October 2024; and US Department of Health and Human Services, Inflation Reduction Act of 2022, Inflation Reduction Act Toolkit; https://www.hhs.gov/inflation-reduction-act/toolkit/index.html

[58] See e.g. TLV's list of governmental appropriation directives, https://www.tlv.se/om-tlv/regeringsuppdrag.html

[59] TLV (2023), Stärkt tillgång till läkemedel vid sällsynta hälsotillstånd - till långsiktigt hållbara läkemedelskostnader, Rapport från regeringsuppdrag, September 2023

[60] See e.g. SKR "kongress 2019". Motionssvar: Motion 10 och motionssvar - Innovativa läkemedel kräver omgående innovativa finansierings- och betalningsmodeller; and SKR "kongress 2023". Motion 26 och motionssvar - Behov av gemensamt ramverk för nya läkemedel samt modeller för införande av läkemedel för patienter med sällsynta sjukdomar. Utvecklingsarbete sker inom ramen för regionernas samverkansmodell för läkemedel.

[61] AMGROS, https://amgros.dk/en/pharmaceuticals/price-negotiations-and-tendering/new-pharmaceuticals-and-negotiations/alternative-agreements/

"LEX TRANSLARNA" – IS IMMEDIATE ACCESS WORTH THE COST OF UNCERTAINTY?

The orphan medicine Translarna[62] is a recent example highlighting the need for robust national processes for introduction of new medicines and pharmaceutical systems that lead to transparent prioritisation of new medicines. In 2014, EMA granted Translarna a conditional approval for Duchenne muscular dystrophy, a genetic disease that gradually causes weakness and loss of muscle function, eventually leading to wheelchair dependence. At the time of approval, and despite the acknowledged need for further data, it was deemed that the benefits of the medicine's immediate market availability outweighed the risks associated with insufficient documentation. Nearly a decade later, in 2023, EMA recommended withdrawing the medicine's marketing authorisation, as its effectiveness could not be confirmed. The manufacturer, PTC Therapeutics, appealed this decision. Following a request from the European Commission, a reassessment was conducted, and in October 2024, EMA reaffirmed— for the third time— that Translarna's efficacy could not be verified. The Commission has yet to make a formal decision on whether to revoke its market authorisation.

Between 2019 and 2022, the medicine was reimbursed in Sweden. Since clinical trials had been conducted within the Swedish healthcare system, patients who had participated in these studies were allowed to continue treatment based on regional agreements with the company, even before TLV's formal decision. The total estimated cost of the medicine's use during this period, before any potential rebates, was approximately SEK 500,000 million for 15 patients. Given the limited actual benefits of the medicine, these resources could have been allocated to other medicines or healthcare services.

The key question remains: Did the advantages of making the medicine immediately available on the market truly outweigh the risks associated with the limited data presented at the time of its approval, and what has been the real societal cost and net health outcome of accepting this uncertainty?

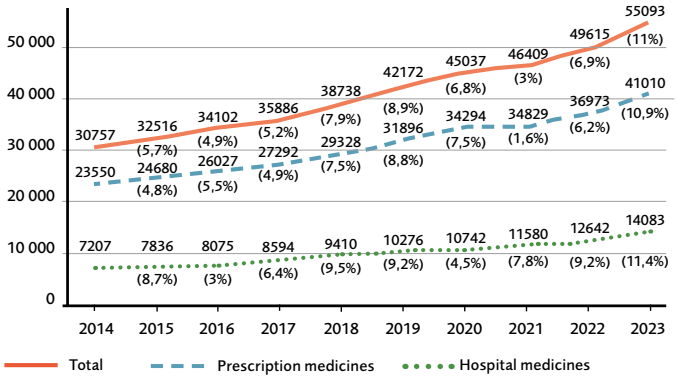
Rising medicine costs - a growing financial challenge

The financing of medicines used by patients in Sweden is jointly borne by the state and the regions, based on current cost-sharing principles for prescription medicines and hospital medicines. Since 2014, the costs for medicines have steadily increased. This is seen as a major challenge for the healthcare system.

