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**Process for appraising orphan and ultra-orphan medicines  
and medicines developed specifically for rare diseases  
Effective from September 2015**

## **Introduction**

From September 2015 the All Wales Medicines Strategy Group (AWMSG) is changing its process for appraising orphan, ultra-orphan and medicines developed specifically for rare diseases to enable even greater involvement of patients and clinicians in Wales. This document explains the background to why such changes have been introduced and explains how the new process will operate.

## **Background**

In May 2013, Welsh Government established a Group to review the process and parameters used by AWMSG for appraising orphan and ultra-orphan medicines in Wales. Specifically the review was to:

- Examine the current AWMSG appraisal process for orphan and ultra-orphan medicines and advise on the appropriateness of the process, and any alternative approach which may be adopted in Wales.
- Determine whether the Quality Adjusted Life Year (QALY) methodology represents an effective tool to calculate cost-effectiveness for orphan and ultra-orphan medicines.
- Advise on the best way to support the timely uptake of new, innovative orphan and ultra-orphan medicines in Wales.
- Explore the equity of access to orphan and ultra-orphan medicines across the UK.

In conducting the review, the intention was to be transparent and inclusive in accessing the wide-ranging views of as many patient groups and other stakeholders as possible. AWMSG has considered the consultation responses and suggested changes to the way it evaluates ultra-orphan and orphan medicines which will give patient groups and clinicians a stronger voice in AWMSG decision making.

The new process was piloted in January 2015 and will be implemented in September 2015. It will be reviewed in light of feedback from all stakeholders.

## Definitions

**Orphan medicine:** “A Medicine with a European Medicines Agency (EMA) designated orphan status, which includes conditions affecting not more than five in 10 thousand persons”, which is equivalent to 1,500 patients in Wales where the population is 3 million (see Appendix 1 for full EMA definition).

**Ultra-orphan medicine:** is a medicine that has been granted EMA designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales).

### **Medicines developed specifically to treat rare diseases**

In addition, AWMSG will apply the same process and principles of consideration to a medicine developed specifically to treat an equivalent size population irrespective of whether it is designated by the EMA as an orphan medicine i.e. if the full population of the licensed indication/s is equal to, or less than, 5 in 10,000 persons (equivalent to 1,500 patients in Wales) which is consistent with the prevalence definition of an orphan medicine.

For all relevant medicines including orphan, ultra-orphan and medicines developed specifically for rare diseases the definitions will apply to the **full population of the licensed indication/s**.

### **Approach to the appraisal of orphan/ultra-orphan medicines and medicines developed specifically for rare diseases**

In recognition of the clinical needs of patients with rare diseases, and acknowledging the potentially high costs of treatment, the appraisal committee will take broader considerations into account when appraising ultra-orphan medicines than those for orphan medicines, or for other medicines.

The incremental cost per QALY of orphan, ultra-orphan and medicines developed specifically for rare diseases will be included as an indicator of relative cost-effectiveness, whenever possible, within the appraisal. It should be noted that the cost per QALY is only part of a wider judgment of the value of a new medicine and societal aspects will also be an important component in the discussions and deliberations.

### **Additional criteria for appraising orphan/ultra-orphan medicines and medicines developed specifically for rare diseases**

Where the cost per QALY is above the normal thresholds applied, additional criteria for appraising these medicines will be considered. These will include, but will not be limited to:

- The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers
- Whether the medicine addresses an unmet need (e.g. no other licensed medicines)
- Whether the medicine can reverse or cure, rather than stabilise the condition

- Whether the medicine may bridge a gap to a “definitive” therapy (e.g. gene therapy) and that this “definitive” therapy is currently in development
- The innovative nature of the medicine
- Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)
- Added value to the patient’s family (e.g. impact on a carer or family life)

### **How will the new process work? (see process flow diagram)**

The submission forms for all medicines, including orphan, ultra-orphan, and other medicines developed specifically to treat rare diseases, as defined above, will be submitted to the All Wales Therapeutics and Toxicology Centre (AWTTC) by the applicant company.

