EXECUTIVE SUMMARY

ANNUAL REPORT ON ACCESS 2025

TO ORPHAN MEDICINAL PRODUCTS IN SPAIN

aelmhu

Status of access to orphan medicinal products (OMPs) with orphan designation and trade name in Spain as of 31 December 2025.

1
Introduction

> 1.1 JUSTIFICATION

Access to Orphan Medicinal Products (OMPs) is a strategic area for the Spanish National Health System (SNS), both because of its impact on equity and because of its relevance to the care and quality of life of people with rare diseases. The complexity of regulatory processes and the constant evolution of the national and European regulatory frameworks make it necessary to have an annual analysis that provides an accurate picture of the status of access in Spain, allowing trends to be anticipated.

The **Annual Report on Access to Orphan Medicinal Products in Spain** has been established as a technical tool that provides objective and up-to-date information on the access situation, contributing to the planning, transparency and continuous improvement of the healthcare system. It has been produced in response to the need for rigorous data to support the development of public policies aimed at more efficient, equitable and sustainable access to orphan medicines.

Since 2018, this **Report** has served as a reference for monitoring progress in access to orphan and ultra-orphan medicines, establishing itself as the **main source of information in Spain in this field**. For our Association, it represents an ongoing commitment to generating knowledge that facilitates decision-making and cooperation between the various stakeholders involved.

Within this framework, AELMHU continues to work to **improve the quality and availability of information**, ensuring that patients, healthcare professionals, industry, public decision-makers and society have reliable data **on therapeutic innovation** in a field as complex and, at the same time, as promising as treatments for rare diseases.

This **Report** is therefore a **key instrument for guiding regulatory and strategic** legislation towards a more coherent, predictable and sustainable access model, contributing to greater equity and the continuous improvement of SNS.

> 1.2

Scope and objectives

The Annual Report on Access to Orphan Medicinal Products in Spain 2025 provides a **rigorous and structured analysis of the main indicators** that enable an understanding of the situation regarding access to orphan and ultra-orphan medicines in Spain. Its scope covers all stages of the process, from orphan designation in the European Union (EU) to their effective availability to patients in the SNS, through the analysis of comparable data and official sources.

The specific objectives of the report are to:

- **Analyse, using a transparent methodology, the situation regarding access** at each of the key stages: marketing authorisation in the EU, assignment of a National Code in Spain, and reimbursement and pricing decisions within Spain's National Health System.
- **Provide reliable, consistent and comparable indicators** that enable the description and analysis of the annual evolution of the processes for accessing Orphan Medicinal Products, facilitating the identification of trends and areas for improvement.
- **Facilitate year-on-year comparison of results**, allowing the evaluation of the evolution of the main access parameters and identifying relevant variations in the functioning of the system.
- **Provide strategic, data-driven information** to support decision-making, aimed at public administrations, healthcare professionals, pharmaceutical industry, the scientific community, civil society and patients.
- **Contribute to the dialogue between the various stakeholders** by providing up-to-date, objective information that serves as a basis for shared analysis and the development of regulatory or health policy initiatives aimed at improving the availability of innovative medicines.

This Executive Summary **incorporates methodological improvements and additions compared to previous editions,** aimed at deepening the analysis of access to OMPs in Spain. The study of access times is reinforced by a greater breakdown of the months elapsed from the assignment of the National Code to the reimbursement decision, the incorporation of the number of evaluations by the Interministerial Commission on Medicines Prices (CIPM), the calculation of medians and the analysis of their evolution over time since 2020. Likewise, comparisons by therapeutic area and graphic support have been expanded, as well as the analysis of approval types, reimbursement conditions and reasons for non-reimbursement.

Overall, this report is conceived as an **institutional reference tool to guide strategic planning and promote a more efficient, equitable, predictable and sustainable access model**, thereby contributing to the continuous improvement of the healthcare system for the benefit of people with rare diseases.

> 1.3 CONTEXT

Access to Orphan Medicinal Products in Spain takes place in a **complex healthcare and regulatory environment** that is constantly changing and marked by a sustained increase in therapeutic innovation. In recent years, the availability of new therapies for rare diseases has increased significantly, reflecting scientific advances and the healthcare ecosystem's commitment to these pathologies. However, this **progress coexists with persistent challenges** in the evaluation, reimbursement and access processes, which continue to condition the effective delivery of innovation to patients.

For AELMHU, these **advances are the result of the joint efforts** of the scientific community, the pharmaceutical industry, patient associations and public administrations. Cross-sector collaboration has accelerated the development of new therapies and improved the visibility of the needs of patients with rare diseases. However, **structural challenges remain that require priority attention**, such as strengthening investment in research and development, optimising evaluation and reimbursement processes, improving early access and consolidating innovative reimbursement models that provide sustainability and predictability.

In this regard, **AELMHU** has intensified its work around analysis, institutional dialogue and evidence generation, consolidating its position as a **key player in monitoring access and** promoting a more agile, equitable and sustainable model **of treatment for rare diseases.**

The year **2025** is a **particularly important milestone for pharmaceutical policy in Spain**, with the simultaneous development of several strategic and regulatory initiatives that directly affect access to Orphan Medicinal Products. These include the **implementation of the Pharmaceutical Industry Strategy**, aimed at strengthening the strategic autonomy, productive capacity and competitiveness of the sector, as well as improving the processes for incorporating innovation into the National Health System. Within this framework, the Joint Committee has established itself as a forum for structured dialogue between the government and the various employers' organisations in the sector, in which AELMHU participates by providing analysis, data and proposals on access to treatments for rare diseases.

At the same time, the update of **Spain's National Strategy for Rare Diseases** is progresssing well, adapting its lines of action to the current reality of scientific knowledge, therapeutic innovation and healthcare organisation. Added to this is the **progressive expansion of the common portfolio of neonatal screening services**, which reinforces early diagnosis as a key element in the comprehensive approach to these diseases.

From a regulatory standpoint, 2025 has been marked by progress on important structural reforms such as the **Draft Bill on Medicines and Health Products**, still pending publication following comments from the sector; the **Royal Decree on Health Technology Assessment**; the **Royal Decree on Medicines Reimbursement and Pricing Procedures**; and the update of **the Royal Decree on Medicines in Special Situations**, which is still pending finalisation.

These regulations represent a **strategic opportunity** to strengthen equity, efficiency and predictability of access, as well as to **consolidate the role of rare diseases within the priorities of the healthcare system, in line with the Pharmaceutical Industry Strategy.** As a country and as a sector, we must ensure that future legislation accurately reflects the needs of the healthcare system and people with rare diseases.

At the same time, the **autonomous communities have continued to develop and update their Regional Plans and Strategies for Rare Diseases**, strengthening healthcare coordination and strategic planning. Among the most significant advances are the expansion of resources for multidisciplinary care, the improvement of referral circuits to reference centres and the progressive incorporation of monitoring and evaluation indicators. These developments contribute to reducing regional inequalities and strengthening the cohesion of the National Health System, a particularly important aspect in a context where equity remains a persistent challenge.

Likewise, the **role of the autonomous communities is decisive in achieving effective access to Orphan Medicinal Products**, given that their participation is key both in the reimbursement processes and in the approval and implementation of their use in clinical practice. Beyond the decision on reimbursement at the national level, **regional evaluation, the definition of criteria for use, budget allocation and the organisation of healthcare circuits directly influence the time taken to access these treatments and the uniformity of their availability.** Differences in management capacity, budgetary priorities and internal procedures can lead to regional variability, reinforcing the need to move towards models of coordination and shared governance that ensure agile, equitable implementation in line with the principles of the SNS.

At the **European level**, access to Orphan Medicinal Products is also at a **key moment from a political and regulatory standpoint, a crucial process that will define the regulatory framework for the coming years**. During 2025, strategic initiatives have been developed to adapt the regulatory framework to developments in biomedical innovation and to strengthen the competitiveness and resilience of the European economic and healthcare system.

Among the most relevant elements is the **European Pharmaceutical Package**, currently under institutional negotiation, which proposes changes to incentives for Orphan Medicinal Products, regulatory procedures and availability obligations in Member States. Likewise, the implementation of **the European Action Plan on Rare Diseases** has begun, which seeks to improve coordination, access to diagnosis and equity in care throughout the EU.