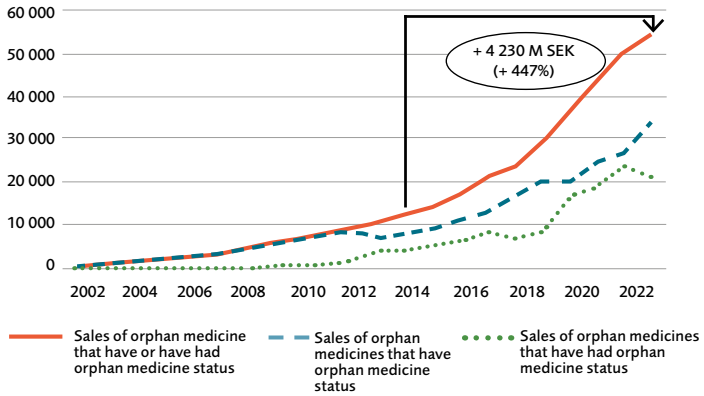
According to the National Board of Health and Welfare, sales of prescription medicines in the pharmaceutical benefit scheme amounted to SEK 41.0 billion in 2023 (65% of the pharmaceutical market). The costs for hospital medicines amounted to SEK 13.4 billion (approximately 21% of the total market). The forecast predicts a cost increase of 6–11% in the coming years. TLV's analysis shows that orphan medicines' share of total costs was approximately 10% in 2022. From 2012 to 2022, the number of orphan medicines sold in Sweden doubled while the costs quadrupled (447% cost increase compared to 40% for non-orphan medicines during the same period). Even though these medicines have been assessed as cost-effective upon introduction, the overall cost development is not sustainable in the long term.[63]

PHARMACEUTICAL COSTS 2014 – 2023 million SEK

Divided into prescription and hospital medicines as well as total costs



SALES OF ORPHAN MEDICINES 2001 – 2022 million SEK



Figures 1 and 2: The upper figure shows pharmaceutical sales in SEK during the period 2014–2023, divided into prescription and hospital medicines. Adapted figure from ESIP/MEDEV (2024), Trends in Pharmaceutical Expenditure, October 2024. Based on data from TLV and the Swedish eHealth Agency. The lower figure shows sales in SEK for medicines that currently or previously held orphan medicine status. Adapted figure from TLV (2023), Stärkt tillgång till läkemedel vid sällsynta hälsotillstånd – till långsiktigt hållbara läkemedelskostnader. Available as a summary report in English (Strengthened access to medicines for rare diseases - at long-term sustainable costs).

[62] Socialstyrelsen (2024), Läkemedelsförsäljning i Sverige – analys och prognos 2024–2027; TLV (2023); SKR (2024), Ekonomirapporten oktober 2024, om kommunernas och regionernas ekonomi

[63] EMA/meeting highlights from CHMP 18 oktober 2024 (https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-14-17-october-2024); Läkemedelsvärlden, Nytt från EMA: Slutgiltigt expertstopp för Translarna, 18 oktober 2024; and sales statistics in the Concise database of the eHealth Agency.

Medicines with high expected sales volume, for many of today's common diseases, are under development, while more targeted advanced medicines are being introduced for rare and severe conditions where relevant treatment options may sometimes be limited or lacking.[64] In many of the recent appropriation directives assigned to TLV by the government, it is specified that proposals for changes in the pharmaceutical system must not result in higher total medicine costs for the state. In the government's financial plan for 2025, significant risks have been identified due to the sharply increasing need for pharmaceutical funding, which may displace other important reforms and investments of the state. The multi-payer system in Sweden is considered a major challenge. Unfortunately, the economic situation in the regions is also strained, and the higher and steadily increasing total medicine costs in the regions are assessed to pose risks of displacing healthcare services and overall public health benefits.[65] The state and regions must therefore find solutions together. In 2024, joint discussion and development efforts were initiated.[66]

The introduction of a new medicine can lead to positive health effects for individual patients, while at the same time posing a risk that the net health effect for society becomes negative. This means that overall public health may deteriorate due to the displacement of other healthcare services if the costs are not financially sustainable from a payer perspective. The opportunity cost in healthcare also involves the health of other patients and is an important factor in prioritisation decisions. Similarly, negative net health effects can arise when medicines are not made available or are withdrawn from the market.[67]

Patient access is more than just introduction and reimbursement

As already stated, the patient access depends on multiple factors. The Swedish healthcare system is founded on the evidence-base, and treatment choices should be guided by scientific evidence and established clinical experience. This principle underpins the rise of "choosing wisely", which aims to avoid unnecessary interventions and focus on efforts that truly make a difference for patients, within the constraints of healthcare resources. The national Council for Healthcare Competence highlights that, despite ethical guidelines for prioritisation, making wise clinical choices and determining who has the greatest need for care is not always straightforward. Medical professionals are often caught between patient expectations, medical and technological possibilities, and resource limitations.

