HTA74

# NOVEL APPROACH TO DECISION MAKING FOR ORPHAN DRUGS

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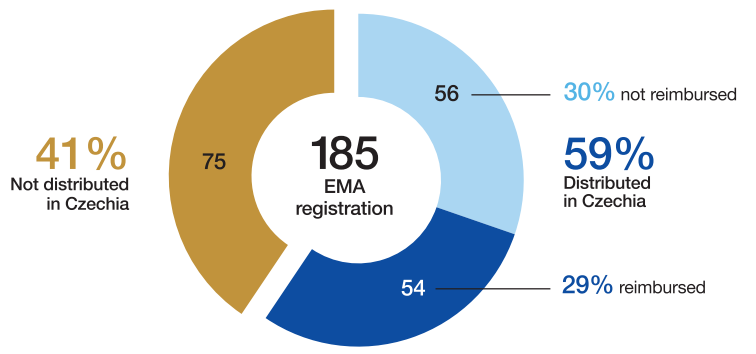
## Background

The assessment of orphan medicinal products (OMP) must reflect the characteristics of rare diseases. Typical difficulties stem from the limited experience with the disease and small population of affected individuals, which results in significant uncertainty regarding clinical outcomes (1). The limited number of patients eligible for treatment also severely limits the market potential and consequently raises the price of OMP to cover research costs. Thus, the cost-effectiveness WTP thresholds are seldom fulfilled to ensure adequate return on investment for pharmaceutical companies (2,3).

## Objectives

This policy perspective presents a unique pricing and reimbursement (P&R) system for OMP recently adopted in Czechia which is specified by Section 39da of the Act on Public Health Insurance (4).

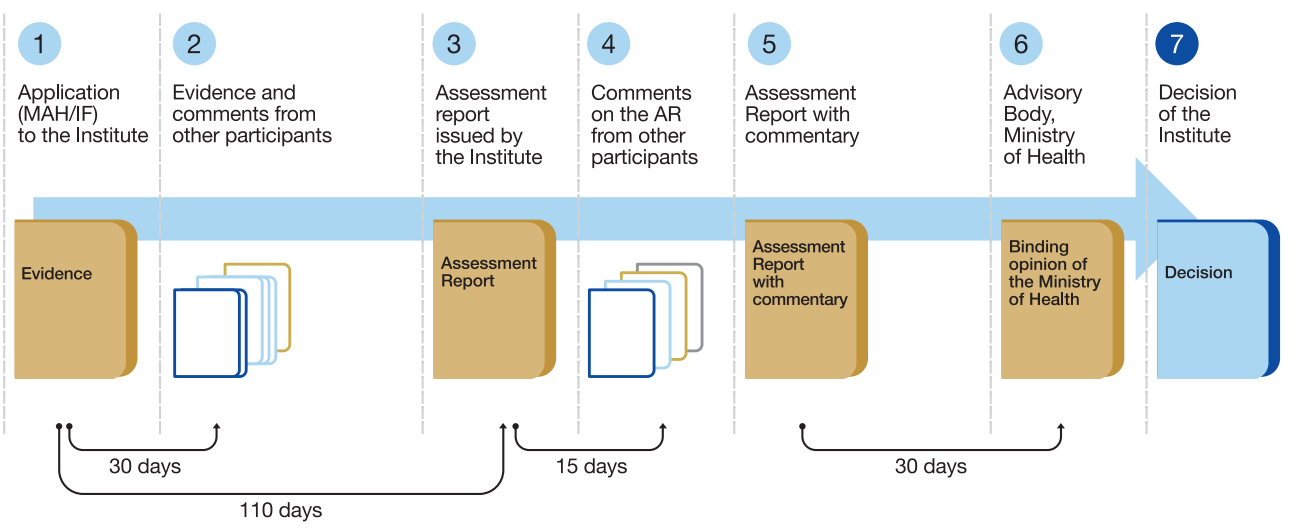
**Figure 1. Availability of OMP (2015–2021)**




## Methods

The updated legislation follows the recommendations for value assessment and funding processes for rare diseases (ORPH-VAL) (5). It also incorporates additional elements of value defined by ISPOR Special Task Force (6). The resulting health policy approach is a real-world application of the proposed recommendations and can serve as an inspiration for other countries.

**Figure 2. Schematic of the administrative procedure**




## Results

Out of 185 OMP registered by EMA from 2015 to 2021, a mere 110 (59%) were available to Czech patients, and only 54 (29%) were officially reimbursed (**Figure 1**) (7–9). After years of public debate induced by this unsatisfactory OMP patient access, the national viewpoint shifted towards creating a special pathway for the reimbursement of OMP. Thus, a rigorous P&R procedure with strict timelines and elaborated methodology has been established. The complete process is depicted in **Figure 2**:

1. The application (containing clinical evidence, cost-effectiveness analysis, budget impact analysis, impact on patients and relevant patient access scheme) is submitted to the governmental HTA agency (the State Institute for Drug Control) by the Marketing Authorization Holder or a Health Insurance Fund.
2. Relevant professional associations and patients organizations as well as health insurance funds are entitled to present evidence and make comments during the 30 days after the initiation of administrative proceedings. This ensures the essential involvement of all key stakeholders in the P&R process.
3. The Institute performs the assessment/appraisal of the evidence. Within 110 days from the initiation of the proceedings, it publishes the Assessment Report summarizing available information.
4. All the participants have the right to comment on the Assessment Report within 15 days from its publication.
5. The Institute then publishes the final Assessment Report and forwards it to the Ministry of Health and its Advisory Body. The Advisory body consists of four stakeholders: [1] patients (not with the given disease), [2] clinical experts (not from the given disease area), [3] public health insurance funds, and [4] the State.
6. The Advisory body critically evaluates the documents and (within 30 days) issues a binding opinion based on the decision-making criteria that are summarized in **Table 1**.
7. The binding opinion is then forwarded back to the Institute, which then issues a final Decision on the P&R in line with the opinion.