In this context, Regulation (EU) 2021/2282 on **Health Technology Assessment (HTA)**, in force since January 2022,**, is being progressively implemented since January 2025**. This regulation establishes a common framework for conducting joint clinical assessments and scientific consultations at European

level, with a significant impact on rare diseases and OMPs. This new system aims to reduce duplication between Member States, increase regulatory predictability and facilitate faster and more equitable access for patients to therapeutic innovations, while respecting national competences in relation to reimbursement and pricing.

This is complemented by other initiatives, such as the development of the future **European Biotechnology Law**, aimed at promoting, coordinating and accelerating the arrival of innovative treatments such as advanced therapies, as well as the **Critical Medicines Law**, which will establish common criteria for identifying these products and strengthening the security of their supply. In this regard, **European institutions and regulatory authorities have emphasised the need to balance innovation, access, sustainability and equity,** principles that are particularly relevant in the field of rare diseases and OMPs.

These **initiatives seek to harmonise processes, promote innovation and ensure that European patients have access to essential treatments** under conditions of equity and safety.

At the global level, **the World Health Organization (WHO and the United Nations (UN** have repeatedly emphasised that **equitable access to essential medicines is a fundamental pillar of the right to health and an obligation of States within the framework of human rights**. Both institutions recognise that rare diseases require specific policies to ensure the availability, affordability and continuity of treatments, **including OMPs**. These international guidelines highlight the need to ensure that people with rare diseases receive adequate and timely pharmacotherapeutic care in accordance with global standards of equity and health justice.

Overall, **analysis of the national, regional, European and global context** shows that access to therapeutic innovation in rare diseases continues to be conditioned by regulatory, organisational and coordination factors, in an environment of regulatory and strategic change. In this scenario, the AELMHU Annual Access Report has established itself as a technical reference tool for monitoring access to Orphan Medicinal Products in Spain. It enables trends to be identified, changes in access times and conditions to be analysed, and an objective, data-based perspective to be brought to the healthcare debate.

Through this Report, AELMHU **reaffirms its commitment to continuously improving knowledge about access to Orphan Medicinal Products and**

to contributing to a healthcare system that incorporates innovation in a coherent, predictable, equitable and sustainable manner, always for the benefit of patients with rare diseases.

The Association **brings together pharmaceutical and biotechnology companies committed to the research, development and marketing of innovative therapies** aimed at improving the quality of life of people affected by rare and ultra-rare diseases.

Its **mission is to contribute to the well-being and health of these individuals** by raising awareness of rare diseases and promoting the value of research and treatments developed for them.

The current members of AELMHU are: Alexion - AstraZeneca Rare Diseases, Alnylam Pharmaceuticals, Amgen, AOP Health, Argenx, Ascendis Pharma, Avanzanite Bioscience, Biocryst, Biogen, BioMarin, Chiesi, CSL Behring, Esteve, Inmunocore, Insmed, Ipsen, Grupo Italfarmaco, Kyowa Kirin, Lundbeck, Novartis, Pharma&, PTC Therapeutics, Sanofi, Sobi, Takeda, UCB, Ultragenyx Pharmaceutical and Vertex.

2
Methodology

Of the **more than 3,000 active substances with orphan designation (OD** granted by the Committee for Orphan Medicinal Products (COMP of the European Medicines Agency (EMA, this Report has identified those with an active OD as of December 31, 2025 (more than 2,000.

OD is granted during the early stages of the medicine's research process. Among the active substances with an active OD, this report identified those with a trade name (more than 250, and duplicates with multiple indications were removed. Eliminating these duplicates results in **221 Orphan Medicinal Products (OMPs with an active OD and trade name** as of December 31, 2025.

Next, an analysis was conducted to determine which of these Orphan Medicinal Products had been withdrawn (or had not yet been included in the European Commission's Register of Orphan Medicinal Products (n=65. As a result, **the number of Orphan Medicinal Products with marketing authorisation (MA)** in the European Union (EU) as of December 31, 2025, was obtained (n=156) .

The third step was to identify which OMPs with a trade name that have a marketing authorisation in the European Union also have **a National Code (NC)** from the Spanish Agency of Medicines and Medical Devices (AEMPS) in Spain (n=134).

Finally, the OMPs and their **reimbursement dates by Spain's National Health System (SNS)** were identified based on information collected from the Ministry of Health's Medicines Reimbursement Information Search Engine (BIFIMED) (n=103). The date when the OMP was first included was used as the reimbursement date.

Notes:

- Because the data cannot be obtained from any publicly available source, this document does not reflect those medicinal products that are available in our country under specific situations and special authorisations framed within Royal Decree 1015/2009 (compassionate use, use in conditions other than those authorised or access to foreign medicines).
- The company indicated for each OMPs throughout this report corresponds, in general, to the owner company; however, in the case of reimbursed medicines, the company offering to the National Health System is identified, provided that it is not a medicine distribution company.
- The values represented in the graphs are usually rounded to whole numbers for ease of understanding. Decimals have been included in exceptional cases where necessary to maintain the consistency and accuracy of the analyzed data.
- The data collected in this Executive Summary comes from the report prepared by Bioinnova Consulting for AELMHU.

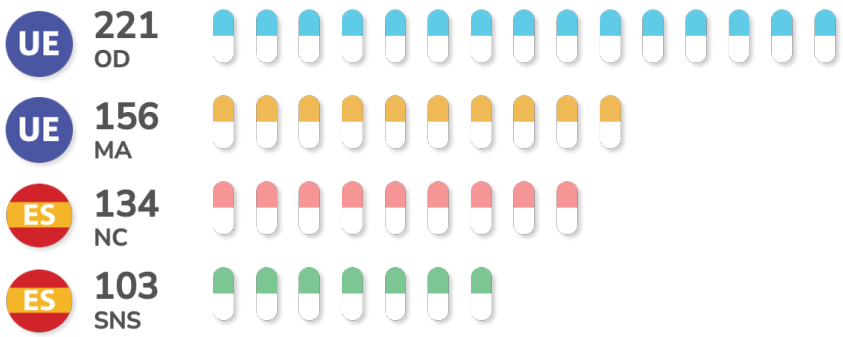
3

Access to Orphan Medicinal Products in Spain 2025

> 3.1

Orphan medicinal products in the EU and Spain

> Key indicators 2025

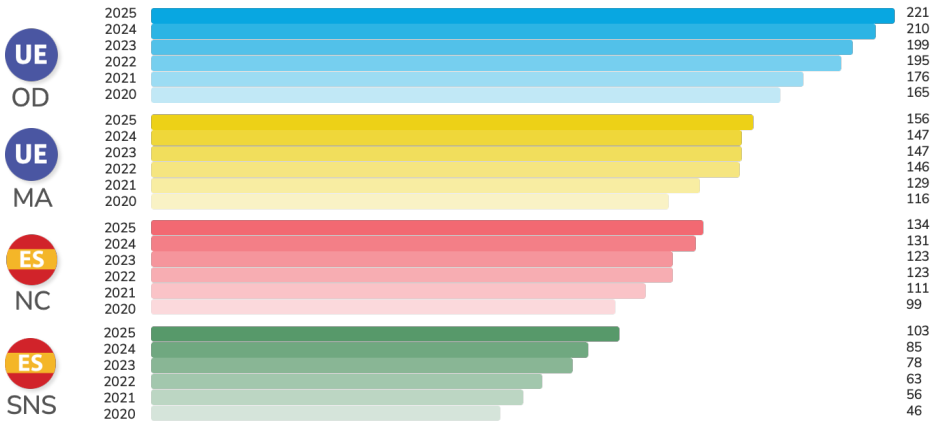


As of 31 December 2025, there are a total of 221 medicines with current orphan designation and a trade name in the EU, of which 156 have marketing authorisation (MA), 134 have obtained a National Code (NC) in Spain and **103 are reimbursed by the National Health System.**

> Evolution of indicators in the EU and Spain 2020-2025

During 2025**, all indicators for Orphan Medicinal Products in the EU and Spain improved**, although it is important to note that this occurred at different rates. The largest increase was recorded in reimbursed medicines, followed by treatments that obtained orphan designation, marketing authorisation and, finally, the National Code.