When making new medicines available, documentation on safety and efficacy for the intended patient group provides the best-available knowledge on added clinical benefit and necessary prioritisation. For older and well-established medicines, documented clinical experience may serve as guidance. The level of evidence is crucial for health economic evaluations and decisions on medicine use. When this information is limited or lacking, new treatment methods should be subject to further evaluation through clinical research and trials.

Increasingly frequent shortages and supply chain disruptions in the pharmaceutical sector create challenges beyond patient access to specific out-of-stock medicines. Such shortages can also disrupt access to other types of care, including advanced therapies that rely on the availability of essential medicines and basic healthcare infrastructure. A current example (as of November 2024) is the shortage of infusion fluids, which are widely used in inpatient care. Similarly, the availability of hospital beds and healthcare personnel can affect the effective delivery of essential treatments to patients. These vulnerabilities in medicine supply chains highlight the importance of ensuring access to competing and interchangeable medicines, as well as the risks of extensive anti-competitive protection incentives and policies that may undermine sound competition and weaken the resilience of the pharmaceutical systems. The need for reasonable reimbursement for basic essential medicines, healthcare infrastructure, and, most importantly, healthcare professionals is critical. A robust and resilient healthcare system is also a cornerstone of civil preparedness.

It is essential to follow up on the real-world effects of orphan medicines used in clinical practice. This helps to complement the limited evidence often associated with these treatments. However, the Swedish healthcare system, like many other systems, is experiencing data-related, technological and legal barriers to advance in terms of real-world follow-up of health outcomes. The same applies to access to other healthcare and cost data, which are necessary for evaluating the relationships between interventions, costs, and outcomes. The ability to conduct meaningful follow-ups is also a prerequisite for more complex payment models and contractual agreements. One possible approach for medicines introduced with limited scientific evidence and clinical experience, as proposed by the Swedish National Council on Medical Ethics (SMER) for innovative methods, is to introduce them within the framework of research studies, following the regulations that apply to clinical research.[68]

[64] See e.g. Lif, Omfattande forskning kring svåra sjukdomar, https://www.lif.se/fokusomraden/en-aktiv-och-hallbar-samhallsaktor/en-fraga-om-liv-och-dod/framtidens-lakemedel/; IQVIA (2023), Orphan Drugs: An Update on Key Selected Pipeline Developments for Rare Diseases, IQVIA Pipeline Link, published 2023-07-17

[65] Prop. 2024/25:1, Finansplan (government's financial plan published by the Finance Department 2024-09-19); SKR (2024), Ekonomirapporten oktober 2024.

[66] Agreement between the state and SKR on state contributions to the regions for the costs of pharmaceutical benefits, (2024)

[67] Siverskog J; Henriksson M (2022), The health cost of reducing hospital bed capacity, Social Science and Medicine, published 2022-09-28

[68] Statens medicinsk-etiska råd (2016), Etiska bedömningar i gränslandet mellan hälso- och sjukvård och forskning

Discussion and concluding remarks

A pharmaceutical system contributing to sustainable healthcare

The pharmaceutical system in Sweden is an integral part of the country's healthcare system. **Its purpose is to promote equitable care and public health – e.g. by ensuring access to safe, effective, reasonably priced, and cost-effective medicines.** The assessment and selection of reimbursed medicines are based on the national framework for ethical prioritisation. While the pharmaceutical system must function in relation to the pharmaceutical market, it is not primarily designed to drive economic growth, attractiveness, or competitiveness from an industrial policy perspective. Evaluating the pharmaceutical system's effectiveness requires analysing its ability to ensure patient access to appropriate treatments at the right time, at a reasonable cost, and based on actual needs—ensuring a sustainable healthcare system in the long term. The system must guarantee access to both new and older, already established essential medicines.

