Healthcare Improvement Scotland | SMC Advice on new medicines

Guidance to Submitting Companies for Completion of New Product Assessment Form (NPAF)

Supplement for medicines for extremely rare conditions (ultra-orphan medicines)

NHS SCOTLAND

Published February 2019 Updated November 2023

www.scottishmedicines.org.uk

1. Background

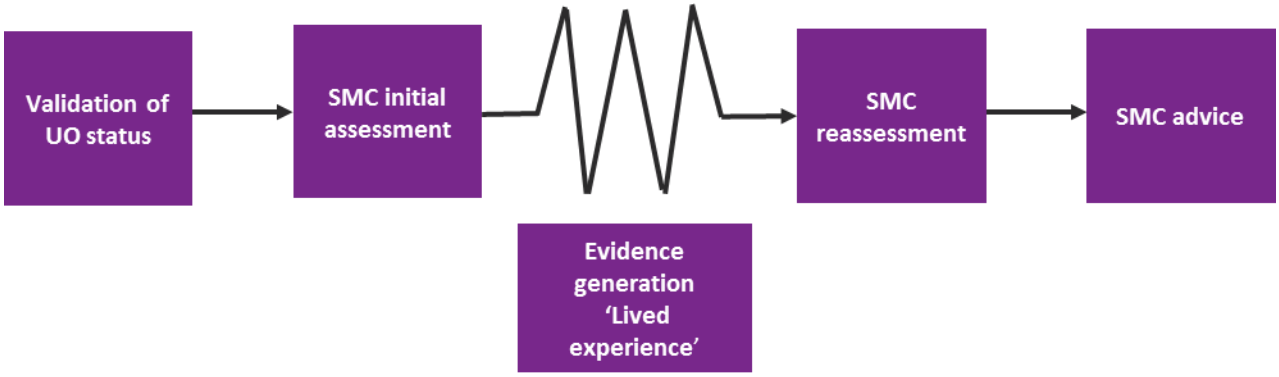
The Scottish Government published a Review of Access to New Medicines in December 2016. This recommended a new definition and pathway for medicines to treat extremely rare conditions (ultra-orphan medicines) in NHSScotland.

From April 2019, submissions for medicines that are validated as ultra-orphan according to the definition will be assessed by SMC and will then be available to prescribers for a period of up to three years while further clinical effectiveness data are gathered. The company should then provide an updated submission for reassessment allowing SMC to make a decision on routine use of the medicine in NHSScotland.

The ultra-orphan pathway involves the following key stages:

- Validation of ultra-orphan status
- SMC initial assessment
- Evidence generation for a period of three years
- SMC reassessment followed by issue of advice to NHSScotland

Figure 1: Ultra-orphan pathway



This supplement provides guidance for submitting companies on ultra-orphan validation, SMC initial assessment, and reassessment within the ultra-orphan pathway. It should be read in conjunction with SMC Guidance on completion of New Product Assessment Form (NPAF) available on the *Making a submission* section of the SMC website.

General guidance on the implementation of the ultra-orphan pathway is also available at https://www.gov.scot/publications/ultra-orphan-medicine-pathways-guidance/

2. SMC ultra-orphan definition

To be considered as an ultra-orphan medicine all criteria listed should be met:

1. The condition[1] has a prevalence of 1 in 50,000 or less in Scotland
2. The medicine has a Great Britain (GB) orphan marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
3. The condition is chronic and severely disabling
4. The condition requires highly specialised management[2]

[1]typically a recognised distinct disease or syndrome. SMC uses the description of the orphan condition within the MHRA's Orphan Register.
[2]for example, within the context of a nationally funded service.

3. Process for submissions for ultra-orphan medicines

3.1 Validation

Companies are encouraged to seek confirmation that a medicine meets the ultra-orphan definition at an early stage by completing the ultra-orphan proforma available on the *Making a submission* section of the SMC website.

The SMC Executive will review the proforma and will confirm whether the medicine has been validated as ultra-orphan within around eight weeks. The outcome of the ultra-orphan validation is shared with NHS Boards in confidence. If the company submits the ultra-orphan proforma to SMC for validation in advance of the MHRA granting a GB orphan marketing authorisation, then the relevant EMA orphan designation can be referenced. The final decision will be contingent on the MHRA granting a GB orphan marketing authorisation.

If the company disagrees with the outcome of the validation, there is the opportunity to appeal. Further information is available on the Policies and publications area of the SMC website. In addition to SMC ultra-orphan status, Scottish Government has outlined three further conditions which must be met to enable a medicine to enter the pathway. The company is required to:

- Make a full submission to SMC to allow an initial assessment of clinical and cost effectiveness
- Offer a Patient Access Scheme (PAS) that complies with the standard terms and conditions considered acceptable by the Patient Access Scheme Assessment group (PASAG)
- Support data collection arrangements that meet evidence generation requirements for assessment under the ultra-orphan pathway

Confirmation of ultra-orphan status is required before the company makes a submission for SMC initial assessment (using the *New Product Assessment Form for Ultra-Orphan Medicines*).