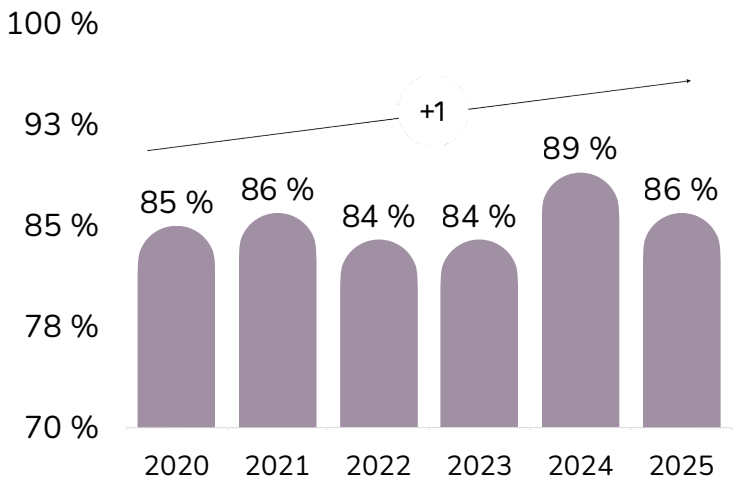
Evolution of indicators in the EU and Spain 2020-2025



> **Comparison between indicators**

The following graphs show the evolution of the comparison of three key indicators.

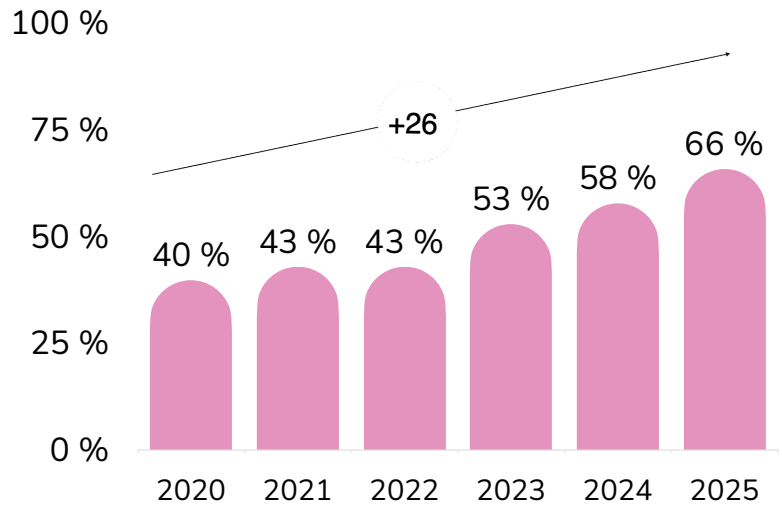
% of OMPs with MA and NC



On the one hand, it can be seen that **the proportion of National Code applications in Spain for orphan medicines with MA in 2025 is reduced to 86**%. Compared to previous years, the percentage is 3 percentage points lower than in 2024, although it is higher than in 2022 and 2023.

However, comparing 2025 with 2020, **there is a slight increase of 1 percentage point**, as in 2020 the percentage of authorised Orphan Medicinal Products with a National Code was 85%.

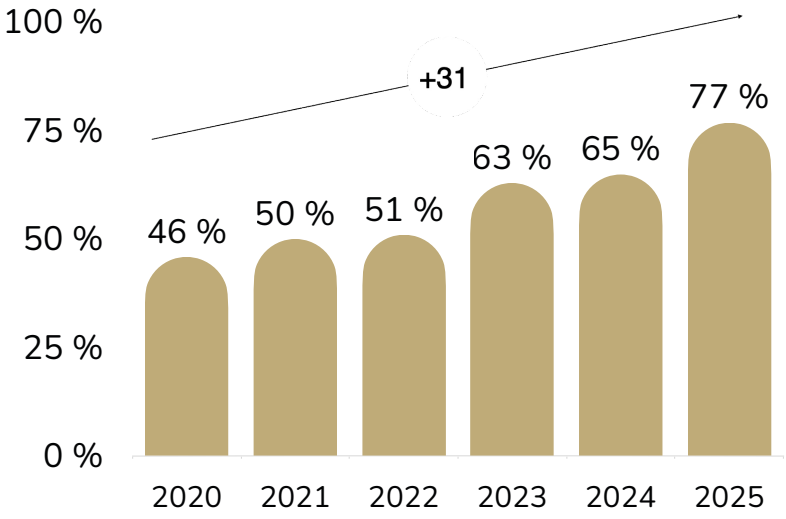
% of OMPs with MA reimbursed by the SNS



The results of the other two indicators included in the graph, which show **the number of Orphan Medicinal Products reimbursed in Spain, evidence a significant improvement**, consistent with the increase observed in 2025.

Firstly, **reimbursed OMPs represent 66% of those with marketing authorisation**, and are clearly on an upward trend since 2020: the increase has been 26 percentage points since 2020 and 8 compared to 2024.

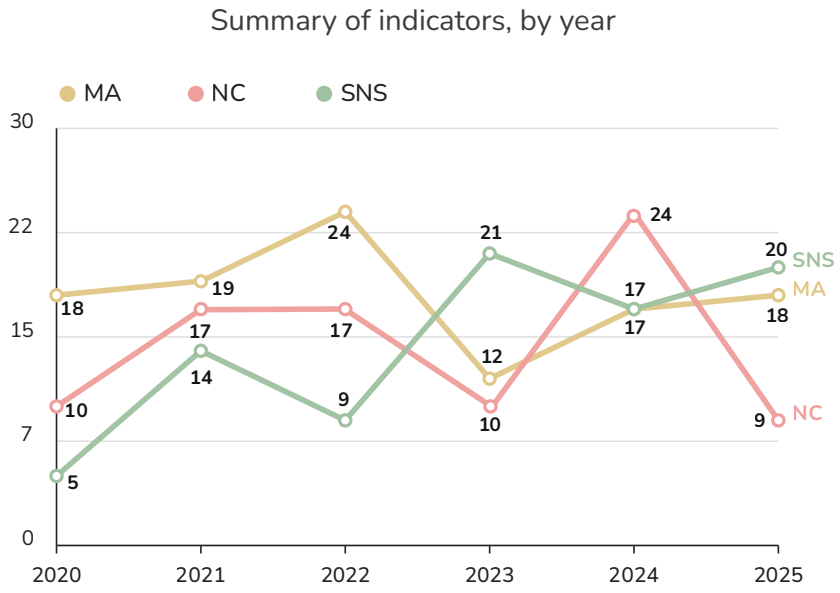
% of OMPs with NC reimbursed by the SNS



If we take Orphan Medicinal Products with a National Code as a reference, the increase in the percentage of reimbursed medicines also shows an upward trend: in 2025, they accounted for 77%. **The increase has been 31 percentage points since 2020, and 8 compared to 2024**.

> **Summary of the evolution of the main indicators by year**

The following graph shows the evolution of new marketing authorisations, national codes and reimbursed products in Spain, year by year since 2020.



In 2025, **two of the indicators improve compared to the previous year**: Orphan Medicinal Products with marketing authorisation and reimbursed by the National Health System. However, the number of these treatments with a National Code (9) worsens compared to 2024 (25).

If we compare what has happened since 2020, **the indicators for 2025 are not the highest in the series**. The year with the highest number of marketing authorisations was 2022, with 24. In terms of National Codes, 2024 was the most notable in the series (25), and 2023 set the record for the number of Orphan Medicinal Products reimbursed in Spain (21).

The number of medicines authorised in the European Union has continued to grow steadily since 2023, the year with the lowest number in the series (12). Despite this increase, it has not yet been possible to match the 24 authorisations in 2022.

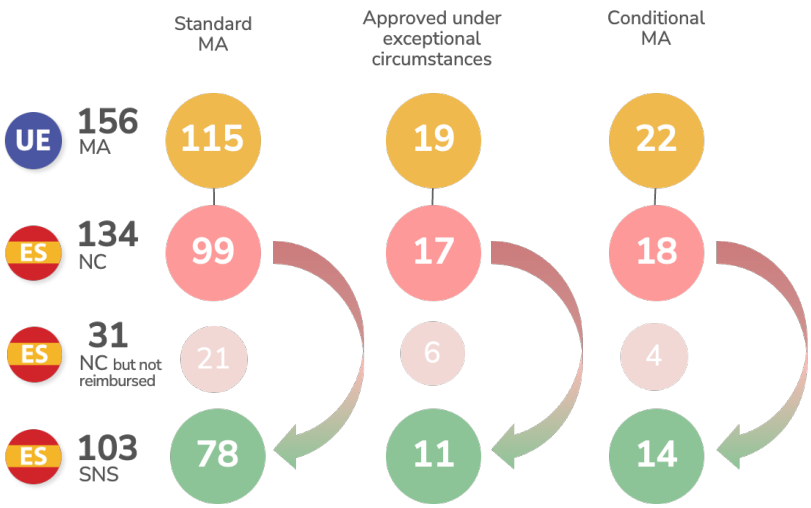
In 2025, **the lowest number of treatments with a National Code since 2020** was recorded, with a 64% reduction compared to 2024. On the other hand, the number of Orphan Medicinal Products reimbursed in 2025 (20) is the second highest in the series, after 2023 (21).

