# Dostopnost inovativnih zdravil v Sloveniji

# Access to Innovative Medicines in Slovenia

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**Ključne besede:**
dostopnost zdravil, financiranje zdravil, postopek razvrščanja, vrednotenje zdravstvenih tehnologij, skupne klinične ocene

**Key words:**
access to medicines, medicines funding, reimbursement procedure, health technology assessment, joint clinical assessment

## Izvleček

*Postopek za razvrščanje zdravil oziroma njihovo financiranje v okviru zdravstvenega sistema je pogosto prepoznan kot ključen pri opredelitvi dostopa do inovativnih zdravil, saj vključuje dostopnost zdravil na eni strani in finančno vzdržnost na drugi. V okviru tega postopka je v Sloveniji na leto ovrednotenih približno 35 novih inovativnih zdravil in dodatno še 20 terapevtskih indikacij, tako s kliničnega kot tudi z ekonomskega vidika. Na ravni Evropske unije potekajo prizadevanja za poenotenje postopkov vrednotenja, ki zajemajo klinične vidike. Te pobude bi morale izboljšati postopek razvrščanja zdravil oziroma odločitev o njihovem financiranju in zagotoviti pravočasen dostop do inovativnih terapij, ki bodo usklajene z razvijajočimi se potrebami zdravstvenih sistemov v Evropski uniji.*

## Abstract

*Reimbursement is acknowledged to be a critical determinant of patient access to innovative medicines, necessitating a balance between accessibility and financial viability. Approximately 35 new innovative medicines and an additional 20 therapeutic indications are assessed from clinical and economical aspects during the reimbursement procedure every year in Slovenia. At the European Union level, ongoing efforts to unify assessment procedures of clinical domains are underway. These initiatives should improve the reimbursement process and ensure timely access to innovative therapies that will be aligned to the evolving needs of healthcare systems across the European Union.*

**Članek prispel / Received**
19. 11. 2023
**Članek sprejet / Accepted**
24. 11. 2023

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## INTRODUCTION

Medicines are a fundamental component of modern healthcare. Indeed, medicines have a major role in treating many diseases and contribute significantly to enhanced patient outcomes and an improved quality of life. Greater than 3100 different medicines encompassing approximately 850 active substances are available for prescription under health insurance coverage in Slovenia; however, 5%–10 % of the medicines are not prescribed (1). More than 18 million prescriptions are issued annually translating into an expenditure of approximately 680 million EUR (1). Additionally, medicines used within hospital settings are financially segregated, constituting an additional expenditure of approximately 150 million EUR/year.

In an international context, the Slovenia per capita expenditure on retail pharmaceuticals, which is expressed in USD purchasing power parity (PPP)/capita, aligns with the European Union average (571 USD PPP/capita). Among the Organisation for Economic Co-operation and Development (OECD) countries, retail pharmaceutical expenditures constitute the third most substantial component of healthcare spending, following inpatient and outpatient care. Specifically, retail pharmaceutical expenditures represent approximately 16% of the total annual healthcare expenditure in Slovenia (2). It is noteworthy that while northern and western countries exhibit higher total expenditures in USD/PPP, this presents a lower percentage of total healthcare spending.

### Procedures – Marketing authorization

To be introduced to the market, all medicines require marketing authorization, a regulatory process overseen by the European Medicine Agency or a national medicine agency, such as the Javna Agencija za Zdravila in Medicinske Pripomočke (JAZMP) in Slovenia. This authorization is contingent upon comprehensively evaluating the safety, efficacy, and quality of the medicine. The assessment procedures and timelines for obtaining marketing authorization are standardized across all European Union (EU) member states, including Slovenia, which is a first step towards equal access to novel medicines across the EU. Furthermore, acknowledging the significance of swift and uniform access to medicinal products, the European Commission has proposed strategic measures and incentives in a new legislative proposal (3).