Applicant companies should aim to include evidence of clinical effects, clearly differentiating between clinical improvement, stabilisation, and reducing rate of deterioration in the condition. The proposed position of the medicine within the clinical treatment pathway should also be identified in the submission.

The evidence provided by the applicant company will be assessed by AWTTC who will provide comment on eligibility as an orphan, ultra-orphan or a medicine developed specifically to treat rare diseases, as defined above. The final decision on eligibility is, however, made by the appraisal committee.

AWTTC will provide the AWMSG secretariat assessment report (ASAR) to the applicant company for comment prior to consideration by the New Medicines Group (NMG). Orphan and ultra-orphan medicines will be considered in a separate section of the NMG agenda (the Orphans/Ultra-orphans section). NMG members will be reminded on each occasion as to the criteria which specifically apply to these medicines (as listed overleaf).

NMG will take account of

- The AWMSG Secretariat Assessment Report (the ASAR), the applicant company response (CR ASAR) and the relevant submission
- The submitted views of clinical experts, particularly their experience of using the medicine
- The submitted views of patients/patient organisations/patient carers
- Discussion at the meeting

If NMG's advice is negative, i.e. NMG's preliminary recommendation does not support use of the medicine within NHS Wales, the applicant company can ask that CAPIG be convened at the earliest opportunity prior to consideration by AWMSG (see description below).

AWMSG will take account of

- The AWMSG Secretariat Assessment Report (the ASAR)
- The NMG preliminary recommendation
- The submitted views of clinical experts, particularly their experience of using the medicine
- The submitted views of patients/patient organisations/patient carers
- The CAPIG statement (if convened)
- Societal and budget impact to NHS Wales
- Applicant company response to the Preliminary Appraisal Recommendation
- Additional criteria as outlined if the cost per QALY is above the normal thresholds applied
- Discussion at the meeting

### **Clinical and Patient Involvement Group (CAPIG)**

The aim of CAPIG is to identify and consider in detail any additional benefits of the medicine from a clinician, societal and patient perspective. The CAPIG Report will be included in the AWMSG meeting papers alongside the NMG preliminary recommendation and will be a major component of the appraisal by AWMSG. This process is likely to add up to 12 weeks to the assessment timeline.

The CAPIG meeting will normally be chaired by an individual with extensive experience of health technology appraisal and will be supported by staff from AWTTTC. A representative from the public and AWMSG's Patient and Public Involvement Group (PAPIG) will be invited to attend CAPIG meetings. In addition, there will be representation from the relevant patient organisation/s and clinicians with appropriate specialist knowledge (identified by clinical networks within NHS Wales).

The applicant company will be invited to attend the CAPIG meeting and present a brief statement. They may input into discussions but will absent themselves prior to any voting.

## **Additional information**

The managed entry of these new medicines within NHS Wales is a shared responsibility between the manufacturer and NHS Wales. To monitor clinical outcome/s against expected clinical effects, specific clinical audits may be specified and, where considered appropriate, a patient register.

**Stopping treatments** - medication should be reviewed regularly by the clinician and continued so long as the medicine's benefits outweigh any side-effects. Whenever possible, stopping criteria for these medicines should be agreed in advance of final appraisal outcome. If agreed, adherence to these criteria will be monitored and reported.