In the last three years, 58 treatments for rare diseases have been reimbursed in Spain, almost 50% more than between 2020 and 2022 (28).

> Type of approval for Orphan Medicinal Products

This year's report also includes information on the types of approval that Orphan Medicinal Products have received, as well as the special conditions associated with them.

Type of approval for Orphan Medicinal Products



Firstly, as shown in the graph above, of the **156 orphan medicines authorised** until 31 December 2025, 74% (115) have obtained standard approval, 12% (19) have been authorised under exceptional circumstances and 14% have been granted conditional authorisation (22).

For those with MA and NC (134), the percentages are similar: **74% (99) have standard approval**, 13% (17) under exceptional circumstances and 13% (17) conditional.

However, for **OMPs reimbursed by the SNS, the percentage with special conditions is somewhat lower (11%)**, the percentage with standard authorisation is higher (76%) and the percentage with conditional approval is similar (14%). If we focus on the percentage of OMPs authorised under special conditions that have not been reimbursed, it is higher, representing almost 20% (6 out of 31).

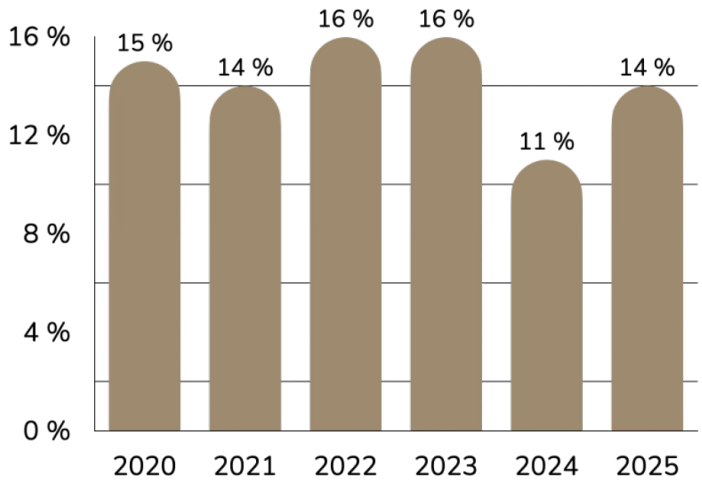
Finally, **of the 18 Orphan Medicinal Products with conditional approval and NC, 14 have been reimbursed (78%,** a percentage similar to those medicines with standard MA and NC (79%; 78 out of 99. However, of the 17 OMPs with NC approved under exceptional circumstances, only 65% (11 are reimbursed.

Special conditions associated with the approval of OMPs

In regard to special approval conditions, **more than half of Orphan Medicinal Products authorised in Europe and/or Spain are subject to additional monitoring**: 65% (102) in the case of those with MA, 63% (85) of those with NC and 61% (63) of those reimbursed in Spain. However, among those not reimbursed by the SNS, the proportion with additional monitoring is higher (71%).

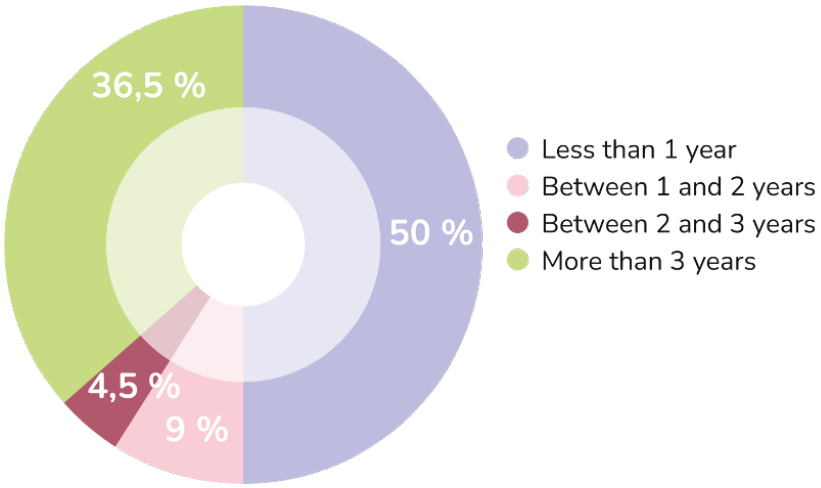
On the other hand, **8% of Orphan Medicinal Products with MA were authorised through accelerated assessment**. This percentage rises to 10% for medicines with a National Code and 9.7% for those reimbursed.

> **OMPs with marketing authorisation but without National Code**



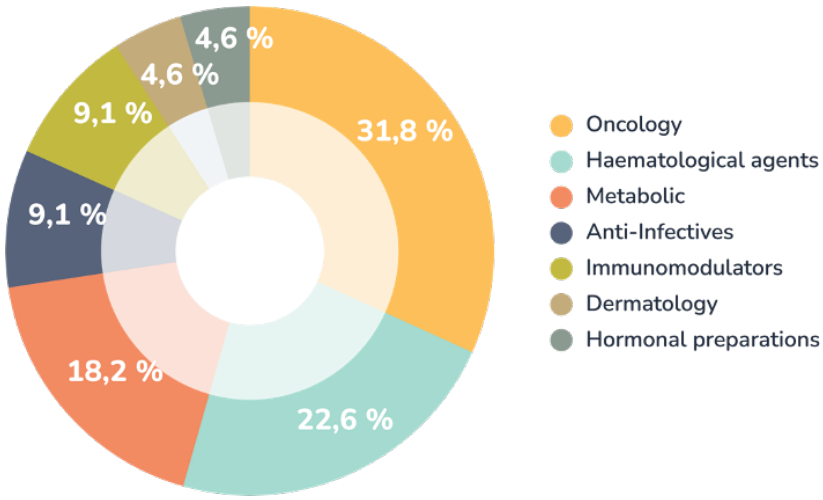
As of 31 December 2025, there were **22 OMPs with marketing authorisation that had not yet received a National Code in Spain**, representing 14% of those authorised at the EU. In 2025, this percentage increased again by 3 percentage points compared to 2024. This result partly reflects the small number of OMPs which applied for a NC in 2025, as shown above.

OMPs with MA but without a National Code by years of waiting



If we look at the time elapsed since these treatments obtained marketing authorisation, we can see that **50% obtained it less than 1 year ago**, 9% between 1 and 2 years ago, and the remaining 41% more than 2 years ago. It is important to note the differences with respect to 2024, since in that year only 13% of Orphan Medicinal Products had obtained MA less than a year ago, while for 81% it had been more than 2 years since that date.

MOMPs with marketing authorisation but without a National Code by therapeutic area

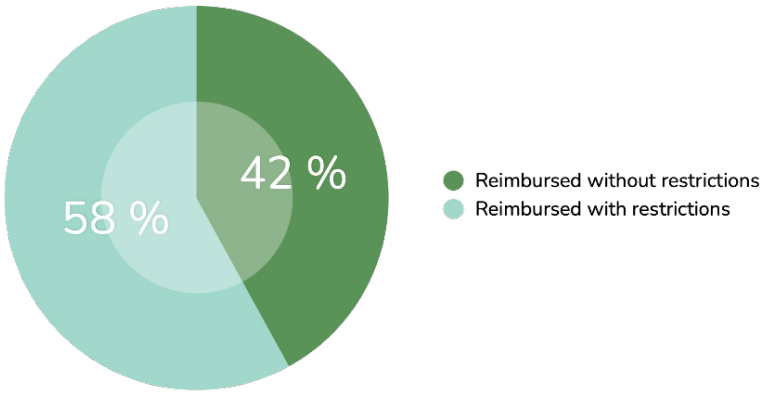


By therapeutic area, **Oncology and Haematological agents continue to be the predominant areas (31.8% and 22.6%, respectively)**, followed by Metabolic, Anti-infectives and Immunomodulators.

> 3.2
OMPs in Spain

As of 31 December 2025, **103 Orphan Medicinal Products are reimbursed in Spain**, representing 77% of the total 134 medicines with a National Code. This percentage is 12 points higher than in 2024.