### Procedures – Pricing and reimbursement

In the process leading to the universal accessibility of innovative medicines for patients, an essential prerequisite also involves pricing and reimbursement procedures. These procedures are in full competence compliance at the national level. First, the JAZMP determines the maximum allowable price using an external reference pricing system, in which the prices in the reference countries are taken into account. Moreover, Zavod za zdravstveno zavarovanje Slovenije (ZZZS) oversees the reimbursement process. Of note, the evaluation of innovative medicines is conducted in accordance with legislatively defined criteria, encompassing considerations of disease relevance, healthcare prioritization, clinical efficacy, comparative effectiveness, safety, economic aspects, and ethical dimensions (4). The expert professional assessment is conducted by a Reimbursement Committee, whose opinions about reimbursement are publicly available. Based on this opinion, the ZZZS engages in negotiations about the price and other conditions, such as prescription restrictions, with the applicant. Although integral to ensuring fiscal prudence and ethical considerations, these procedures are occasionally perceived as cumbersome, which contributes to a delay in accessing innovative therapies.

## METHODOLOGY

### Review of the reimbursement procedure in Slovenia

The evaluation process within the reimbursement procedure was explored. The primary data source was the publicly available reports issued by the

Reimbursement Committee in the last 4 years (5). The information about medicines assessed at meetings, types of recommendations and possible re-evaluation, recommendations about the settings of use and dates of application, and recommendations issued were retrieved from the reports. The extracted information was then combined with data of medicines in the central base of medicines in Slovenia.

## RESULTS & DISCUSSION

### Performance of the Reimbursement Committee

As per a comprehensive review of reports spanning the period from January 2019 to April 2023, the Reimbursement Committee held 34 meetings, typically convening 8 times each year, except for 2022 when 7 meetings were held. Only three reports are publicly available thus far in 2023. Throughout this time period, the Committee assessed a total of 148 innovative medicines containing new active substances, resulting in an average rate of 4.2 (range, 1 – 9) assessments of new medicines per meeting and 33.8 (range, 29 – 42) assessments of new medicines per year. In addition, extended evaluations of 83 previously reimbursed medicines with new indications were completed, with an average rate of 19.8 (range, 14 – 31) assessments of new indications per year. Furthermore, 16 additional applications encompassing alterations in pharmaceutical form, strength, or modifications in prescribing restrictions were assessed during the observation period.

It should be noted that 26 applications underwent scrutiny across multiple meetings with one particular medicine undergoing assessment in 4 meetings. This process can be due to objections raised by applicants regarding the Committee opinions, Committee requests for new evidence, or expert opinions from the clinic. Such cases highlight the nature of the assessment process, which reflects a commitment to thorough review and consideration of all relevant aspects in determining reimbursement eligibility.

With respect to the Reimbursement Committee opinions, nearly 90% of invested indications advocated for reimbursement under the condition of economic agreement between ZZZS and the applicant. In 2% of cases, the Committee recommended reimbursement without any conditions, while in approximately 7% of the cases the Committee issued an initial recommendation against reimbursement. In nearly all instances, applicants responded by providing additional evidence or redefining the target populations that would benefit the most. In 60% of the cases, the Committee acknowledged and accepted the supplementary information, subsequently recommending reimbursement under the condition that economic aspects are resolved in negotiations with ZZZS.

Seventy-five percent of the investigated indications received recommendations for prescriptions with an intended use in outpatient conditions. The remaining 25% of the investigated indications were designated for utilization in hospitals or ambulatory care settings.