After a medicine has been validated as an ultra-orphan, the company can request a meeting with SMC before making the initial submission.

Ultra-orphan validation decisions will expire after 2 years. Thereafter if a product has GB marketing authorisation from the MHRA; if there are eligible patients in NHSScotland; and if no submission is forthcoming, SMC will move to issue not recommended advice.

Further details on early engagement with companies are available under the *Making a submission* section of the SMC website.

3.2 SMC initial assessment

An initial assessment of the clinical and cost effectiveness of the medicine will be conducted. This will highlight uncertainties within the available evidence-base and will help to inform the data collection stage of the ultra-orphan pathway.

SMC will use a broad framework to assess ultra-orphan medicines which takes account of the following:

- Nature of the condition
- Impact of the medicine
- Value for money
- Impact of the technology beyond direct health benefits and on specialist services
- Costs to the NHS and Personal Services

3.21 Completion of the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines – SMC initial assessment

Companies should complete the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines available in the *Making a submission* section on the SMC website. This is structured to mirror the framework described above. This supplement provides companies with guidance on the additional information requirements for this group of medicines and should be used in conjunction with general SMC Guidance to submitting companies.

Nature of the condition (Ultra-orphan NPAF section 3)

This section should provide a description of the ultra-orphan disease or condition and its impact on patients and carers, including:

- Severity of the condition, symptoms, pattern of disease progression, level of disability, overall effect on morbidity and mortality.
- Effect on functioning e.g. ability to work, participate in education, self-care, undertake activities of daily living.
- Effect on the patient's quality of life and on family and carers' quality of life.
- Description of currently available treatment options. These may include disease-specific treatments and/or supportive therapies.

- Limitations of currently available treatments including side-effects, burden in terms of administration and monitoring, hospitalisation and clinic attendance.
- Level of unmet need in NHSScotland.

Impact of the new technology (Ultra-orphan NPAF section 4)

In addition to information on clinical efficacy, safety and clinical effectiveness, companies should consider:

- How outcomes from observational studies including disease registries or early access schemes could supplement conventional clinical study data.
- Effect of the medicine on patient experience and patient reported outcomes such as health-related quality of life, health status, physical functioning, activities of daily living, adherence to treatment, patient satisfaction with treatment etc.
- How the medicine would be expected to address any areas of unmet need.
- For the initial submission, identification of uncertainties or evidence gaps and how these might be addressed.

Value for money (Ultra-orphan NPAF section 5)

While SMC recognises the challenges in providing a robust economic evaluation for a medicine used to treat an extremely rare condition due to limitations in the data available, an economic evaluation to indicate the value for money is required.

SMC has a preference for a cost-utility analysis for such medicines, where appropriate and feasible, as this allows comparability with other medicines across the value for money spectrum. However, where an evaluation using quality adjusted life years (QALYs) is not feasible, SMC will accept cost effectiveness analysis using appropriate natural outcome measures. Cost-consequence analysis may also be provided where the submitting company judges that there are multiple relevant outcomes not readily captured within a QALY based assessment or cost effectiveness analysis using a single outcome measure. The company would be expected to provide supporting rationale for the approach taken. SMC appreciates that in some conditions the economic evaluation will have significant uncertainty, but an estimate of the likely costs and benefits is still required.

Given the nature of extremely rare conditions, submitting companies may also wish to provide a sensitivity analysis supporting the base case economic evaluation that adopts a wider perspective than the conventional NHS perspective. This will permit the evaluation to reflect wider costs and benefits relevant to the patient and their carer, such as out of pocket expenses, lost earnings and carer quality of life gains from the new treatment.

Costs to the NHS and Personal Social Services (Ultra-orphan NPAF section 6)

In addition to completion of a standardised Excel template to show an estimate of the NHS budget impact, companies should include an assessment of any significant budget impacts for any non-NHS organisations.

Impact beyond direct health benefits and on specialist services (Ultra-orphan NPAF section 7)

This section should describe potential impact of the medicine other than clinical benefits, adverse effects and on health-related quality of life, this may include:

- Opportunity for patients to contribute to society, improve family functioning, continue in employment or education.
- Impact on carers' quality of life (e.g. using tools such as the Carer Experience Scale) and ability to work.
- Impact of adopting a wider perspective on the cost effectiveness of the medicine (e.g. incorporating loss of earnings, carer disutility).
- Implications of the introduction of the new medicine on the NHS including staffing, infrastructure and training requirements.