The pharmaceutical system's ability to ensure patient access to orphan medicines

This review has analysed patients' access to orphan medicines. The results indicate **that most relevant medicines reach patients in Sweden**—particularly those approved for conditions where there is truly unmet medical needs and treatment gaps due to limited effective alternatives, or where new treatments are expected to provide added clinical benefit for patients. The orphan medicines not used in Sweden are generally those where no patient population exist or where alternative treatments exist. Many newly approved medicines are not deemed relevant for Swedish healthcare or are not prioritised for introduction through existing national processes. In a decentralised healthcare system, it is natural that decentralised, regional, introduction will be deemed more appropriate in some cases. Sales data show that Sweden's healthcare system has financed orphan medicines, with a **very high rate of cost increases** as a result. Orphan medicines now account for one-tenth of total pharmaceutical expenditures but serve less than one-thousandth of the population. This trend raises concerns about its long-term sustainability and the potential strain on the healthcare system. Despite a high willingness to pay, the publicly funded system cannot bear the costs of introducing medicines at any price. This challenge is not unique to Sweden. Additional incentives for orphan medicine development should be carefully considered. Especially in light of possible lowered willingness to pay for older, yet essential, medicines that are critical to healthcare.

In alignment with Sweden's pharmaceutical strategy, the **appropriate medicine use and pricing that is reasonable relative to the treatment effect and available resources should be premiered.** Therefore, not all medicines can be accepted and introduced. Prioritisation sometimes involves difficult choices. In several of the cases presented in this review, it is evident that while higher costs may be justified for treating rare and severe diseases, there are limits. Sometimes, uncertainties—mainly due to limited or lack of evidence—are too great, making it impossible to determine whether costs truly correspond to the expected, claimed benefits. Similar conclusions have emerged from Nordic collaboration efforts.

Sweden is often recognised in international comparisons for efficient introduction processes and universal patient access, as well as its reimbursement policies and medicine use – EFPIA's annual WAIT report being a clear exception. However, it still remains relevant to analyse patient access and timelines within the pharmaceutical system from a national perspective, as explored in the 2023 briefing paper. Simply looking at total timelines reveals little about why certain medicines are introduced quickly while others face delays. When introduction processes are disaggregated and subsections are analysed, it is possible to identify bottlenecks in the system. Delays may arise from pending applications or incomplete documentation from pharmaceutical companies, preventing health economic assessments to be initiated. For hospital medicines resource constraints and capacities at TLV can impacted the timeliness of evaluations. Additionally, negotiations between regions and companies can prolong decision-making before reimbursement is granted and recommendations for use issued. A negotiation always requires that the contracting parties come to a mutual agreement. Ultimately, **all stakeholders share the responsibility for ensuring timely patient access. Every day counts.**

Targeted reforms are necessary for the pharmaceutical system

The Swedish pharmaceutical system must remain sustainable and need to adapt to rapid changes, also in relation to the changes within the pharmaceutical market. The evolving regulatory landscape in Europe, along with scientific and technological advancements, necessitates a **review of the system while preserving its existing strengths**. A deeper understanding of how the pharmaceutical and healthcare systems in Sweden function is needed at multiple levels. Pharmaceutical companies planning to launch medicines in the Swedish market need to understand the Swedish system. Lif can play a key role in clarifying roles and responsibilities of the state and the regions, fostering realistic expectations regarding introduction processes, the requirements for reliable health economic data, and expectations of reasonable pricing strategies in the Swedish context. **Pharmaceutical companies can significantly influence patients' access to their medicines.**

In further **dialogue about pharmaceutical system reforms and modernisation**, it is essential to move beyond misleading statistics and inaccurate claims about the Swedish system. Drawing conclusions based on questionable international comparisons does not benefit continued collaboration between the government, mandated authorities, regions, and pharmaceutical companies in Sweden.

A **deeper understanding of the claimed inefficiencies** of the Swedish system is necessary. Is Sweden's system more complex than other countries, in what way? Are processes unnecessarily time-consuming, what parts? What can different stakeholders do to streamline introduction? How do Sweden's willingness to pay and accepted prices for new medicines compare with those of other countries? Given that actual prices are largely confidential, particularly for new medicines, it remains difficult to assess Sweden's pricing position in an international context. How does the actual use of various medicines differ across countries, and what are the real added clinical benefits and health outcomes for patients? Is the rapid cost increase sustainable? Should all new medicines be integrated

into healthcare? How can ethical prioritisation principles be applied to ensure more appropriate medicine use, at a reasonable cost in relation to effectiveness and available resources?