*Table 1: Number of assessments performed by the Reimbursement Committee and the outcome*

| Year | Number Of Meetings | Assessment | | | Recomendation for innovative medicines | | |
|---|---|---|---|---|---|---|---|
| | | Innovative medicines | New indications | Other | Reimbursement | Conditional reimbursement | Not to reimburse |
| 2019 | 8 | 42 | 17 | 7 | 0 | 37 | 5 |
| 2020 | 8 | 34 | 14 | 3 | 0 | 30 | 4 |
| 2021 | 8 | 31 | 17 | 3 | 2 | 28 | 1 |
| 2022 | 7 | 29 | 31 | 2 | 0 | 29 | 0 |
| 2023* | 3* | 12 | 4 | 1 | 0 | 12 | 0 |

* publicly available reports for 2023 for 3 meetings (until April 2023)

## Accessibility of medicines

A comprehensive assessment of nearly 150 innovative medicines with new active substances was undertaken for the purpose of reimbursement. Given that most of these assessments resulted in recommendations for reimbursement, it can be anticipated that these medicines are or will be made accessible to Slovenian patients in the near future pending agreements between the ZZZS and applicants on the economic aspects. Concurrently, during the equivalent period spanning 2019-2022, a total of 164 innovative medicines with new active substances (30, 39, 54, and 41 by each year, respectively) received positive opinions from the European Medicines Agency (6). This positive opinion resulted in granting marketing authorization across the EU. Combining these results indicates that a significant proportion of EU-approved medicines are accessible to Slovenian patients. However, caution is required when comparing these figures for many reasons. Delays between marketing authorization and the application for reimbursement were observed, especially in central and eastern Europe (7). Furthermore, several procedures for obtaining marketing authorization exist within the EU, such as the decentralized and mutual recognition procedures performed by national medicine agencies. Timely access to innovative therapies is of paramount importance for patients. A study exploring the time to access novel anticancer drugs in Slovenia revealed that the duration from European Medicines Agency (EMA) approval to the national reimbursement decision averaged 422 days, with a range from 154–892 days (8). Remarkably, the study did not detect significant differences in time to access based on the clinical benefit, which is expressed as the European Society for Medical Oncology (ESMO)-Magnitude Clinical Benefit Score. Similarly, the most recent Patients W.A.I.T. (Waiting to Access Innovative Therapies) indicator survey, which has been presented in evolving formats since 2004, reported a median time to access novel therapies in Slovenia of approximately 500 days (9).

The Patients W.A.I.T. indicator also highlights substantial variability between countries with respect to availability rates and time to access. Germany is recognized as the country with the highest availability rate (nearly 88%) and the shortest time to market availability (median time = 47 days from market authorization). Slovenia ranks in the average range among European countries. It is noteworthy that the time to reimbursement decision can be divided into the following three segments: the duration from marketing authorization to the submission of the reimbursement file by the applicant; the time required for the Reimbursement Committee assessment; and the time for negotiations between ZZZS and the applicant regarding price and other conditions.

Considering the size of the market in Slovenia and its perceived attractiveness from an industry perspective, it can be asserted that patient access to novel therapies is relatively favorable. While Slovenia may lag behind Western countries, Slovenia is among the best in central and eastern European (CEE) countries (7, 10). This observation is in agreement with the results of a focus group comprised of Slovenian experts, which concluded that Slovenia provides satisfactory patient access to anti-diabetic medicines (11). The position of Slovenia in this context reflects a commendable balance between market dynamics, industry engagement, and a commitment to ensuring patient access to innovative therapies within the region.

## Health technology assessment (HTA)

As previously discussed, the Reimbursement Committee has a crucial role in the reimbursement procedure by providing opinions on various aspects. As medicines are considered one type of healthcare technology, the evaluation process is often referred to as an HTA in the literature (12, 13). Over the past decade, an HTA has gained significant importance, particularly in evaluating the clinical benefit in relation to value-for-money evaluations. Recognizing the resource-intensive nature of these assessments and the potential for more efficient utilization of human resources through collaboration, cooperation among member states commenced in 2004. The Employment, Social Policy, Health and Consumer Affairs Council (EPSCO) meeting on health services and medical care marked the initiation of this collaboration with the agreement to establish an HTA network in Europe.

