A Guide to the Ultra-Orphan Pathway

This guidance is intended to provide information to Health Boards, clinicians, pharmacists, patient groups and pharmaceutical companies on the new approach to the assessment of ultra-orphan medicines which was introduced in Scotland in October 2018, with applications for new medicines available from April 2019.

The changes mean if the medicine meets the new definition of an ultra-orphan medicine and undergoes a full assessment of its clinical and cost-effectiveness by the Scottish Medicine Consortium (SMC), then it will be available on the NHS for up to three years while further evidence on its effectiveness is generated. The SMC will then review the evidence after three years and make a final decision on its routine use in NHS Scotland

To enable an ultra-orphan medicine to be available through the pathway, there are four conditions that must be met. They are that a pharmaceutical company:

- has the medicine validated as an ultra-orphan according to the SMC definition;
- makes a full submission to the SMC for the initial assessment stage that meets SMC requirements for assessment under the ultra-orphan process;
- offers a Patient Access Scheme (PAS) that complies with the standard terms and conditions considered acceptable by the Patient Access Scheme Assessment Group (PASAG); and
- supports the data collection arrangements that meets the evidence generation requirements for assessment under the ultra-orphan pathway.

The new pathway comprises of four key stages:

1. **Validation** – the medicine must be validated as an ultra-orphan medicine by the SMC under a new definition which includes set criteria;
2. **Initial SMC Assessment** - a full submission (along with a PAS) must be made by the pharmaceutical company to the SMC to allow an initial assessment of the clinical and cost effectiveness of the medicine;
3. **Evidence Generation** - the pharmaceutical company must undertake to collect data in order to generate evidence over a period of up to three years to increase the SMC's confidence in the clinical and cost-effectiveness of the ultra-orphan medicine at time of reassessment; and
4. **Reassessment** – a full update of the submission offered at stage 2 should be made to the SMC by the company following the three year data collection period. The SMC will make a decision as to whether the medicine is to be accepted for general use in NHS Scotland.

This guidance outlines each stage of the pathway, including the PAS requirements. A diagrammatic illustration of the process can be found at the end of this guidance document.

Stage 1: Validation (around 8 weeks)

In the first instance, a medicine must be validated by the SMC as an ultra-orphan medicine under revised criteria. All criteria listed below should be met:

1. the condition has a prevalence of 1 in 50,000 or less in Scotland,
2. the medicine has a European Medicines Agency (EMA) orphan designation for the condition and this is maintained at time of marketing authorisation,
3. the condition is chronic and severely disabling; and
4. the condition requires highly specialised management.

A company can apply for validation by completing the SMC ultra-orphan proforma (which can be found at the following link - https://www.scottishmedicines.org.uk/how-we-decide/revised-process-ultra-orphan-medicines-for-extremely-rare-conditions/).

Companies are encouraged to engage with the SMC at the earliest opportunity for validation, and ideally prior to receiving a positive opinion from the EMA's Committee for Human Medicinal Products (CHMP).

The SMC will review the application and will confirm whether or not the medicine has been validated as ultra-orphan within around eight weeks. Confirmation that the medicine is validated for the ultra-orphan pathway is required before the company can make a full submission for SMC initial assessment.

The SMC will contact companies with the outcome of the validation process and, in the case of disagreement, there will be an opportunity for the company to appeal. The outcome of the ultra-orphan validation is shared with Health Boards in confidence.

Stage 2: Initial SMC Assessment (around 18 weeks)

Once a company has been informed that the medicine has been validated as an ultra-orphan and if they have received a positive opinion from the EMA's CHMP, they can then make a full submission (which must include a PAS) to the SMC for an initial assessment of the clinical and cost effectiveness of the medicine. This assessment will highlight uncertainties within the available evidence-base and will help to inform the data collection and evidence generation stage of the ultra-orphan pathway.

Companies should complete the New Product Assessment Form (NPAF) for Ultra-Orphan Medicines (which can be found at https://www.scottishmedicines.org.uk/how-we-decide/revised-process-ultra-orphan-medicines-for-extremely-rare-conditions/)

It will take around 14 weeks from submission to the SMC formally meeting to consider the medicine. During the assessment, the SMC will use a broad framework to assess the ultra-orphan medicine, taking into account 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; and
- costs to the NHS and Personal Services.

Patient Group submissions will inform the initial assessment report. A Patient and Clinician Engagement (PACE) meeting will not take place at the initial assessment stage but it will form part of the SMC's reassessment stage.

The SMC will publish its initial assessment report within standard timelines.

Further guidance and information on completing the NPAF for ultra-orphan medicines and making a full submission to the SMC can be found on the *Making a submission* section of the SMC website: https://www.scottishmedicines.org.uk/making-a-submission/

Patient Access Scheme (PAS)

Pharmaceutical companies must offer a PAS to enable an ultra-orphan medicine to be available through the pathway. The purpose of the PAS is to improve the cost-effectiveness of the medicine and to enable patients to receive access to cost-effective innovative medicines.