Consensus on key areas for improvement and mutual trust among stakeholders is essential for strengthening the system, making it more robust, and ensuring sustainable patient access to both new and older, well-established medicines.

System reforms involve all stakeholders

Reforms must be based on strategies and measures that **enhance critical components of the pharmaceutical system** and its impact on the healthcare system. **System reforms need to consider a more holistic perspective and ensure long-term sustainability.**

Pharmaceutical companies can contribute by providing more **robust documentation on safety and efficacy when applying for market authorisation—not only to meet regulatory requirements for risk-benefit assessment** but also to facilitate introduction, reimbursement and use. Companies can also **adjust pricing expectations, particularly when introducing medicines with significant uncertainties.** Lower initial prices are a simple form of risk-sharing that companies can help implement. While prices must allow for reasonable profitability, high prices for orphan medicines should not be taken for granted. Willingness, mandate and ability to explore payment models and agreements beyond globally predefined models by company headquarters will be necessary. The pharmaceutical market is global, but sales and usage are ultimately local. Companies operating in the Swedish market have a key role to play for enhanced patient access.

Public stakeholders within Sweden's pharmaceutical system must proactively acknowledge and adapt to market developments. The 21 regions are currently engaged in collaborative efforts to enhance patient access, including the development of a framework for alternative payment models and agreements based on the Swedish context. This will increase transparency regarding possible strategies for negotiation on the introduction of new medicines. Nonetheless, access to relevant data and documentation from the companies will still be needed.

Regions, together with governmental actors, should work toward measures that improve the core conditions for sustainable patient access and financing of medicines in Swedish healthcare. This includes ensuring sufficient resources and expertise at regulatory agencies, within regional structures, and in the local healthcare setting. Administrative and legal prerequisites should also be considered. Questions regarding financing, the rising pharmaceutical costs, and co-sharing of costs between the state and the regions remain important and require joint commitment to joint solutions. Various policy instruments could be explored to promote sound competition and mitigate risks of abuse of market power in cases where competition is limited, as is often the case with orphan medicines.

Accepted pricing for both new and older, well-established medicines must balance reasonable profitability for companies with cost levels that are justifiable from medical, humanitarian, and economic perspectives. Aligning prices with added values for both companies and payers will also benefit patients' access to necessary treatments. **A robust supply of all essential medicines is also critical for pharmaceutical security of supply, resilience and civil preparedness.** Regulatory incentives for decentralised and more local medicine development, production, and supply chains should be considered to reduce system vulnerabilities.

At the local and regional levels, capacity for clinical research and development can be strengthened. Enhancing follow-up capabilities, participation in clinical studies, and real-world evidence generation for newly introduced treatments can drive healthcare innovation. As suggested by SMER, innovative treatments with limited or lacking relevant evidence, can in some cases be introduced within a research framework. Healthcare providers and companies can jointly generate new evidence and knowledge for scientific and technological advancements. This contributes to industrial development. **If further industrial policy dimensions are expected to be considered within the pharmaceutical system and if this perspective should influence de facto medicine use in healthcare, it is a matter for the government to address,** including its financing. The focus of the regions as the mandated healthcare providers must continue to be the health of patients – based on best-available scientific evidence and proven experience. Prioritisation efforts should premiere safe, effective, and cost-effective medicines based on ethical principles.

A pharmaceutical system that contributes to long-term sustainability in healthcare, ensures that **residents and patients in Sweden have the best possible conditions to live a healthy life, today and in the future.** This is not contradictory to, but rather a prerequisite for, favourable and long-term predictable growth opportunities and competitiveness for research-intensive pharmaceutical companies in Sweden.

Appendix 1. The pharmaceutical system and its relationship to healthcare

The pharmaceutical system and its relationship to healthcare in the Swedish context are described in more detail in this appendix. It also includes perspectives on the role and responsibilities of companies. The different components of the system interact with each other, contributing to medicine development and supply, which affects patients' access to medicines.[69]

Clinical research and development

The foundation of all medicine development is research and new knowledge about various diseases, their causes, and disease mechanisms. Scientific and technological advancements are key. A significant portion of this research takes place within academia but also within healthcare, in the form of clinical research, development, and innovation aimed at improving diagnostics and patient treatment. University hospitals are often at the centre of this effort. Collaboration also occurs with companies.

