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Short communication

Meeting the affordability challenges in the access of drugs for rare disease in RN Macedonia

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Introduction

Rare Diseases (RDs, orphan) are a clinically heterogeneous group of diseases, characterized by a low population prevalence, usually genetic predisposition, occurrence mostly after birth or early childhood and progressive unfavorable course. Despite the diversity in etiology, rare diseases have many common elements - inadequate recognition, inadequate and/or non-existent classification, insufficient availability of diagnostic procedures, as well as limited and expensive therapeutic options. Orphan Medicinal Product (OMP) are products for the "diagnosis, prevention or treatment of life threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union" (*Regulation EC No141/2000 of the European Parliament and of the council, 16 December 1999*). In addition to unique scientific, legal and ethical challenges associated with OMPs development, the needs of rare disease patients have been neglected because of issues pertaining to small markets. A substantial increase in OMP development is seen after 2000 with the adoption of EU "Orphan Medicinal Product Regulation" which embodied a significant incentive for manufacturer investment in OMP. Despite all, patients access to OMPs, is still a concern (ICER, 2022). There is a substantial variation in OMP access across different European jurisdictions as a result of diverse value assessment frameworks (VAFs) used by decision – makers, ranging from designation of special status to OMPs in which reimbursement is granted in spite of high prices and undemonstrated effectiveness to obligation for country specific health technology assessment (HTA) or use of utilitarian healthcare approach, maximizing health benefits within a limited budget (Blonda et al., 2021). HTA that utilizes a standard economic evaluation, traditionally focuses on drug's safety, efficacy and economic consequences (cost – effectiveness; CA and budget impact; BI), treats both OMPs and non-OMPs in the same way and it is assumed that discards the impact of disease rarity, severity and unmet need which influences the OMPs health benefit (Chambers et al., 2020). In recent years, VAFs based on Multi- criteria decision analysis (MCDA) for OMPs are emerging, but despite of multiple strengths, these frameworks have also weaknesses (Postma et al., 2022). Because of the high acquisition costs of and the uncertainty of (cost-) effectiveness, the challenges in the OMPs access are mostly expressed in countries with low and middle income, small population and limited financial possibilities that lack relevant epidemiological data, experience and interest of the health care professionals, legislation for RD. According to the 2018 official data in the RN Macedonia there are 406 patients with rare diseases patients, of whom 135 are treated within the obtained budget for RDs of 6 000 000 € and the largest funds from the state budget are allocated for the treatment of spinal muscular dystrophy (SMA). Among the obligations of the National RDs Committee is managing the list and quantities of OMPs per year for treatment of the patients included in the RD registry. In this paper, we explore the role of the standard economic evaluation in managing the access and affordability of risdiplam in our country.

Materials and methods

A six state Markov model was used to compare three treatment protocols used in the therapy of SMA type 1 and type 2/3: 1) risdiplam, 2) nusinersin and 3) best supportive care (BSC). The assumed population of patients enter the model in one of a total of four states of SMA type 1 (do not sit, sit, stand and walk), i.e. 5 states of SMA type 2 and 3 (do not sit, sit with support, sit without support, standing and walking), defined according to the Motor-Function-

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Measure (MFM) 32 items scale. Over time, patients remained in the initial health state or moved to another health state according to the probability of disease progression or regression to a stage with higher or lower MFM and the probability of permanent ventilation (state 5) in SMA type1, or the probability of death (state 6). The analysis was conducted from the public payer perspective, in a Life time horizon of 80 years with a cycle length of 1 month. Patient data and transition matrices used in the model were based on a systematic literature review and clinical trial results (Firefish, Sunfish, ENDEAR for SMA Type 1 and SUNFISH Part 2 and CHERISH studies of SMA Type 2 / 3). Utility and disutility parameters for each of the transition states were based on the data indicated in NICE ERG TA588. The CEA did not take into account the probability of occurrence of treatment-associated adverse, the health benefit parameters for care givers. Only the direct and indirect medical costs associated with OMPs, drug administration and monitoring, disease monitoring, hospitalization, engagement of health personnel, supportive medication and physical therapy were included. Taking into account that risdiplam and nusinersin did not had a marketing authorization in the RN Macedonia at the time of analysis, the direct medical cost/ cycle for risdiplam was calculated according to the official methodology for defining the maximal drug price while the price of nusinersin was in accordance with the official price on the last tender of the Ministry of Health for the procurement of the OMPs. The resulting outcomes, presented per patient with 3% discount rate, included total cost (EUR), Effectiveness (Quality adjusted Life Years-QALY), Cost Effectiveness Ratio (C/E; EUR/QALY) and Incremental Cost-Effectiveness Ratio (ICER; EUR/QALY). The analysis was carried out using the Tree Age Pro Healthcare 2019 software. Probabilistic sensitivity analysis with 5000 iterations, with Gamma distribution for variables related to efficiency and quality of life and Uniform distribution for cost, varied within an interval of ± 25% of the baseline value, was conducted. The budget impact analysis over a 5-year time horizon (2020-2025) was carried out to assess the economic effect of adopting risdiplam in our country.

Results and discussion

According to results from the base-case scenarios, the C/E ratio of risdiplam was lower compared to nusinersin and BSC when used in SMA treatment (445,174.7268 vs. 671,652.6056 vs. 3,726,725,046 EUR/QALY for SMA type 1 and 236,316.49 vs. 248,225.8253 vs. 75,325.71 EUR/QALY for SMA type 2/3, respectively). Since nusinersin was an extensively dominated therapy in relation to other treatment strategies in both SMA models, in the absence of a nationally defined limit value of "Willingness to pay for", only the ICER of risdiplam versus best supportive care was determined and resulted in 401,826.25 EUR/QALY for SMA type 1 and 436,325.28 EUR/QALY for SMA type 2/3. For comparison, the C/E of risdiplam with 20-40% reduced price ranged in an interval of 377,093.00-280,482.07 EUR/QALY for SMA type 1 and 204,009.04 -158,168.06 EUR/QALY for SMA type 2/3. The probabilistic sensitivity analysis showed that base –case scenario results are robust and consistent and that the cost of risdiplam is the main factor affecting the pharmacoeconomic outcomes in R. Macedonia. Introduction of risdiplam, parallel with an increasing market share of 30%-90% during 5 years, resulted in an increase of total direct costs by 2,182,158.00 - 2,030,103.60 EUR, respectively and reduction of indirect medical costs by 86,756.75 - 269,042.45 EUR. The tendency to decrease the overall cost while simultaneously increasing the number of patients who are on risdiplam, confirmed the value of including the treatment as the first line treatment for SMA patients.

Conclusion

There is still much debate as to whether OMPs deserve a special treatment over non-OMPs in decision-making process regarding their affordability and limitations of cost- effectiveness analysis applied to assessing their access. The findings from this standard pharmacoeconomic evaluation provided comprehensive summary of the economic implication of adopting risdiplam in our country. Subsequently it contributed for including risdiplam in the national program for RDs. Appling the concept of accountability for reasonableness (A4R) in justification of decision-maker choice for a specific VAF for OMPs and transparency of evaluation process is highly recommended.

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