OMPs with MA but without a National Code by therapeutic area

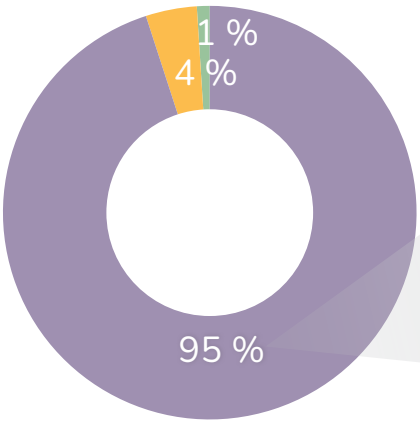


Of these 103 medicines with a positive price resolution and reimbursed by the SNS, **58% (60) are reimbursed with restrictions**, either due to restrictions on the authorised indication(s) or because they have an indication that is not reimbursed.

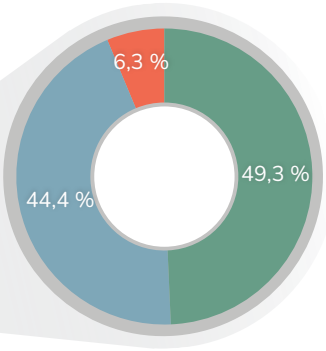
> **Status of authorised indications for reimbursed OMPs**

These 103 medicines have **a total of 151 indications authorised by the European Commission**, of which 135 are reimbursed by the SNS. Of these 135, as detailed in the graph below, almost 50% are reimbursed according to the authorised indication, while 44% have a restricted indication. The rest of the indications are not reimbursed.

File status by indication



Resolution of the reimbursement file by indication



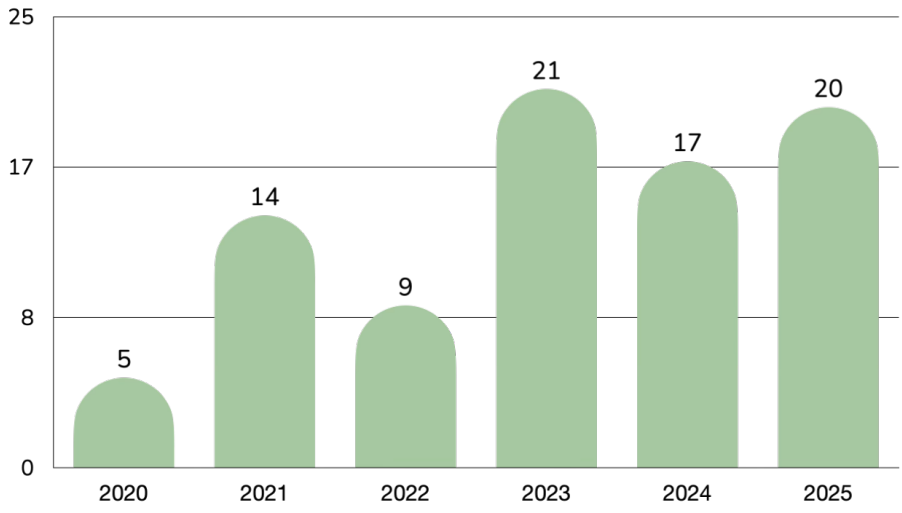
- Resolved
- Under study
- No reimbursement request
- Authorised indication reimbursed
- Restricted indication reimbursed
- Not reimbursed

> 3.2.1

OMPs reimbursed in 2025

During 2025, 20 new Orphan Medicinal Products were reimbursed in Spain: five during the first quarter, 14 in the second, and one in the third. **The 2025 number is the second highest since 2020**, only below the historic high of 2023 (21).

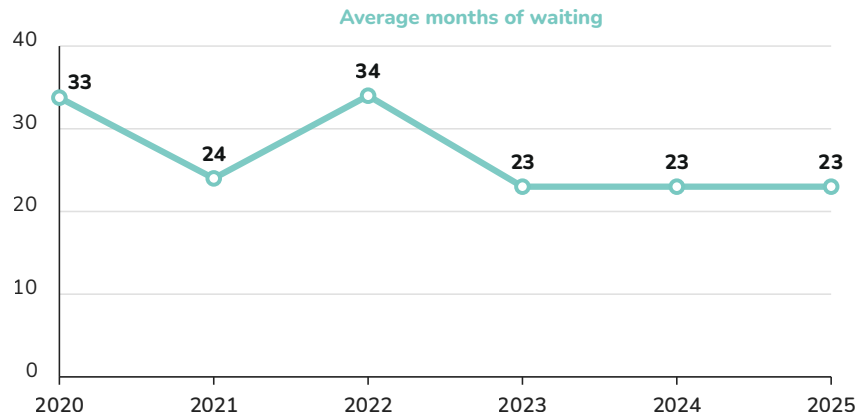
Number of OMPs reimbursed in Spain (2020-2025)



The **average time** between marketing authorisation and obtaining a National Code for the 20 new reimbursed OMPs was four months (two months less than in 2024), with a median of less than one month.

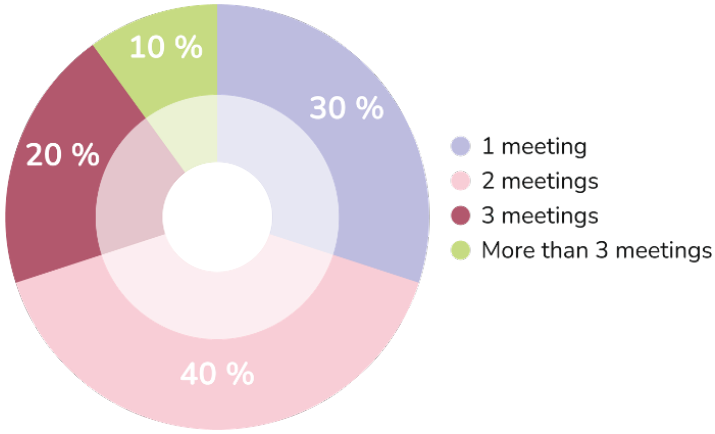
The average waiting time from obtaining the NC to being reimbursed by the SNS was 23 months (median of 12 months), with the average being the same as in 2023 and 2024.

Average waiting time from NC to reimbursement (2020–2025)



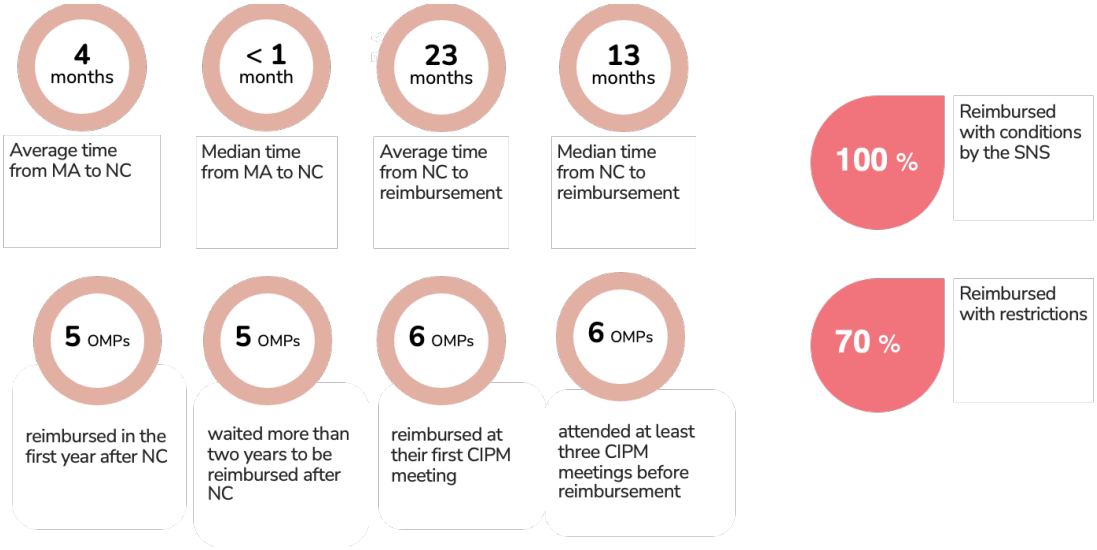
Of the 20 new OMPs reimbursed during 2025, 25% waited less than a year to obtain reimbursement, 50% waited between 1 and 2 years, and 25% waited more than 2 years. **The percentage that waited more than 2 years decreased slightly compared to 2024**, by 4 percentage points.