Companies are encouraged to offer a fair price in return for the additional flexibility offered by the ultra-orphan assessment approach; giving market access for a period of three years and the further data collection opportunities to address uncertainties in the clinical data.

Pharmaceutical companies should complete either the concise or full PAS application pack, as appropriate. Once completed, the PAS application pack should be submitted

to the SMC Secretariat along with the New Product Assessment Form (NPAF) and associated documents.

The PASAG will review the PAS proposal and will advise the SMC on the feasibility of the proposed scheme for implementation. It operates separately from the SMC to maintain the integrity of the assessment process.

The company has the opportunity to submit a new or revised PAS following the SMC's New Drugs Committee meeting (which comes before the SMC initial assessment meeting).

The PAS will only become available for implementation if approved by the PASAG and following initial assessment by the SMC.

For more information and guidance, companies may contact the PASAG secretariat (NSS.NP-PASAG@nhs.net).

NHS Financial Risk Sharing Scheme

It is the intention to establish a financial risk-sharing scheme (Health Board pooled funding) for the ultra-orphan pathway. Further information will be provided to Health Boards on this.

Stage 3 : Evidence Generation (up to three years)

Following the SMC initial assessment and its published report, pharmaceutical companies will be required to develop a data collection plan to capture relevant clinical and patient reported outcomes which aim to address as much as possible the uncertainties identified in order to increase the SMC's confidence in the clinical and cost-effectiveness of the medicine at the time of reassessment.

In particular, pharmaceutical companies should:

- undertake to collect data on the ultra-orphan medicine for the duration of its availability through the pathway;
- ensure that the focus of the data collection activity attempts to address the uncertainties within the existing evidence-base, including those highlighted in the initial SMC assessment report;
- draw on any existing data collection activities from other parts of the UK and beyond as part of the overall package of evidence generation;
- seek to collect Patient Reported Outcome Measures (PROMs), where appropriate, and data on the impact beyond direct health benefits and on specialist services; and
- cover all the costs associated with the data collection.

Whilst it is recognised that the data collection plan and evidence generation stage is unlikely to be fully developed until after the SMC's initial assessment report is issued, there will be aspects that can be established in advance. Companies are therefore encouraged to plan the data collection work as soon as possible, and ideally following a positive validation from the SMC.

Companies must submit a short initial report outlining their data collection plan to the Scottish Government (SG) (medicines.policy@gov.scot) within three months of the publication of the SMC initial assessment report (more time may be granted in exceptional cases). This report will be the evidence that the company has data collection arrangements in place. It should also include a prospective timeline for data collection and a probable date for the updated submission for SMC reassessment. The data collection period will normally be three years, but companies may resubmit earlier if sufficient data is available.

Some companies may welcome external support in the development of their data collection planning, to ensure that the critical weaknesses in data have been accurately reflected and that the plans in place can be expected to address the identified data uncertainties. Work is underway to develop a service from NHS Research Scotland (NRS) which companies will be able to choose to use. Further information on this service and any associated costs will be available as an addendum to the separate guidance document on the evidence generation phase.

Companies will be responsible for determining whether the data being produced during the evidence generation period is adequately measuring and achieving the outcomes identified in their data generation and collection plan, and whether any additional action is required. However, they may use the services of NRS to support them in this.

For more guidance and information on this part of the pathway, please see: https://www.sehd.scot.nhs.uk/publications/DC20190430UltraOrphan.pdf

Access to NHS Scotland for the three year data collection period

Once the SMC initial assessment report and agreed PAS are in place and the company submit their short report outlining their data collection plan to the SG, access to the three year data collection period will commence. Health Boards and the company will be notified of the effective start date by the SG.

Stage 4. Reassessment (around 22 weeks)

Companies will be expected to submit an updated full submission to the SMC for reassessment of the medicine following the three year data collection and evidence generation stage.

The SMC will review the information presented in the decision-making framework, as before, but will also consider the additional evidence generated during the three year period of availability of the medicine within the ultra-orphan pathway.

As part of its review, the SMC will assess the information the company has provided within its updated ultra-orphan NPAF as well as other sources of evidence, for example clinical experts, patient group submissions and, where relevant, the output from a PACE meeting.

The SMC decision options at reassessment include:

- Accepted for use (where the medicine becomes routinely available in NHS Scotland)
- Accepted for restricted use (where the medicine becomes available in NHS Scotland on a restricted basis); or
- Not recommended (the medicine does not become available in NHS Scotland).

In the event that a medicine is not recommended for routine use at reassessment:

- where the patient continues to derive clinical benefit, the treatment should continue until the patient and clinician consider it appropriate to stop, as per current guidance and best practice;
- all Health Boards have procedures in place to consider requests when a healthcare professional feels that a medicine which is not recommended by SMC, is right for a particular patient; and
- companies will be expected to agree to ensure continuity of supply at the previously agreed PAS price.

Ultra-Orphan Pathway

UO – ultra-orphan
PAS – Patient Access Scheme
SG – Scottish Government
PACE – Patient and Clinician Engagement meeting