**Table 1. Criteria and parameters for OMP assessment**
(according to Order n. 53/2021 from the Minister of Health)

| Evaluated criteria | Methodology | Criteria for decision |
|---|---|---|
| a) Therapeutic effectiveness (1) and safety (2) | (1) Effect on survival, morbidity, quality of life, or other significant clinical outcomes<br>(2) Severe adverse events profile, the occurrence of adverse events leading to treatment discontinuation | (1) Prioritize OMP with significant efficacy on major clinical outcomes (survival, QoL, complications, hospitalizations, long-term disability), with regard to the level of clinical evidence (incl. RWE) and corresponding level of uncertainty<br>(2) Prioritize OMP with significant improvement in safety profile in case SoC toxicity is a major limitation |
| b) Severity of disease | Expected life expectancy without treatment, QoL, incidence of (irreversible) complications | Prioritize OMP for diseases that severely decrease life expectancy and/or QoL without treatment |
| c) Reimbursed treatment alternatives | Description of the current treatment algorithm | Prioritize OMP indicated for rare diseases with no treatment alternative |
| d) Societal impact | (1) Costs assessed from the societal perspective, including loss of productivity<br>(2) Dependency of others – family, caregivers, need for home-care, long-term hospitalization, or institutionalization | (1) Prioritize OMP reducing costs from the societal perspective, including indirect costs (loss of productivity, social care costs)<br>(2) Prioritize OMP, decreasing family/ caregiver/societal burden |
| e) Quality of life (QoL) | Treatment effect on the patient's QoL | Prioritize OMP with robust evidence, ideally measured in clinical studies |
| f) Network of specialized medical centers | Existing network of healthcare providers and diagnostic tools | Provision of effective continuous care delivered by qualified healthcare professionals |
| g) Clinical guidelines | Nationally and internationally recognized clinical guidelines relevant for the OMP | Prioritize treatment included in the guidelines, with a high level of evidence and/or grade of recommendation |
| h) Managed entry agreements (MEAs) with payers | Proposed managed entry scheme (simple discount, budget cap, and pay-back, price-volume or outcomes-based agreement) | Prioritize outcome-based models where the manufacturer covers costs associated with ineffective treatment (outcome guarantees) |
| i) Cost-effectiveness | Costs per QALY critically assessed by the Institute, absolute QALYs gain | |
| j) Budget impact | Healthcare payers costs using a 5-year time horizon | Prioritize OMP delivering high benefit with acceptable budget impact |

OMP, Orphan Medicinal Products; QALYs, Quality-adjusted life-years; QoL, Quality of Life; RWE, Real-World Evidence

## Conclusion

### Strenghts:

- The major strength of the Orphan drug legislation is the loosening of the WTP threshold, allowing OMP (with naturally higher ICER/ICUR) to enter the health care system with an agreed patient access scheme, clear indication criteria and funding. Thus, they do not bypass the health care system.
- We can also expect less restrictive budget caps and discount requirements from healthcare payers compared to standard reimbursement pathway.
- The OMP value is assessed from the perspective of patients, the healthcare system as well as the wider society. This is ensured by the involvement of patient organizations as well as healthcare professionals in the procedure and by incorporating the societal perspective into the evaluated criteria (i.e. impact on patients, burden of disease, cost-effectiveness and budget impact analyses). Thus, the new strategy fosters multi-stakeholder dialogue and consensus.
- Finally, the orphan legislation reflects the newest scientific research derived from rigorous and proven methodologies (5,6).

### Limitations:

- One of the limitations is the necessity of a valid orphan designation status from the EMA during the whole administrative proceeding. If orphan designation status expires, the manufacturer can no longer apply. This brings a clear barrier for older orphan drugs that cannot use this reimbursement pathway.
- Moreover, the MAH is usually forced to propose a managed entry agreement (MEA). However, the role of MEA is crucial in OMP assessment since they help manage the uncertainty associated with the introduction of OMP (10). Moreover, it is favourable from the perspective of budget planning and sustainability of the whole health care system.
- It is also important to note that in cases where reimbursement is provided at the request of the MAH and the OMP costs exceed the amount presented in the budget impact analysis, the MAH will reimburse the overbudget costs. This, again, might be considered a strength from the perspective of budget planning and financial predictability of the future costs.
- Finally, a permanent reimbursement is not granted „forever" since it is possible to re-evaluate it after at least a year and reassess any uncertainties in the decision (e.g. reflect any recent clinical data etc.). However, this can be viewed positively from the perspective of the entire system since it allows faster access and lowers the long-term uncertainty of the decision.

Considering all the benefits and drawbacks, we firmly believe that the described policy is fit for the purpose. There is no doubt that without special conditions for OMP, pharmaceutical companies lack the incentive to invest in OMP research. Moreover, OMPs would bypass the system under pressure from patients or the public. The OMPs now have a functional transparent framework with clear rules and procedures.

We strongly believe that this novel approach may inspire many countries worldwide that are struggling to offer satisfactory patient access to orphan drugs. Moreover, it serves as a real-world example of "value-based" decision-making.

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