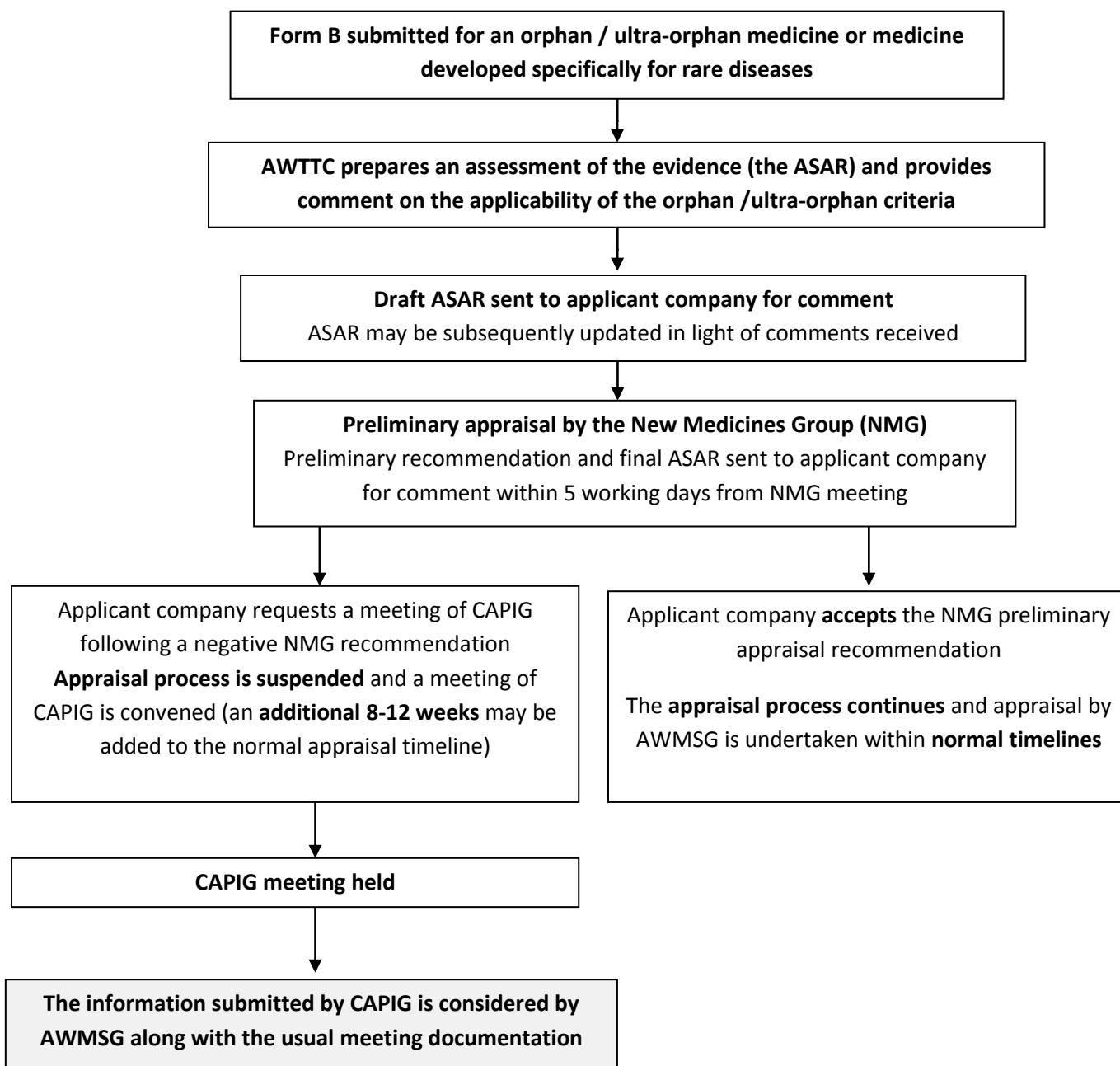
An appraisal **review date** will be set pending review of additional clinical trial evidence or clinical audit data.

**Implementation** will be the responsibility of individual Health Boards. Monitoring the use and budget impact of orphan/ultra-orphan and medicines licensed specifically for rare diseases will be managed by the Welsh Analytical Prescribing Support Unit within AWTTTC.

**End of life medicines** - a policy was established in 2011 which enabled AWMSG to take additional criteria into account when appraising medicines with evidence of being life extending (3 months) [refer to policy on AWMSG website [www.awmsg.org](http://www.awmsg.org)]. This approach for appraising end-of-life medicines will continue.

## Process for appraising orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

### PROCESS FLOW DIAGRAM



## **Appendix 1**

### **European Medicines Agency (EMA) definition of an orphan medicine (as stated on the EMA website on 13<sup>th</sup> May 2015)**

To qualify for orphan designation, a medicine must meet a number of criteria:

- (a) it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- (b) the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- (c) no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.