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

Scotland	**Standard reimbursement and HTA process**	**Patient and Clinician engagement PACE (add-on)**	**Ultra-orphan decision-making criteria (add-on)**
Overview of health system and P&R/HTA process	Tax based system [1] The Scottish Medicines Consortium (SMC) is a consortium of NHS Scotland's 14 Health Boards. The SMC issues advice to the Health Boards and their Area Drug and Therapeutics Committees on the use of all newly licensed drugs and major new indications and formulations. The Health Boards then consider inclusion of SMC accepted medicine in local formularies, and it is up to the clinicians to decide whether or not to prescribe them.		
Differentiation of rare disease treatments in the P&R system	EMA orphan designation recognised, or a medicine to treat an equivalent size of population irrespective of whether it has designated orphan status (i.e. this also includes medicines licensed for specific sub-populations with a given condition, as well as medicines to treat a rare condition in the unusual situation where the company has not requested EMA orphan designation). Ultra-rare diseases: The SMC ultra-orphan definition Apr 2014 – Mar 2019: a medicine used to treat a condition with a prevalence of 1 in 50,000 or less (~ 100 people or less in Scotland). *Note.* In practice this prevalence threshold has been applied in an enabling way to focus on the licensed indication rather than the wider condition.		
Eligible medicines	All new medicines and indications	OMP and end of life treatments [5] - If the company's case for orphan or end of life status is validated internally - If the medicine is not recommended by the initial Scientific Committee (New Drug Committee (NDC)) - If the company requests the medicine is assessed via the orphan/end of life process	UOMPs (Apr 2014 – Mar 2019) - Prevalence <1:50,000 in Scotland - If the company's case for ultra-orphan status is validated internally - If the medicine is not recommended by the NDC - If the company requests the medicine is assessed via the ultra-orphan process
Process	- Company submits application		In addition, if medicine is not recommended by NDC, MAH

	- SMC team of pharmacists/HSRs/health economists assess the evidence and take account of clinical expert responses to generic and tailored questions - Evaluation considered by SMC's NDC, who make a recommendation to SMC - Company can comment on the NDC recommendation - Patient groups can make a submission to SMC - SMC recommends or not - Advice given to NHS boards and published - If positive recommendation: NHS boards required to consider advice and make the medicine available, or an equivalent SMC accepted medicine - If negative recommendation: company can resubmit with new evidence/price or can request an independent review panel (appeal); NHS boards required to consider SMC advice. Requests for individual patients to receive treatment can be considered [3] 18 week timeline	In addition, if medicine not recommended by NDC, MAH can request a PACE meeting: - Meeting invites patient groups and clinical experts (disease-specific) to describe the added benefit of the treatment that may not be fully captured with conventional clinical and cost-effectiveness - Attendees: NDC vice-chair + clinical experts + patient group representatives - Outcome: PACE statement presented at SMC meeting [2, 5] 22 week timeline	can request it is considered through the UO process. For ultra-OMPs, additional criteria are accounted for beyond clinical and cost-effectiveness (UO framework). Opportunity for a PACE meeting, which can help to inform some of the broader criteria. [2, 4] 22 week timeline
Disease specific expert input (e.g. clinicians or patients in any stage of the process)	- Clinical experts (via responses to generic and tailored questions) - Patient groups via submission	Same + clinical and patient experts involved via PACE submission	Same + clinical and patient experts involved via PACE submission
Key domains in assessment	- Clinical effectiveness - Cost-effectiveness - Other [6]	Same + outcome of the PACE meeting (patient and clinician based evidence)	Ultra-orphan framework • Nature of condition • Impact of new technology • Value for money