Numerous projects and joint actions within the EU Health Program have since been initiated to strengthen cooperation, develop the network, and standardize procedures and methodologies for conducting HTAs. Such cooperation was and still is necessary because recommendations from various HTA agencies across Europe differ (14). The differences can be attributed to several factors, including differences in methodologic approaches and variations in the standard of care across European countries, leading to disparities in the selection of comparators, (sub)populations, and relevant outcomes in assessments (15). The multifaceted nature of healthcare systems across Europe contributes to the challenge of achieving uniformity in HTA recommendations and underscores the ongoing complexities in this domain.

After nearly 2 decades of voluntary cooperation through joint actions and significant development, Regulation 2021/2282 of the HTA was adopted in 2021. Regulation 2021/2282 will become applicable from January 2025 onward (16). A primary objective of this regulation is to establish a new framework for the joint work on assessments that would facilitate timely and consistent access to innovative medicines across the EU. Under this regulation, cooperation between member states becomes mandatory, but only with respect to assessment of clinical domains. These domains encompass the current utilization of technology for treating specific diseases, the technical characteristics of the new technology under assessment, and the safety and clinical effectiveness of the new technology with a particular emphasis on comparative effectiveness. However, other domains of assessment, such as cost and economic aspects, as well as ethical and organizational perspectives, remain within the jurisdiction of individual member states.

Leading up to the implementation in 2025, procedural guidance, methodologies, and other necessary implementing acts are being prepared and are expected to be adopted. The resulting comprehensive report about the technology containing all relevant evidence up to the publication date is anticipated to be publicly available and utilized in reimbursement processes in member states. This report could potentially serve multiple purposes, including serving as a source for clinical decision-making. The regulation introduces the concept of parallel assessment initiated before the medicine obtains marketing authorization. The aim of this approach is to contribute to earlier patient access to innovative therapies. This regulatory framework represents a pivotal step towards enhancing collaboration, standardizing assessments, and ultimately ensuring more efficient access to innovative healthcare technologies across the EU.

Indeed, implementing the new EU HTA framework is anticipated to necessitate adjustments in the reimbursement procedures in Slovenia. The existing workload, with an average of 34 assessments of innovative medicines with new active substances and 20 new indications annually, places a substantial burden on the members of the Reimbursement Committee. This work, undertaken as an additional responsibility alongside their primary roles, highlights the need for streamlining and improving efficiency. The collaborative efforts at the EU level, particularly the joint assessments and the production of common reports are expected to lighten the workload at the national level, reduce the time required for assessments, and nevertheless enhance the overall quality of the reports.

However, the joint assessment addresses only a specific aspect of the reimbursement procedure. The other two components should also be incentivized to secure faster access. To this end, the proposal for new pharmaceutical legislation presented by the European Commission in April 2023 (3) introduced incentives aimed at streamlining the reimbursement process. One notable recommendation is the extension of regulatory protection for medicines that demonstrate widespread accessibility across EU countries.

This proposed extension of regulatory protection aligns with the overarching goal, already identified in the HTA regulation of fostering faster and more uniform access to innovative medicines throughout the EU. This strategic approach, linked with regulatory measures aimed to strike a balance between safeguarding intellectual property rights and expediting patient access to novel therapies on a broader European scale.

## CONCLUSION

Access to innovative medicines is paramount for achieving optimal treatment outcomes. Procedures designed to ensure access to safe and effective drugs within financial constraints are being revised. While the current accessibility to innovative therapies in Slovenia is in alignment with the EU average, there is an opportunity for processes to improve, potentially leading to accelerated and expanded patient access in the future. The ongoing revision reflects a commitment to enhancing healthcare systems, fostering timely access to cutting-edge treatments, and ultimately improving the overall quality of patient care.