Number of CIPM meetings until reimbursement



Of these 20 Orphan Medicinal Products, **6 were reimbursed at their first meeting of the Interministerial Commission on Medicines Prices (CIPM)**, but another 6 attended at least three meetings of the Commission before being reimbursed (4 attended 3 times and 2 more than 3 times). The rest of the Orphan Medicinal Products (8) attended twice.

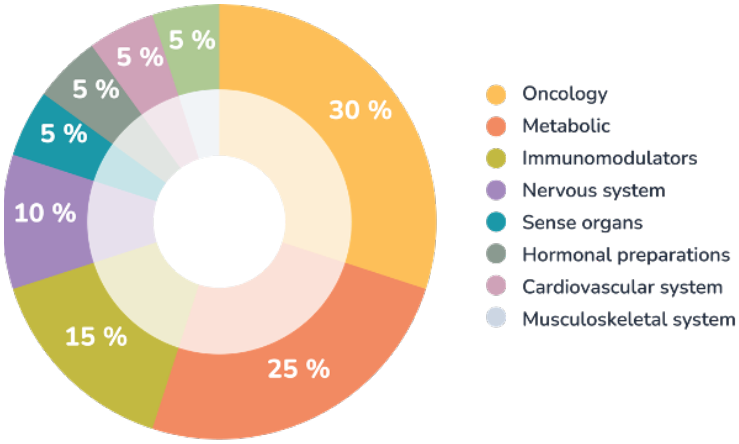
On the other hand, **70% (14) of the 20 new OMPs were reimburesd with restrictions** (based on the indications approved in the European Union) and 100% of them are reimbursed with conditions.



All 20 OMPs have monitoring conditions (they are included in SEGUIMED, and 14 are subject to two or more reimbursement conditions. Of the remaining six OMPs with a single reimbursement condition, five are subject to a sales threshold and one to a price-volume agreement.

All treatments were reimbursed according to criteria a) and c) set out in current legislation for the reimbursement of new medicines, which relate to the severity, duration and sequelae of the disease, and the therapeutic and social value of the medicine, respectively. In addition, criterion b), which refers to the specific needs of certain groups, was included for two OMPs.

OMPs reimbursed in 2025 by therapeutic area

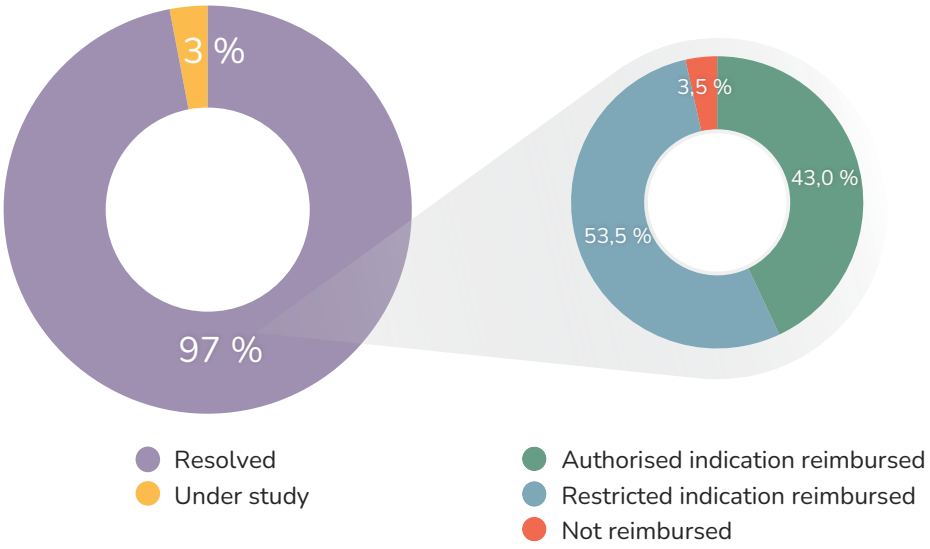


By therapeutic area, of the 20 new Orphan Medicinal Products reimbursed last year, **30% are for oncological diseases and 25% for metabolic diseases**.

Finally, the 20 Orphan Medicinal Products reimbursed in 2025 have **29 authorised indications**. Of these, 97% (28 out of 29) have been resolved, with the result that 43% (15 out of 28) are reimbursed according to the authorised indication, 53.5% (12) with restricted indications, and 1 is not reimbursed.

File status by indication

Resolution of the reimbursement file by indication



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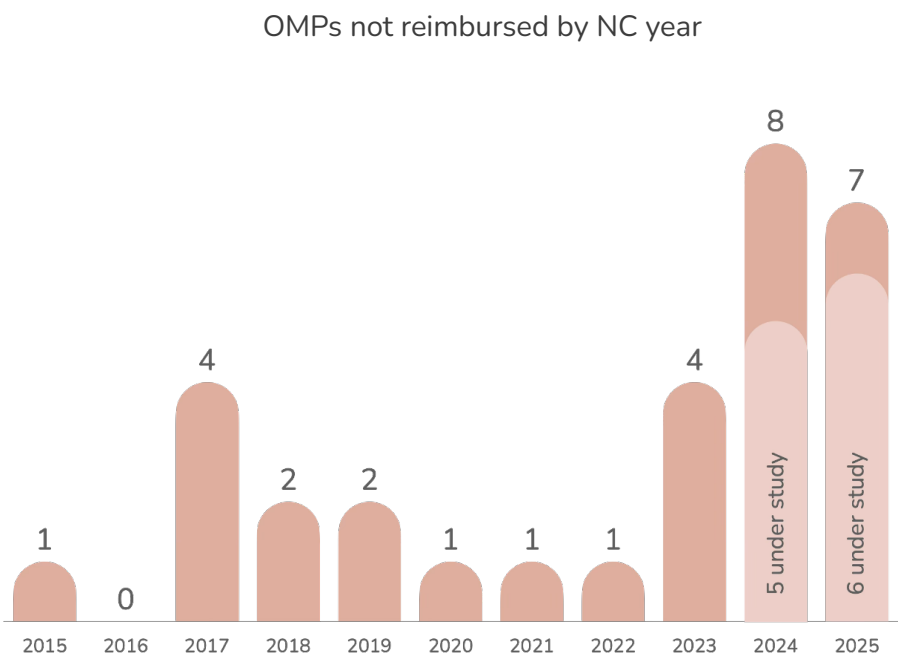
> 3.2.2

OMPs NOT REIMBURSED

There are currently **31 Orphan Medicinal Products with a National Code** in Spain **that are not reimbursed**. Of these, 20 have received a negative reimbursement resolution (1 of them with a NC of 2025), while 11 are under review or their reimbursement has not yet been requested (5 from 2024 and 6 from 2025).

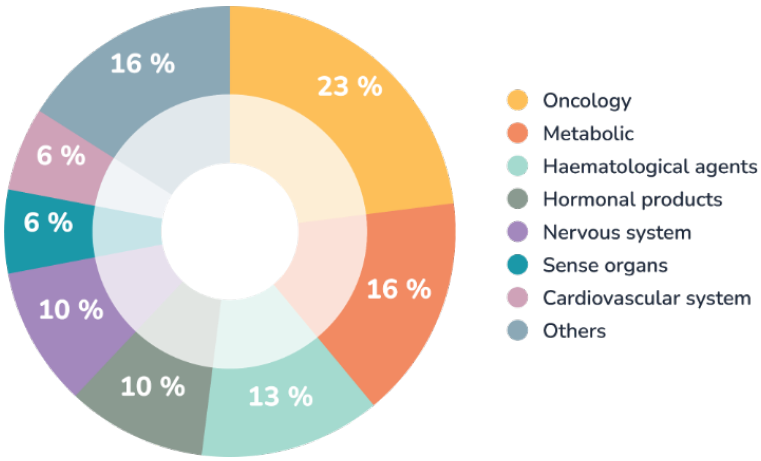


As shown in the graph above, of these 31 orphan medicines:

- **32% (10) have been awaiting public reimbursement** since the 2015-2020 period.
- **45% (14) in the 2021-2024 period remain without reimbursement** from the SNS.
- **The remaining 23% (7) received a National Code** in 2025.

Therefore, these numbers show that **more than 40% (13) of Orphan Medicinal Products with NC but not reimbursed have been waiting more than three years to be incorporated into the SNS**, although it is true that almost 20% (6) have been in this situation for less than a year.

