Scope of vignette:
- authorised products (with marketing authorisation)
- decision process about routine use (and not individual requests for reimbursement)
- submissions for P&R made by manufacturers

Green = related to/any special considerations for rare disease and ultra-rare disease treatments
Orange = latest changes (September 2020)

Lithuania	**Standard process (non-orphan drugs) - Common Reimbursement Process (CDR)**	**Special processes (orphan and ultra-orphan drugs)**
Overview of health system and P&R/HTA process	Tax based system [1] HTA exist only at national level: The SMCA (state medicine control agency), the Ministry of Health and the NHIF (payer) are the main parties in P&R/HTA process Formally, the final decision is made by the Minister of Health based on the recommendations from the Reimbursement Committee and NHIF The Reimbursement Committee (representatives from the Ministry of Health, NHIF, University hospitals, PAG, NGO of GP's, Academy) advises the Minister of Health on reimbursement decisions. Advice is issued within an assessment report The SMCA is responsible for the assessment of new medicine submissions and issuing the assessment report to the decision-makers, which then becomes public. It includes assessment of the key domain (see key domains in assessment section) Responsibilities of NHIF in common process: -assessment of the budget impact of each new medicine submission; -assessment of the company's OB-MEA in case it is a part of submission; -contracting whatever risk sharing agreement (PVA, „capping", OB-MEA) -paying for medicines -procuring high-cost pharmaceuticals via public tenders	This special process has been recently updated, and updates are effective since September 29, 2020 [4]. The special process has its own regulation, but the actors (SMCA, NHIF) are the same. Decision bodies and budgets are different. It was developed about 10 years ago when the common process together with evidence "requirements" was introduced and rare diseases had emerged as "different". The update in September 2020 included a "mandatory added benefit assessment based on comparative trial non-surrogate endpoint outcomes". A special process applies to Very Rare health Conditions (VRC), which is the focus of this special process (not a medicine) An OMP (or any other medicinal product) will be routed through this special process only if it is intended to treat a VRC (see details in section "Appraisal framework") The reimbursement of medicines to treat a VRC is regulated by a special order of the Ministry of Health The decision-making body in this special process is the Very Rare Conditions Committee (VRCC)

Lithuania	Standard process (non-orphan drugs) - Common Reimbursement Process (CDR)	Special processes (orphan and ultra-orphan drugs)
	The MoH issued order No. 159 regulates the inclusion process for placing medicines on a reimbursable (positive) list [3]	
Differentiation of rare disease treatments in the P&R system	A very rare (<1/200,000 newly diagnosed cases of the Lithuanian population per year) human health condition (referred to as "very rare condition" - VRC) is defined as a health disorder, which is life-threatening and/or causing significant permanent disability, and may be subject to an effective etiological (a factor affecting the onset of the disease) or a pathogenic (the factor responsible for the clinical course of the disease) treatment, when the treatment costs of this very rare condition are not reimbursed, and when the treatment can increase the patient's survival and (or) reduce disability (or prevent the increase in disability). Eligibility to the special process (individualised-VRC and generalised VRC) is based on whether the medicine is considered rare according to the criteria stated in the previous paragraph. The number of patients living with a rare condition relies on the orpha.net statistics. The submission will include the precise definition of health condition and is assigned an ORPHA code. Other approaches to define the rarity of a condition accepted within the VRC process includes, e.g. good quality year by year statistics from a recognised center, etc.	
Eligible medicines	The submission drives both the special process and CDR process. If there is no submission, neither the special nor the common-reimbursement process starts. This is the only route through which products would be selected for the special (very rare condition) process. Without an application and consequent appraisal, the product is not reimbursed and can only be accessed commercially	
Process	The MoH issued an order, No. 159, that outlines the guidelines for assessment (for the entity preparing the submission), and the appraisal framework (see appraisal framework section [3] - The standard process starts with the submission (comparative efficacy and effectiveness, cost-effectiveness, budget impact, etc.) from industry to the SMCA directly - The four key domains (see section "Key domains in assessment") are assessed and the SMCA makes its conclusions on the added health benefit and cost-effectiveness, and the NHIF on the budget impact - The assessments' conclusions are approved/rejected/corrected during deliberation process by Reimbursement Committee (RC), who	The MoH's order regulates the special process that is in place The special process starts with the submission to the VRCC Two types of submission are intended: **Individual-VRC-case** are based on hospital submissions (hospital acts as applicant) to the VRCC for the treatment of an individual patient. **Generalized-VRC-case** are based on university hospital or physicians society submissions to the VRCC requesting for the medicinal product to be included into the special positive list for a VRC treatment

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	then issues a final recommendation to the Minister of Health on whether to include or not onto the positive-waiting list - After each review by NHIF of the budget, medicines from the positive-waiting list are included into the positive-actual list (effective reimbursement)	The main differences of this special process (for very rare conditions) with the CDR process are: - cost-effectiveness is not assessed - no waiting list in case of positive (to reimburse medicine for a very rare condition) decision
Disease specific expert input (e.g. clinicians or patients in any stage of the process)	Specialty medical societies and patient organizations are proactively asked to provide their structured opinion about submission related topics (positioning, current treatment problems, unmet needs, etc.)	University hospitals representing physicians (Concilium) act as submitters of individual patient applications
Key domains in assessment	- Comparative efficacy - Comparative effectiveness - Cost-effectiveness (based on cost-effectiveness analysis; part of submission) - Budget impact	For a positive decision, it is mandatory that the conclusions from the SMCA involve a positive added benefit assessment, based on proof that the medicine prolongs survival and/or reduces disability (or prevents it come increasing) in comparison to Lithuanian's current standard of care. The proof should be based on the assessment of trial direct (non-surrogate) endpoints
Evidentiary requirements	Systemic literature review of published RCTs are prioritized; other systemic reviews of peer-reviewed evidence are accepted; indirect treatment comparisons are accepted	Peer reviewed publications
PROMs	None	
Appraisal framework	The appraisal of **comparative efficacy** may result in: 1) a positive recommendation if comparative efficacy is superior or non- inferior[1]; 2) a negative recommendation if superiority or non-inferiority are not proven, or if the quality of	The appraisal process aims to determine compliance (or not) to ALL of the following criteria: 1) The medicine should have one of the following: • OMP designation;