			• Impact beyond direct health benefits and on specialist services • Costs to NHS (Outcome of PACE meeting captured in above)
Evidentiary requirements	Clinical case – clinical trial evidence (ideally controlled) Economic case – ideally cost-utility analysis	Same + patient and clinician based evidence via PACE	In addition to the broad decision–making framework, companies have greater flexibility in the economic analysis they present in terms of the outcome measure, type of analysis, and perspective of sensitivity analysis, which can reflect wider costs and benefits relevant to the patient and carer. + patient and clinician based evidence via PACE. Assessment via the ultra-orphan framework is a more qualitative approach with less focus on cost per QALY.
PROMs	A validated generic utility instrument such as EQ-5D is preferred for QALYs, although SMC also allows use of alternative well-designed methods of utility measurement if generic utility data are not available.	PACE is essentially a qualitative aspect of assessment, but this could involve any PROM as part of patient-based evidence put forward by the company, clinicians or patient organisations.	Wider benefits relevant to the patient or carer can be incorporated into the sensitivity analysis, e.g., carer QoL using the University of Birmingham Carer Experience Scale.
Appraisal framework	Modifiers: life-extending, quality of life improvement, curative intent, unmet need. [2]	Same as standard process + orphan modifier: greater uncertainty in the economic case accepted. PACE output may allow SMC to accept a higher cost/QALY.	Ultra-orphan framework (more qualitative approach) + orphan modifier: greater uncertainty in the economic case accepted + higher WTP accepted.
Reimbursement decision	Accepted/Accepted restricted/Not recommended Additionally, there is an interim accepted option for medicines with a conditional MA [7]		

Pricing process	NHS list price or patient access scheme (PAS) confidential discount
Managed entry agreements	- Confidential discount (*Can be for all indications or specific indications if feasible to isolate utilisation data. All schemes are assessed by the Patient Access Scheme Assessment Group and must be feasible to operate in NHScotland) - Budget cap (less common) - Outcome based scheme for individual patients, only paying for certain performance (less common)
Main challenges in appraising medicines for rare diseases (tick all that apply)	X Lack of good quality clinical data ☐ Lack of real world data X Introducing value for money ☐ Monitoring treatment efficacy X Managing budget impact ☐ Lack of criteria/transparency of OMP P&R processes X Making arrangements to work for all stakeholders X Lack of long-term meaningful outcomes
Impact of special processes	Increased SMC acceptance rate, increased patient access
Proposed policy change	Following an independent Review of Access to New Medicines published in December 2016, SMC was asked to develop, agree and implement a new definition of 'true ultra-orphan medicine' to take account of low-volume, high cost medicines for very rare conditions. A further recommendation from this review was that a new assessment and approval pathway should be developed for these medicines. SMC's new ultra-orphan definition was introduced in October 2018 and requires the following criteria to be met: - the condition has a prevalence of 1 in 50,000 or less in Scotland - the medicine has EMA orphan designation, maintained at the time of MA - the condition is chronic and severely disabling - the condition requires highly specialised management [4] The new ultra-orphan pathway has been fully operational since April 2019. Submissions for medicines validated as ultra-orphan are assessed by SMC and are then available to prescribers for a period of up to three years while further clinical effectiveness data are gathered. The SMC will then conduct a reassessment and make a decision on routine use of the medicine in NHS Scotland [4]
Joint initiatives	--
SOURCES	
1	http://www.euro.who.int/__data/assets/pdf_file/0008/177137/E96722-v2.pdf
2	https://www.scottishmedicines.org.uk/media/3565/modifiers.pdf
3	https://www.scottishmedicines.org.uk/media/3574/20180712-a-guide-to-the-scottish-medicines-consortium.pdf
4	https://www.scottishmedicines.org.uk/how-we-decide/revised-process-ultra-orphan-medicines-for-extremely-rare-conditions/
5	https://www.scottishmedicines.org.uk/media/4731/pace-overview-document.pdf

6	https://www.scottishmedicines.org.uk/how-we-decide/
7	https://www.scottishmedicines.org.uk/how-we-decide/interim-acceptance-decision-option/

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This vignette was compiled based on information provided by country experts and desk research. The information provided may be incomplete or contain inaccuracies. If you have any comments or updates, please email us at the following email addresses:

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