3.22 Evaluation of medicines used to treat ultra-orphan conditions – SMC initial assessment

New Drugs Committee (NDC) meeting:

The clinical and economic evidence to support an ultra-orphan medicine will be assessed by NDC before being considered by the SMC Committee. An economic evaluation on the value for money of the medicine remains a requirement, but with the flexibility in approach described in section 3.21 above. An ultra-orphan assessment report will be structured according to the ultra-orphan framework. Following review of the medicine by the NDC, the draft NDC assessment report will be shared with the submitting company and company comments invited for consideration by the SMC Committee.

Following NDC the company has the opportunity to submit a new or revised PAS aimed at improving the cost effectiveness of the medicine. Refer to section 6.15 of the SMC Guidance to submitting companies for details of updated analyses required within the company comments document.

A Patient and Clinician Engagement (PACE) meeting will not take place at the time of the initial assessment but will play an important role in the reassessment and decision-making post evidence generation.

SMC meeting:

SMC will review the information presented in the ultra-orphan framework, examining the nature of the condition, impact of the medicine, value for money, costs to the NHS, and impact beyond direct health benefits using the criteria set out above.

As part of the review process, SMC will also consider other sources of evidence to supplement the framework presented within the draft NDC assessment report, e.g. from clinical experts and Patient Group submissions. This will ensure the Committee has as complete a picture as possible of the condition and the potential impact of the medicine. At the initial assessment, SMC will appraise the evidence presented prior to the medicine

being made available for an initial period as part of the ultra-orphan pathway. SMC will not make a decision on use of the medicine at this point.

The SMC ultra-orphan assessment report will provide a critique of the evidence-base presented, including key limitations and uncertainties in the clinical and economic evidence to help inform data collection during the period of initial availability of the medicine. SMC will publish this document on its website within standard timelines.

3.3 Evidence generation

Data collection development can begin at an early stage in parallel with SMC initial assessment. Scottish Government guidance to support the evidence generation phase of the ultra-orphan pathway is available at https://www.gov.scot/publications/ultra-orphan-medicine-pathways-guidance/

3.4 SMC reassessment

3.41 Completion of the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines – SMC reassessment

The company will be required to provide a full updated submission within three months following the period of evidence generation. Companies should complete the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines available in the *Making a submission* section on the SMC website as outlined in section 3.21 above. Results of further controlled studies, observational, registry or other real world data gathered during initial availability of the medicine within the ultra-orphan pathway should be included in relevant sections of the NPAF to address uncertainties identified at the time of the initial assessment. The updated submission must be provided in line with standard SMC Guidance to submitting companies including the relevant comparator(s) and within the context of the current treatment pathway in NHSScotland at the time of reassessment.

Value for money (Ultra-orphan NPAF section 5)

The guidance relating to value for money for the initial assessment above remains valid for reassessment. However, at reassessment, value for money will be taken into account as part of the decision-making process. This section provides additional guidance to inform a submission for reassessment.

Incremental cost effectiveness

Guidance notes:

The SMC does not have a fixed upper limit on willingness-to-pay for a QALY and this applies equally to ultra-orphan medicines.

The challenge for decision-making for ultra-orphan medicines reflects that of all other medicines; it is to strike a balance between decision-making based upon explicit, stated principles and the need to retain some flexibility to respond to the circumstances of any particular case.

This section sets out some general principles but in any individual decision it is the responsibility of the SMC to weigh the factors and issue guidance that it feels to be consistent with the full range of evidence (economic and other, quantified and qualitative).

SMC may also consider other factors in relation to end of life and orphan medicines such as added benefit from the patient, carer and clinician perspective that may not be fully captured in conventional clinical and economic analysis (these are included in the PACE statement). SMC conventional modifiers may be applied to all new medicines assessed, if appropriate. Guidance on the application of modifiers can be found here.

As mentioned above, the SMC does not have a fixed upper limit on willingness-to-pay for a QALY for ultra-orphan medicines. As such, ICERs are not considered in isolation by SMC and are used as part of their decision-making process. However, it is recognised that other HTA agencies do set out levels of acceptable levels of willingness-to-pay. SMC notes sections 6.2.23 to 6.2.25 from the NICE guidance for their Highly Specialised Technologies (HST) process, as follows:

NICE guidance NICE Health Technology Evaluations: The Manual (January 2022):

6.2.23 For highly specialised technologies, the committee will consider the size of the incremental QALY gain in relation to the additional weight that would need to be assigned to the QALY benefits for the cost effectiveness of the technology to fall within the highly specialised technologies £100,000 cost per QALY level.