## REFERENCES


1. Zavod za zdravstveno zavarovanje Slovenije. (2023). Letno poročilo ZZZS 2022. https://www.zzzs.si/?id=126&detail=538C71578F0FD063C-125896C0047B208
2. OECD. (2021). Health at a Glance 2021: OECD Indicators. OECD Publishing, Paris, https://doi.org/10.1787/ae3016b9-en
3. European Commission (26.4.2023). Reform of the EU pharmaceutical legislation. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en
4. Pravilnik o razvrščanju zdravil na listo. (2013). Uradni list RS, št. 35/13. http://www.pisrs.si/Pis.web/pregledPredpisa?id=PRAV11493
5. Zavod za zdravstveno zavarovanje Slovenije – Komisija za razvrščanje zdravil na listo (2023). Zapisniki komisije za razvrščanje zdravil na listo. https://www.zzzs.si/?id=126&detail=C3AC26656FADB67EC-1257E0700333D7F
6. EMA – European Medicines Agency. (2023). Medicine evaluation figures - Human Medicines Highlights 2019-2022. https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/medicine-evaluation-figures
7. Kandolf Sekulovic L, Guo J, Agarwala S, Hauschild A, McArthur G, Cinat G, et al. Access to innovative medicines for metastatic melanoma worldwide: Melanoma World Society and European Association of Dermato-oncology survey in 34 countries. Eur J Cancer. 2018 Nov;104:201-209. doi:
8. Janzic U, Knez L, Janzic A, Cufer T. Time to access to novel anticancer drugs and the correlation with ESMO-Magnitude of Clinical Benefit Scale in Slovenia. Expert Review of Pharmacoeconomics & Outcomes Research, 19:6, 717-723, DOI: 10.1080/14737167.2019.1702879
9. EFPIA - European Federation of Pharmaceutical Industries and Associations (26.4.2023). EFPIA Patients W.A.I.T. Indicator 2022 Survey. https://www.efpia.eu/media/s4qf1eqo/efpia_patient_wait_indicator_final_report.pdf
10. Ades F, Senterre C, Zardavas D, de Azambuja E, Popescu R, Parent F, Piccart M. An exploratory analysis of the factors leading to delays in cancer drug reimbursement in the European Union: the trastuzumab case. Eur J Cancer. 2014 Dec;50(18):3089-97. doi: 10.1016/j.ejca.2014.09.011.

11. ŽEROVNIK S, MARĐETKO N,, LOCATELLI I, KOS M. (2021). Regulatory and clinical perspective on patient access to antidiabetic medicines in Slovenia = Regulatorna i klinička perspektiva dostupnosti antidijabetike pacijentima u Sloveniji. Srpski arhiv za celokupno lekarstvo : journal of Serbian Medical Society. 2021, vol. 149, iss. 7-8, str. 461-466, ilustr. DOI: 10.2298/SARH210125058Z.
12. O'Rourke B., Oortwijn W., Schuller T. (2020). The new definition of health technology assessment: A milestone in international collaboration. International Journal of Technology Assessment in Health Care, 36(3), 187-190. doi:10.1017/S0266462320000215
13. Belfiore A, Scaletti A, Lavorato D, Cuccurullo C. The long process by which HTA became a paradigm: A longitudinal conceptual structure analysis. Health Policy. 2023 Jan;127:74-79. doi: 10.1016/j.healthpol.2022.12.006.
14. Fischer KE, Heisser T, Stargardt T. Health benefit assessment of pharmaceuticals: An international comparison of decisions from Germany, England, Scotland and Australia. Health Policy. 2016 Oct;120(10):1115-1122. doi: 10.1016/j.healthpol.2016.08.001.
15. Akehurst RL, Abadie E, Renaudin N, Sarkozy F. Variation in Health Technology Assessment and Reimbursement Processes in Europe. Value Health. 2017 Jan;20(1):67-76. doi: 10.1016/j.jval.2016.08.725.
16. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. UL L 458, 22.12.2021, str. 1–32. ELI: http://data.europa.eu/eli/reg/2021/2282/oj