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Short communication

Availability of rare disease medicines in North Macedonia: a comparative analysis of registered orphan medicines in North Macedonia vs. European Union

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Introduction

The design and approval of orphan drugs in order to treat rare diseases poses a significant challenge since these drugs are intended for a very small percentage of the population. The cost of developing, thus using an orphan designated drug could not be covered without additional incentives (Gianuzzi et al., 2017). The development of orphan drugs in the European Union was supported by developing specific legislation on these medicines in 2000 - Orphan Medicinal Product Regulation in response to earlier regulation provided in the United States (Bachman et al., 2012). Since then, significant number of orphan drug designations, as well as marketing authorizations were made, with varying trends, all aimed at improving the access to orphan medicines (Bouwman et al., 2024). Additional challenges and barriers exist when these drugs are to be approved and used in non-EU country with limited resources, as North Macedonia. In addition to recent efforts to regulate and closely define the field of rare diseases where these medicines are most often used, by adopting a 2026 Program for rare diseases in North Macedonia (Official Gazette, No. 33/2026), the main aim of this paper was to make a comparative analysis of the medicines registered or designated as orphan medicines in North Macedonia, and the drugs for rare diseases/orphan drugs in the European Union, in order to improve the understanding in this area and foster future actions aimed for improvement in this regard.

Materials and methods

Official document and literature research were performed using official websites of the European Medicines Agency (EMA) and Macedonian Agency for Medicines and Medical Devices (MALMED), including North Macedonia Drug registry and Official Gazette of the Republic of North Macedonia. Relevant information was extracted from publicly available reports, in addition to scientific literature on the topic. A descriptive statistical analysis was applied to the obtained results.

Results and discussion

By December 2025, a total of 57 medicines were included in the Program for rare diseases in North Macedonia. 38 (66.66%) originate from the EU, 8 (14.03%) from Switzerland, and the remaining originate from UK, USA, Turkey, Serbia, Russia and

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India. From the medicines included in the Program, 35 (61.4%) received marketing authorization from MALMED, and the remaining 22 (38.6%) are not registered in North Macedonia. From total 57 medicinal products used in rare disease program, 26 (45,61%) have received Orphan status in the EU, whereas the rest 31 (54,39%) are used without the designation, or the designation has been withdrawn or expired.

Regarding the ATC classification of the medicines approved for rare diseases in North Macedonia, 26.3% belong to the group A, intended for treatment of alimentary tract and metabolism, 19.3% belong to the group L, antineoplastic and immunomodulating agents, 15.8% to the group B - blood and blood forming organs and 14% to the group N aimed to treat the nervous system. Other ATC groups are represented by less than 10%.

When compared to orphan medicines approved in the EU, the total number of orphan designated medicines is 177, vs. 28 in North Macedonia (EU, Community Register of orphan medicinal products 2026). The distribution of medicines according to ATC classification is different: most of the approved medicines belong to the group L (36,4%), followed by group A (17,9%), and group B (9,3%).

The performed comparative analysis of the medicines approved for rare disease treatment in North Macedonia and EU clearly shows substantial differences especially in the number of approved rare disease medicines.

Conclusion

Substantial disparities exist in the number of officially registered orphan medicines in North Macedonia compared to EU countries, as well as represented ATC groups. These disparities contribute significant barriers and limitations in the treatment of the patients with rare diseases. In an environment of a small country with constrained economic capacity, small market attractiveness, and limited regulatory capacity, additional efforts are needed to strengthen regulatory and approval pathways, improving regional collaboration, and provision of financial incentives in order to improve rare disease treatment. Additionally, legislative reforms and the establishment of a coherent regulatory framework for orphan medicines are urgently required to align North Macedonia with EU standards and to address existing regulatory barriers, procurement delays, and limitations in patient access.

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