OMPs with NC but not reimbursed by therapeutic area



Of the Orphan Medicinal Products with NC that are not reimbursed, **23% (7) are for oncological diseases and 16% (5) are for metabolic diseases**, among others.

The report **also includes information on CIPM meetings that have considered these medicines** and the criteria agreed upon for denying their reimbursement.

Of these 31 orphan medicines, **20 (65%) have been reviewed by the CIPM during the period 2015-2025**. In 17 of them (85% of those that have been reviewed by the CIPM), criterion d (rationalisation of expenditure) is included for not reimbursement, while criteria c (therapeutic and social value) and e (existence of other lower-priced alternatives) have been included in decisions for 7 (35%) and 6 (30%) treatments, respectively.

> 3.3

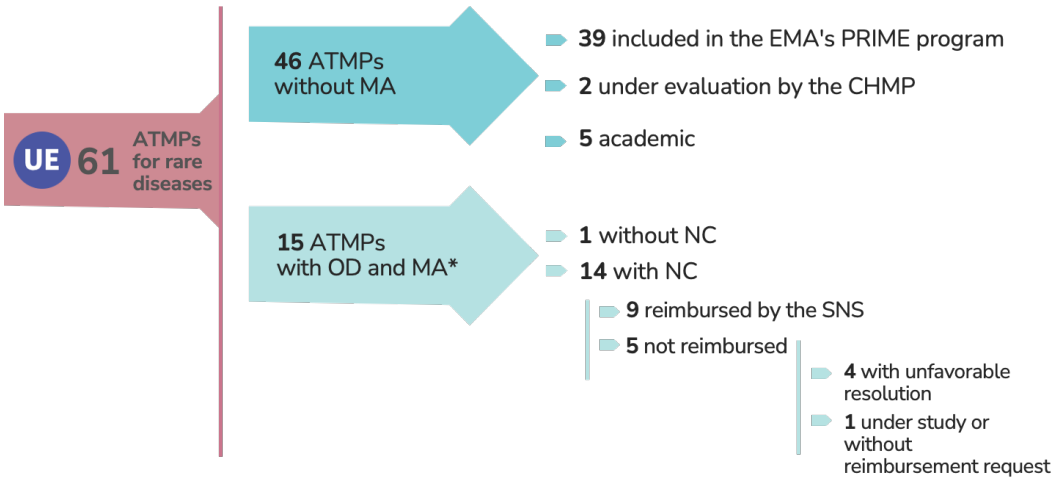
ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs) FOR RARE DISEASES

An Advanced Therapy Medicinal Product (ATMP) is a biological medicinal product for human use based on:

- **Genes**: gene therapy, which introduces, corrects or replaces genes within the patient's cells to treat a disease.
- **Cells**: cell therapy, a treatment that uses living cells that may come from the patient themselves or from a donor and are administered to repair or replace damaged cells or to act against a disease.
- **Tissues**: tissue therapy, a treatment that uses cells or tissues created or modified in the laboratory to repair, regenerate or replace parts of the body.

Many of the advanced therapies currently under development are targeting rare diseases and also have an orphan designation. For this reason, they are included in this report, as they represent one of the areas of greatest innovation and unmet medical need.

These therapies **are particularly relevant because they offer new treatment possibilities for conditions that, in many cases, lack effective therapeutic options or only have symptomatic approaches**. For patients, this can translate into a significant improvement in quality of life, a change in the natural course of the disease, and even potentially curative therapeutic opportunities.



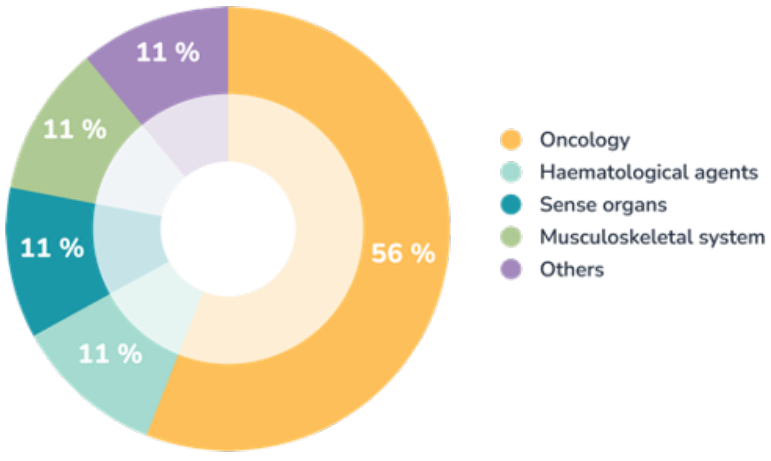
As of 31 December 2025, there are 61 ATMPs for rare diseases, but only 25% have marketing authorisation (15).

Of these 61, **2 are currently being evaluated by the CHMP, 5 are academic ATMPs, and 39 are included in the EMA's PRIME program**. PRIME is designed to support the development of medicines targeting unmet medical needs through greater interaction and early dialogue with innovative medicine companies so that these therapies can reach patients sooner.

The 15 advanced therapies that have marketing authorisation are included in the 156 OMPs referred in this report. Of these, 14 have a National Code and 9 are reimbursed by the SNS.

Of the **five therapies with a National Code but not reimbursed**, four have been denied reimbursement and one is under review or has not requested reimbursement.

Advanced therapies with OD reimbursed by therapeutic area

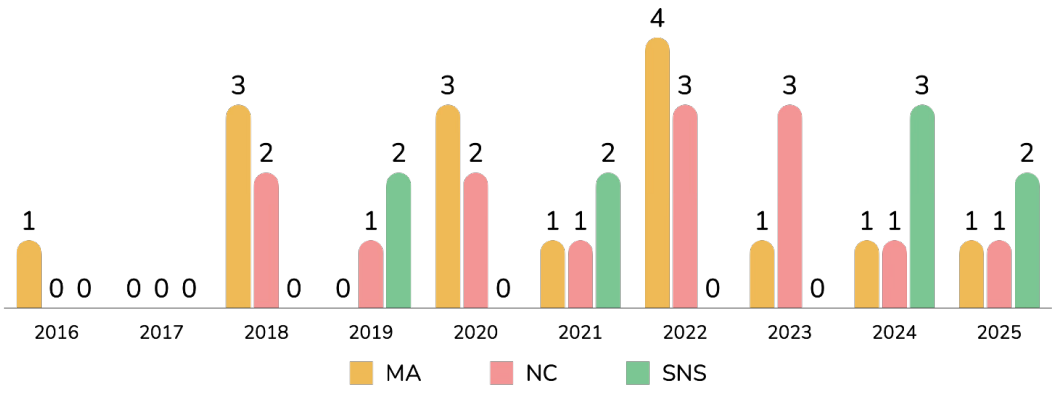


Five of these ATMPs are oncological, and the rest are: one haematological, one for sense organs, one for the musculoskeletal system and one for the nervous system, respectively.

In addition, **all 9 therapies are monitored through the SEGUIMED procedure**, and 8 are required to comply with the pharmacoclinical protocol through VALTERMED. All 9 therapies have at least 2 additional reimbursement conditions, including payment for results in 8 of them.

The average time from European marketing authorisation to obtaining the National Code in Spain is three months, and from the NC to reimbursement by the SNS, 24 months. Three of the nine therapies have been reimbursed at their first meeting with the CIPM, two at the second meeting, three at the third, and one has needed four meetings with the Commission.

ATMPs evolution by indicator (2016-2020)



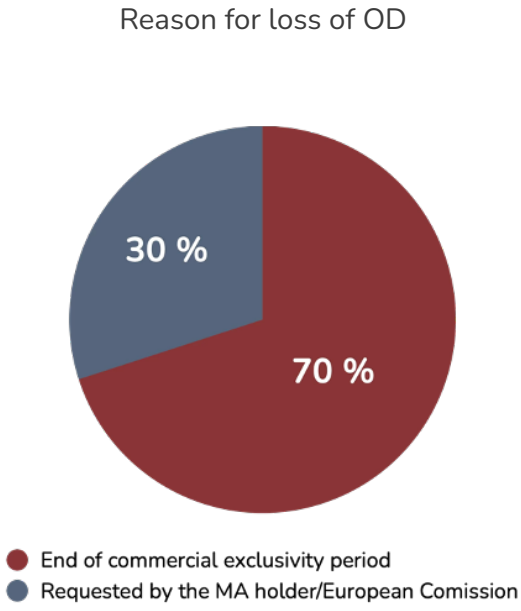
The graph above shows the evolution of ATMPs from 2016 to 2025. **Spain has incorporated two advanced therapies with orphan designation into the National Health System in the last year**, one less than in 2024. Even so, more advanced therapies have been reimbursed in the last two years than in the previous six years.