Commercial development and marketing authorisation

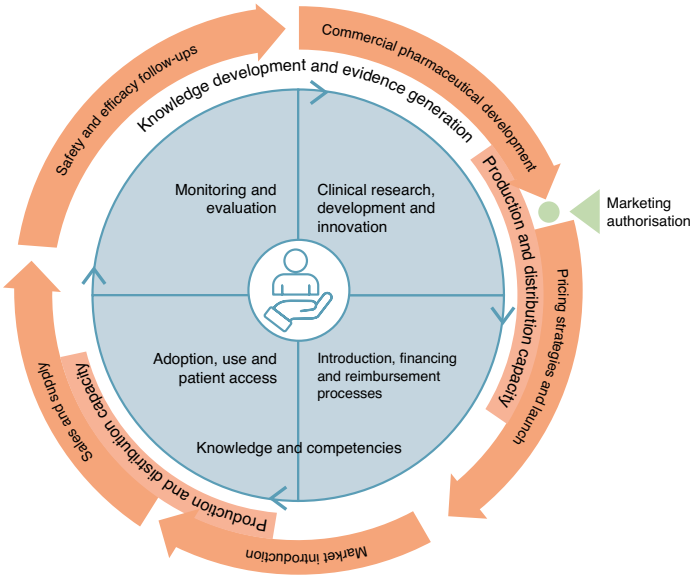
The further development and commercialisation of medicines are usually driven by companies—sometimes in collaboration with academia and healthcare. Before pharmaceutical products can be used, they must obtain marketing authorisation. Commercial medicines intended for sale in Europe undergo quality assurance and validation of their documented safety and efficacy at the European level, by EMA. The Swedish Medical Products Agency (Läkemedelsverket) is responsible for authorising medicines under development, non-commercial medicines, and commercial medicines intended solely for the Swedish market. To obtain marketing authorisation, the benefits of the medicine must outweigh the risks for the patient. Cost-effectiveness is not considered at this stage.

To enable healthcare to identify new relevant medicines, market analyses and needs assessments often occur alongside medicine development. This process is systematically conducted in collaboration between Sweden's regions within the framework of "horizon scanning." In recent years, this collaboration has deepened between several European countries.

Sweden has extensive and unrestricted prescribing rights for physicians, enabling rapid and broad access to new treatments if they are medically justified based on patient needs and supported by scientific evidence and proven experience. Medicines with marketing authorisation can be prescribed regardless of whether companies actively market and supply them in Sweden or not. Neither reimbursement decisions nor recommendations for use are formally required for a medicine to be prescribed and used in clinical practice.

Pricing strategies and marketing on the Swedish market

The national processes for introduction, reimbursement and use are formally initiated after marketing authorisation. In Sweden, companies can apply free pricing, but value-based pricing is used for formally reimbursed medicines. Companies' officially



stated prices often differ from the actual prices. Prices also vary across different markets – between different countries. Companies can choose to launch their medicines at different speeds in different countries. Many countries in Europe apply reference pricing policies. Official pricing in Sweden can sometimes be used as a reference price for other countries. This can influence pricing strategies in Sweden. For medicines where there is competition between different treatment options, or where generics and other interchangeable medicines are available, Sweden has regulations in place for price competition which can affect companies' pricing.

Introduction processes, reimbursement of medicines and cost-coverage for patients

Different countries apply different types of introduction processes and have different systems for reimbursement. The Swedish Pharmaceutical Benefits Act regulates the subsidy scheme and pharmaceutical benefits in place for e.g. prescription medicines. The beneficiaries in this scheme are eligible residents and patients. It serves as a social protection and entails a reduction of costs at the individual level. Reimbursed medicines are part of the publicly funded health insurance system. Medicines where the costs of use appear reasonable based on medical, humanitarian, and socio-economic aspects, and for which there are no other available medicines or treatment methods that are considered significantly more suitable, can be included in the scheme. The price for these medicines is assessed based on value.

Companies can apply for their medicines to be included in the pharmaceutical benefits scheme. It is however not a right to be included. TLV processes the applications and conducts health economic evaluations to determine if the medicine can be considered cost-effective. For new medicines, the assessments primarily rely on scientific data and evidence generated prior to marketing authorisation. Willingness to pay also considers the severity and rarity of the condition. Increasingly, a tripartite dialogue, subsequent negotiations and agreements between companies and regions are required before TLV can make a formal decision. The tripartite process is still depending on the availability of relevant data and documentation.[70]

[69] More info via EMA (https://www.ema.europa.eu/en/medicines); Swedish Medical Products Agency/Läkemedelsverket (https://www.lakemedelsverket.se/sv); TLV (https://www.tlv.se/); the 21 regions' collaboration model for medicines (https://samverkanlakemedel.se/).