6.2.24 For this weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained.

6.2.25 The weighting is applied as described in table 6.2 below.

Table 6.2:	
Incremental QALYs gained (per patient using lifetime horizon)	***Weight***
• *Less than or equal to 10*	*1*
• *11 to 29*	*1 -3 (using equal increments)*
• *Greater than or equal to 30*	*3*

3.42 Evaluation of medicines used to treat ultra-orphan conditions – SMC reassessment

NDC meeting:

The clinical and economic evidence to support an ultra-orphan medicine will be assessed by NDC before consideration by the SMC Committee. The draft NDC Detailed Advice Document (DAD) will be structured according to the ultra-orphan decision-making framework.

Following review of the medicine by the NDC, the draft NDC DAD will be shared with the submitting company and company comments invited before consideration by the SMC Committee.

If the draft NDC advice is 'not recommended', the submitting company will be offered the opportunity to request a PACE meeting and/or to submit a new or revised PAS. Refer to the general guidance notes section of SMC Guidance to submitting companies for further information.

SMC meeting:

SMC will review the information presented in the decision-making framework, examining the nature of the condition, impact of the medicine, value for money, costs to the NHS, and impact beyond direct health benefits using the criteria set out above. SMC will also consider the additional evidence generated during the period of initial availability of the medicine within the ultra-orphan pathway.

As part of its review, SMC will assess the information the company has provided within the ultra-orphan NPAF as well as other sources of evidence to supplement the framework within the NDC DAD, e.g. from clinical experts, Patient Group submissions and the output from a PACE meeting. This will ensure SMC is provided with as complete a picture as possible of the relevant aspects upon which the final decision will be based.

The SMC decision options at reassessment include:

- Accepted for use
- Accepted for restricted use
- Not recommended

3.5 Patient Access Schemes (PAS)

Provision of a PAS to improve cost effectiveness of the medicine is a condition of the ultra-orphan pathway specified by Scottish Government. The company will offer the PAS at the time of initial SMC submission.

At the time of reassessment, where the updated submission includes a PAS, the submitting company must provide a new PAS application in line with PAS guidance (refer to NHSScotland PAS Guidance available on the *Making a submission section* of the SMC website). The company has the opportunity to propose a new or revised PAS post-NDC. If the medicine is accepted for use at the time of reassessment the updated PAS will come into effect.

In the event that the medicine is not recommended for use at reassessment, or due to non-submission, the previously established PAS at initial assessment would continue to be in effect until such time as the PAS Agreement was terminated or replaced.

Frequently Asked Questions

1. Why has the SMC definition of an ultra-orphan medicine changed?

The 2016 Review of Access to New Medicines recommended development of a new definition of 'true ultra-orphan medicine' to take account of low-volume, high-cost medicines for extremely rare conditions. The definition is available on the *How we decide* section of the SMC website under U*ltra-orphan medicine for extremely rare conditions*.

Of note, the definition is based on the prevalence of the condition rather than the target population described in the licensed indication. SMC will use the description of the condition within the MHRA's Orphan Register. In addition, the condition must be chronic and severely disabling and require highly specialised management.

2. How will the company know if a medicine meets the definition?

The company needs to submit an ultra-orphan proforma and have this validated by SMC **before** making a submission. A submission for initial assessment of an ultra-orphan medicine must be made using the New Product Assessment Form (NPAF) for ultra-orphan medicines. Both the ultra-orphan proforma and the ultra-orphan NPAF are available on the *Making a submission* section of the SMC website.

3. What does the ultra-orphan pathway involve?

Within the pathway, ultra-orphan medicines will undergo an initial SMC assessment of clinical and cost effectiveness and will then be available for period of up to three years while further evidence is gathered to support SMC reassessment and a decision on routine use of the medicine in NHSScotland.

In addition to SMC ultra-orphan status and making a full submission to SMC, the company must also agree to provide a Patient Access Scheme (PAS) to improve cost effectiveness of the medicine, and to collect further data on clinical effectiveness over the initial period of availability of the medicine.

If preferred, a company can choose to submit under the current orphan assessment process, with the opportunity for a Patient and Clinician Engagement (PACE) meeting. In addition, for medicines with GB conditional marketing authorisation, SMC would also have the option of accepting the medicine for routine use on an interim basis. Please refer to *Guidance on*

submissions for medicines with GB conditional marketing authorisation on the *Making a submission* section of the SMC website.

4. What happens if the company does not make an updated submission for reassessment?

If the company does not provide an updated submission for reassessment following the period of data collection, SMC will issue not recommended advice.

5. What are the arrangements for existing patients if the medicine is not recommended on reassessment?

Where a patient continues to derive clinical benefit, it is expected that they would remain on the medicine until the patient and clinician consider it appropriate to stop treatment.

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