> 3.4

MEDICINAL PRODUCTS INDICATED FOR RARE DISEASES THAT HAVE LOST ORPHAN DESIGNATION

The report also analyses those medicinal products that, despite having lost orphan designation between 2008 and 2025, continue to be reimbursed by the National Health System. As of 31 December 2025, **90 medicines have been identified in this situation**. Of these:

- 30% have lost their orphan designation at the request of the marketing authorisation holder or following a decision by the European Commission.
- 70% was due to the end of the established period of commercial exclusivity.



4
Assessments and recommendations

> 4.1
Assessments

For AELMHU, **the data on access to Orphan Medicinal Products in 2025 maintain the positive trend observed in the reports of the last two years**. This is good news for patients and their families, especially those who do not yet have a treatment for their conditions and place their hope in pharmaceutical innovation.

We can highlight four particularly positive results. Firstly, a key indicator of access to Orphan Medicinal Products in Spain is the proportion of medicines that, having received marketing authorisation by the EU, are reimbursed in our country. In 2024, Spain reimbursed 58% of the OMPs, while **in 2025 this percentage has increased to 66**%.

In terms of waiting times in 2025, 5 Orphan Medicinal Products received reimbursement within the first year after obtaining the National Code, and six obtained reimbursement at their first meeting with the CIPM. **Reducing the time between key milestones is essential to improving access to these treatments in Spain**. For this reason, AELMHU and its members remain committed to working collaboratively with the various stakeholders in a trusted environment.

Thirdly, when analysing the number of Orphan Medicinal Products that have a National Code but are not yet reimbursed, we observe that a significant proportion (one in five have been waiting less than a year for a favourable decision. **Based on the above data,** the Association **hopes that these medicines will gain access within a reasonable time frame** and without the need for a new CIPM meeting.

Fourthly, with regard to advanced therapies, two new ones were incorporated into the SNS in 2025, bringing the total number reimbursed to nine. It seems that we are leaving behind the situation of 2022 and 2023, years in which none were reimbursed. **It is essential that these therapies continue to be incorporated in Spain, given their growing future relevance.** However, once reimbursed, they are often subject to strict controls, so it is necessary to ensure that the conditions and restrictions applied do not limit patient access.

These positive results reflect the significant effort made by all stakeholders in recent years. However, AELMHU believes that we must continue to move forward so that the system is prepared for the arrival of these innovative

treatments for rare diseases in the coming years, advancing in the development of flexible reimbursement models, agile evaluations, adequate infrastructure and public-private collaboration.

However, **some indicators have not experienced this positive trend and are less favourable**. Waiting times between the assignment of the National Code and the reimbursement decision have remained unchanged over the last three years, with an average of 23 months.

Furthermore, **a significant proportion of OMPs reimbursed in 2025 took more than two years to obtain reimbursement after receiving the National Code**, and required at least three CIPM meetings. We therefore consider it necessary to continue working together to reduce these delays and make improving access times one of the central objectives of the expected regulatory development, both in Europe and in Spain, as we are currently still far from meeting the deadlines established in current legislation.

The situation of some Orphan Medicinal Products with a National Code that still do not have reimbursement is also **worrying**, as more than 4 out of 10 have been waiting more than three years to be included in public reimbursement.

On the other hand, **14% (22) of OMPs with European marketing authorisation have not yet received a National Code in Spain**. Of these, half were authorised more than a year ago, while the other half did so in the last year. If access is maintained and improved, it is expected that by 2026 the number of OMPs applying for a National Code will increase. This is key to bringing innovation to the Spanish market, as it represents a fundamental requirement for access to treatments in our country. It is therefore **necessary to ensure that, as a country, we guarantee an attractive environment that encourages the arrival of new treatments for rare diseases**, which in many cases are the only therapeutic alternative for patients.

> 4.2
RECOMMENDATIONS

Based on the findings of the report, AELMHU presents a series of recommendations aimed at improving access to Orphan Medicinal Products in Spain:

- The European initiatives mentioned in the introduction will be a determining factor in access to these medicines in our country. We must take advantage of European structures and align them with our needs. To this end, **it is essential to closely monitor regulatory developments in Europe and ensure that Spain can positively influence them**, promoting competitiveness in the biopharmaceutical sector and incentives for research, development and access to Orphan Medicinal Products. We must not forget that approximately **94% of rare diseases recognised to date remain untreated**, so reducing this percentage must be a strategic objective at all levels.

- Once the European regulation on health technology assessment has been implemented, it will be necessary to make progress in 2026 with pending legislation through the future Law on Medicines and Health Products and the various Royal Decrees. In this process, **it is essential to incorporate the social value of OMPs into their evaluation for pricing and reimbursement by the Spanish National Health System (SNS)** and to move beyond a narrow view based solely on traditional cost-effectiveness analysis. These medicines bring value not only to the patients who receive them, but to society as a whole. Failure to do **so risks limiting access to these treatments for patients with rare diseases**.

- It is also important to highlight the role of the various agents involved in the evaluation, pricing and reimbursement processes. During 2025, special emphasis has been placed on the relevance of patients and

healthcare professionals, particularly in the field of rare diseases, where there is great uncertainty and a lack of knowledge. **It is essential to integrate into the National Health System the idea that patients not only receive treatment: they also generate evidence, define and evaluate value, guide policies and contribute to ensuring equity**. A key objective for 2026 must be to strengthen patients' capacities so that the healthcare system truly responds to their needs and they can contribute with their experience and knowledge to decision-making, promoting faster and more equitable access. At the same time, **it is necessary to facilitate the work of healthcare professionals**, who act as a bridge between regulation, scientific evidence and the real needs of patients, turning pharmaceutical innovation into tangible benefits for society.

> Finally, beyond the figures in the report, **it is essential to ensure equity in access to Orphan Medicinal Products among the different autonomous communities.** These play a key role, as they not only implement access within the National Health System, but also transform reimbursement into real access for patients. Once a medicine has been reimbursed by the SNS, it is the autonomous communities that determine when and how it actually reaches the patient. At AELMHU, we want to be their allies, offering them support to improve access to Orphan Medicinal Products in Spain in an efficient, sustainable and equitable manner.

> The Association is confident that this new regulatory and legislative framework, if finally approved, **will promote research, development and the arrival of innovation in our healthcare system** in a more equitable and rapid manner. This will foster innovation in the pharmaceutical sector, particularly in the field of Orphan Medicinal Products and other treatments for rare diseases.

AELMHU reiterates its willingness to collaborate so that, together—patients, the scientific community, professionals, industry, and public officials—, we can join forces **with the aim of finding solutions that improve the quality of life of people living with a rare or ultra-rare disease.**

5
Bibliography

- Medicines with orphan designation from the European Medicines Agency
- Community Register of Orphan Medicinal Products
- CIMA (AEMPS)
- BIFIMED (Spain's Ministry of Health)
- Agreements of the Interministerial Commission on Medicines Prices (CIPM)
- PRIME Program: Priority Medicines of the European Medicines Agency

6
Acronyms

- **MA**: European marketing authorisation by centralised procedure
- **AEMPS**: Spanish Agency for Medicines and Medical Devices
- **BIFIMED**: Search engine for information on the reimbursement situation of medicines in Spain
- **CHMP**: Committee for Medicinal Products for Human Use of EMA
- **CIPM**: Interministerial Commission on Medicines Prices in Spain
- **NC**: National Code
- **COMP**: EMA's Committee for Orphan Medicinal Products
- **EMA**: European Medicines Agency
- **OMPs**: Orphan Medicinal Products
- **ATMPs**: Advanced Therapy Medicinal Products
- **OD**: Orphan Designation
- **PRIME**: Priority Medicines program by EMA
- **SEGUIMED**: Monitoring of medicine supply in the national market of Spain
- **SNS**: Spain's National Health System
- **EU**: European Union
- **VALTERMED**: Information System for determining the Therapeutic Value in Real Clinical Practice of Medicines with High Health and Economic Impact in the Spanish National Health System

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