[70] See legislation on pharmaceutical benefits (2002:160) and the official report of the Swedish government, SOU 2018:189, Tydligare ansvar och regler för läkemedel (final report/ Läkemedelsutredningen)

Hospital medicines are not included in the pharmaceutical benefit scheme. Nonetheless, there is generally no cost for the patients. The regions cover these costs and medicines are procured according to public procurement law. The regions determine the process for selecting medicines for procurement and introduction. The 21 regions have established a collaboration model for joint national introduction of medicines. The model aims to strengthen the coordination of procurement processes and promote equal access and sustainable medicine use. The regions select the medicines that are managed through joint introduction. For companies, this means a single-point-of-contact. An introduction process is then initiated, often requiring negotiations with pharmaceutical companies.[71] For these medicines, regions request data from companies for health economic evaluation and TLV is responsible for the assessment. While waiting for health economic data, the NT Council usually issues a "waiting recommendation" to temporary withhold the use of the medicine. Positive health economic assessments or negotiated agreements with companies can lead to a positive recommendation for use. These medicines are recommended as "should use" or "may use" based on factors such as patient needs, disease progression, availability of alternative treatments, and the medicine's relative effectiveness and costs. Ethical prioritisation principles always apply. Jointly managed introduction result in nationally prepared agreements. Due to the decentralised nature of the Swedish healthcare system, each region signs the agreement with the pharmaceutical company on bilateral terms.

For certain medicines, where treatment administration for all patients is geographically concentrated to a few specialist centres, agreements are only signed with the regions that provide the treatment. If no agreement can be reached with the company, the general recommendation is negative ("no use").

Since 2015, Nordic collaboration on pharmaceutical procurement has been conducted within the Nordic Pharmaceutical Forum. Joint Nordic assessments and negotiations can be initiated in some cases. A wider collaboration with the Beneluxa initiative has also been initiated (Belgium, the Netherlands, Luxembourg, Austria, and Ireland).[72]

Hospital medicines that are not included in the nationally coordinated joint introduction process are managed independently by regions through regional procurement, supported by expert groups and pharmaceutical committees. Medicines with negative reimbursement decisions or recommendations can still be used under exceptional circumstances through processes for regional exemption.

Financing of medicines

Medicines included in the pharmaceutical benefits scheme are funded by the state. The financing mechanism is regulated in an annual agreement with the regions. Patients cover a co-payment proportion up to the high-cost protection threshold. Hospital medicines are fully funded by the regions, managed through regional budgets and resource allocation. For reimbursed medicines with negotiated rebate, the rebate is shared between the state (40%) and the regions (60%). The state reduces its funding to regions in advance, based on the expected total rebates for the following year, as forecasted by Socialstyrelsen and TLV. For medicines used under the provision of regional exemptions, individual subsidies can be granted. Patients do not pay for these medicines. Since total expenditure must be covered within limited healthcare resources available, significant cost increases for medicines pose risks of unintended displacement of healthcare interventions and budget cuts in other areas of the healthcare system.

Equal access to medicines

Access to medicines should be equitable, considering the needs and solidarity principle. Reimbursed or recommended medicines are generally introduced in all 21 regions. For some medicines, implementation and administration may be geographically concentrated. This is common for ATMPs that require healthcare providers to undergo qualification processes before administering treatment. Treatment is typically administered at the university hospitals and patients from other regions can access treatment – on equal terms – through the cross-regional care system in place between the 21 regions. Geographical differences due to this type of concentration is therefore not necessarily the same as unequal healthcare.

Security of supply and medicine shortages

Sweden's pharmaceutical supply is dependent on European and global markets. Factors such as raw material availability, manufacturing capacity, supply chains, procurement, and stock management affect the security of supply. Reduced willingness to pay or relatively low prices on older medicines can result in withdrawal of essential, well-established medicines from the market. Managing shortages, especially of critical medicines where no treatment alternatives exist, increase the administrative burden for regions, demands significant time and resources from the healthcare system and may force the use of more expensive alternatives. Medicine shortages also pose a risk to patient safety and care. The regional collaboration model for medicines also includes joint monitoring and management of shortages.