[1] Also referred to as "levelled difference", which doesn't limit the added benefit assessment to clinical efficacy but in broader terms would also be applicable to (demonstrating a levelled difference in terms of) effectiveness and cost-effectiveness

Lithuania	Standard process (non-orphan drugs) - Common Reimbursement Process (CDR)	Special processes (orphan and ultra-orphan drugs)
	evidence presented is not acceptable The appraisal of **comparative effectiveness** may result in: 1) a positive recommendation if comparative effectiveness is deemed to add benefit (or non-inferior) to patient health 2) a negative recommendation if added or non-inferior benefit to patient health is not proven The appraisal **of cost-effectiveness** may result in: 1) a positive recommendation if the intervention proves to be cost-effective 2) a negative recommendation if the intervention does NOT prove to be cost-effective **Summarizing conclusion (one of the following):** 1) superior comparative efficacy, added patient health benefit (clinical effectiveness), cost-effective (based on cost-utility analysis) compared to 3 different thresholds based on relative (proportional) magnitude of quality-adjusted-life-expectancy (QALE) shortfall, compared to the current available treatment. The QALE shortfall ranges of [0-0,49], [0,5-0,74], [0,75-1] correspond to 1, 3, 5 times the national GDP/per capita; with or without a patient-access-scheme (PAS) 2) non-inferior comparative efficacy, with similar patient health benefit (clinical effectiveness) and cost-minimization; with or without PAS. 3) superior comparative efficacy with equivalence (the exact wording – "levelled difference in patient health benefit") in clinical effectiveness, and being cost-effective (based on cost-utility analysis) if there is an outcomes-based risk-sharing-agreement arranged or cost-minimization presented (based on non-inferiority[1] or levelled difference in added benefit)	• the registered indication should specify treatment of a VRC-in-Lithuania; • proof from a peer-reviewed publication that the medicine has potential to treat a VRC by its mode of action; • proof from a peer-reviewed publication and/or guidance that the medicine could be used to treat a VRC, AND 2) There should be a proof of a therapeutic benefit (see section – "Key domains in assessment"), AND 3) Funding is available
Reimbursement decision	Decision is made by the reimbursement committee based on the summarizing conclusion (see section "Appraisal framework") after deliberation. They approve/reject/remake the summarizing conclusion. If Committee members vote against the recommendation, they would have to make a strong case as to their reasons.	The reimbursement decision is made by the VRCC and is positive, only if **all** criteria (see section "Appraisal framework" are met

Lithuania	Standard process (non-orphan drugs) - Common Reimbursement Process (CDR)	Special processes (orphan and ultra-orphan drugs)
Pricing process	Price negotiation informed by cost-effectiveness	If the cost per patient is more than EUR 29,000/per year, but less than EUR 100,000/per year, the price should be negotiated (special regulation; country expert's remark: based on referencing to international prices of the medicine (i.e. not more than the average of the three cheapest within a grouping of reference countries similar to Lithuania from an economic development perspective) If the cost per patient is more EUR 100,000/per year, an OB-MEA should be implemented
Managed entry agreements	The order of the MoH regulates the risk-sharing agreements that are in place The actual schemes include discounts, capping of patient numbers, price-volume, or OBMEAs In 2020, changes were made including discounted treatment initiation for individual patients, capping of individual patient costs, capping of individual patient medicine utilization, specifying money-back guarantee, conditional treatment continuation agreements	The same order of the MoH regulating risk-sharing agreements than in the common process is applicable to VRC
Main challenges in appraising medicines for rare diseases	-The primary focus of the VRC concept and process in Lithuania is not related to appraising medicines for rare diseases - Lack of well-organized real-world data - Lack of data collection and analysing system in case OBMEAs are introduced.	
Impact of special processes	- Currently, 9 medicines are included in the special (very rare condition treatment) reimbursement list - Altogether 136 applications for the treatment of individual patients were submitted since 2016, with 44% of them being oncology treatments	

Lithuania	Standard process (non-orphan drugs) - Common Reimbursement Process (CDR)	Special processes (orphan and ultra-orphan drugs)
Proposed policy change	The current changes made in the VRC process ("mandatory added benefit assessment based on comparative trial non-surrogate end points outcomes") have resulted in some confusion around the application of specific criteria around the added benefit evidentiary requirements.	
Joint initiatives	Are not known by author in the field of appraising medicines for rare diseases	
SOURCES		
1	http://www.vlk.lt/sites/en/health-insurance-in-Lithuania/health-insurance-system	
2	http://www.who.int/health-laws/countries/ltu-en.pdf	
3	https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/7d7024009a9411eaa51db668f0092944?jfwid=5ob7msq1q	
4	https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/652656b0b00311e59010bea026bdb259/asr	

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