Follow-Up

Patient and pharmaceutical registries are key sources of information for monitoring medicine use at a group level. Socialstyrelsen manages many of these registries. Follow-up is particularly important for new medicines, where aggregated data of safety and efficacy can be gathered and enhanced knowledge can be generated. Healthcare providers report to these registries, which support ongoing research, development, and real-world evidence in the pharmaceutical system. Pharmaceutical companies are required to conduct pharmacovigilance and, in some cases, additional effectiveness studies. Medicines introduced through agreements require continuous administration, communication, and follow-up. Initial recommendations and agreements may be revised and renegotiated, especially when new treatments emerge, and competition increases.

Medicines introduced through agreements require continuous

[71] See legislation on public procurement (2016:1145); the regions' collaboration model for medicines (https://samverkanlakemedel.se/) and https://skr.se/skr/tjanster/rapporterochskrifter/publikationer/prissattningintroduktionochuppfoljningavlakemedelisamverkan.65382.html

[72] See process for joint national introduction (https://samverkanlakemedel.se/) and Nordic Pharmaceutical Forum (https://nordicpharmaceuticalforum.com/)

administration, communication, and follow-up. Initial decisions and recommendations may be reconsidered and adjusted, and agreements can be renegotiated, especially if new treatment alternatives are introduced and competition arises. For reimbursed medicines, TLV conducts regular evaluations to ensure cost-effectiveness throughout their lifecycle. Medicines with marketing authorisation older than 15 years may be subject to automatic, limited price reductions under the so-called "15-year rule." Cost monitoring occurs both nationally and regionally. Confidential pricing can make actual costs unknown to prescribers and healthcare managers, complicating communication and financial oversight. This increases administrative work for regions, although the benefits may sometimes outweigh the challenges.

The entire pharmaceutical system influences patients' access to medicines – throughout a medicine's lifecycle.

HOW WAS THE REVIEW CONDUCTED?

The analysis focused on orphan medicines with European marketing authorisation obtained during the period 2017-2022, based on data from EMA's EPAR database (updated August 14, 2024). The availability and marketing of medicines in Sweden, including the first marketing date, were assessed using information from the Swedish eHealth Agency's VARA database. FASS was not used as a source in this review since its information is primarily based on the marketing authorisation, whereas the eHealth Agency's LiiV database confirms that packaging information for approved medicines is available. The VARA database was considered more accurate for measuring medicine availability as it includes the date of active marketing in Sweden. Medicines registered in VARA are available for ordering. For availability dates, the first registration was used, regardless of packaging size. The cut-off date was 30 June 2024. The variable for use in Swedish healthcare was based on complete sales statistics from the eHealth Agency's Concise database (inclusion from 1 January 2019 to 30 June 2024). A limitation is that sales data for medicines delivered directly to clinics, including certain ATMPs, are not fully recorded in Concise. Therefore, additional information on ATMP usage was gathered through the regional collaboration model for medicines. ATMP data covers the period from 1 January 2019 to 31 December 2023. The identification of ongoing or completed national implementation processes and cost coverage was based on publicly available information on reimbursement decisions (TLV) and national recommendations (NT Council). To gain deeper insight, supplementary information on collaboration decisions and ongoing processes was collected through the regional collaboration model. Cut-off date was 30 June 2024.

Whether a medicine has undergone a regional process for introduction and use was assessed through an exclusion method: medicines with recorded sales in the eHealth Agency's Concise database but lacking a decision from a national process were assumed to have been managed within regional processes. Cost coverage from public resources was assumed for all medicines priced above a threshold of SEK 10,000 per patient per year. This assumption may introduce a margin of error, as exemption management and individual subsidy decisions can vary, even though most regions apply similar criteria for such decisions. Cut-off date was 30 June 2024.

The medicines included in the analysis are all disclosed in the figure on page 6. A qualitative assessment of medicines was conducted by medical and pharmacological experts from within the Swedish healthcare system, in addition to a review of supplementary literature and references cited in the text.

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BRIEFING PAPER ON PATIENTS' ACCESS TO MEDICINES IN SWEDEN
Sustainable patient access to orphan medicines in Sweden
Core factors in the pharmaceutical system that enhances long-term sustainability in healthcare

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