Action for AWMSG:

AWMSG is requested:

1. To note feedback from the pilot
2. To consider and endorse the related documentation:
   - Process for appraising orphan and ultra-orphan medicines and medicines developed for rare diseases
   - Clinician and Patient Involvement Group (CAPIG) - Terms of Reference
   - Clinician and Patient Involvement Group (CAPIG) Information

Purpose:

In May 2013, the Minister for Health and Social Services established a Group to review the process and parameters used by AWMSG for appraising orphan and ultra-orphan medicines in Wales. This Group recommended changes be made to the way medicines for rare diseases are appraised in order to give patient groups and clinicians a stronger voice in AWMSG decision-making. A new group has been established, the Clinician and Patient Involvement Group (CAPIG), to identify and discuss in more detail any additional benefits the medicine may have from both a clinician and patient perspective.

A pilot of the new process has run from January 2015 until the end of August 2015. It is proposed that pending endorsement by AWMSG the new process will be implemented from September 2015.

Summary:

During the pilot two submissions that met the criteria for inclusion in the new process have gone through the appraisal process. Both received a positive preliminary recommendation from NMG; there was therefore no requirement for a CAPIG meeting to be convened. There are currently three submissions that have been identified as potentially meeting the criteria, but which are still ‘in process’. It should be noted that the new process for appraising orphan and ultra-orphan medicines, and medicines developed specifically for rare diseases, has not been ‘tried and tested’ in full during the eight month pilot.

The attached documentation provides clarification of the new process and the terms of reference of CAPIG.
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, the Minister for Health and Social Services 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.

Reviewed by AWTTC August 2015
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

Reviewed by AWTTC August 2015
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 AWTTC. 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 AWTTC.

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]. 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

Form B submitted for an orphan / ultra-orphan medicine or medicine developed specifically for rare diseases

AWTTC prepares an assessment of the evidence (the ASAR) and provides comment on the applicability of the orphan / ultra-orphan criteria

Draft ASAR sent to applicant company for comment
ASAR may be subsequently updated in light of comments received

Preliminary appraisal by the New Medicines Group (NMG)
Preliminary recommendation and final ASAR sent to applicant company for comment within 5 working days from NMG meeting

Applicant company requests a meeting of CAPIG following a negative NMG recommendation
Appraisal process is suspended and a meeting of CAPIG is convened (an additional 8-12 weeks may be added to the normal appraisal timeline)

Applicant company accepts the NMG preliminary appraisal recommendation
The appraisal process continues and appraisal by AWMSG is undertaken within normal timelines

CAPIG meeting held

The information submitted by CAPIG is considered by AWMSG along with the usual meeting documentation
Appendix 1

European Medicines Agency (EMA) definition of an orphan medicine
(as stated on the EMA website on 13th 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.
Clinician and Patient Involvement Group (CAPIG)

Terms of Reference

1. Purpose and remit:

The introduction of the Clinician and Patient Involvement Group (CAPIG) allows for a new stage in the All Wales Medicines Strategy (AWMSG) appraisal process, in circumstances when, having reviewed the scientific evidence, the New Medicines Group (NMG) did ‘not recommend’ the use in NHS Wales of an orphan or ultra-orphan medicine, or a medicine developed specifically for rare diseases where the patient population is small.

The role of CAPIG is to identify and discuss in more detail any additional benefits the medicine may have from both a clinician and patient perspective. The CAPIG Report will be presented to AWMSG and this will help AWMSG make a decision that takes greater account of the patient and clinician perspective.

CAPIG will consider:

- Aspects of additional value to the patient, e.g. ability to work or continue in education, convenience of treatment, ability to maintain independence and dignity
- The degree of severity of the disease in terms of survival and quality of life impacts on patients and their family/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
- Whether there are any specific patient groups for whom the medicine is particularly beneficial

2. Membership:

Chair
Meetings will be chaired by an individual with extensive experience of health technology appraisal and patient involvement.
1 PAPIG representative
A representative from AWMSG’s Patient and Public Interest Group (PAPIG)

Patient organisation representatives

Representatives from appropriate patient organisations or nominated individual patient experts (up to 3 organisations may be represented)

Clinical experts normally nominated by a specialist advisory group (maximum of 3). Clinical experts are likely to be consultant level doctors; however, when appropriate, they may be clinical nurse specialists or clinical pharmacists

1 Public representative normally nominated by Community Health Councils

1 AWMSG Lay member and/or deputy

The applicant company (max 2 persons) will be invited to attend and present a short statement at the meeting. They may input into discussions but will absent themselves prior to any voting, completion of the CAPIG report template or agreement of the final statement

AWTTC will provide the following secretariat support:

- 1 Appraisal Lead
- 1 Administrator/medical writer
- 1 Liaison Manager

AWTTC will not have voting rights.

3. Reporting responsibilities:

The output of a CAPIG meeting will be a report highlighting the added value of the medicine from a patient and clinician perspective. The information will be presented to AWMSG.

4. Meetings:

CAPIG meetings will be scheduled as required.

Attendance in person is preferable; however, where necessary, members may join the meeting via teleconference or video conference.

The following papers will be forwarded to CAPIG members at least one week prior to the meeting:

- The submitted views of clinical experts considered by NMG
- The submitted views of patients/patient organisations/patient carers considered by NMG

CAPIG members will be required to declare any conflicts of interest and sign a confidentiality agreement
5. **Quorum:**

The meeting quorum will be one clinician and one patient organisation representative in attendance in addition to the Chairman.

6. **Record of business:**

A report will be prepared by the AWMSG Secretariat and the content will be agreed by CAPIG members. This document will be included in the AWMSG meeting papers.

7. **Review:**

The Terms of Reference will be reviewed initially after six months and annually thereafter.
Clinician and Patient Involvement Group (CAPIG) Information

The purpose of this document is to explain what to expect from the new Clinician and Patient Involvement Group (CAPIG) which is part of the All Wales Medicines Strategy Group (AWMSG) health technology appraisal process for new orphan/ultra-orphan medicines and medicines used to treat a rare disease. This information is for anyone who may be involved in CAPIG or who may wish to become involved.

About the All Wales Medicines Strategy Group (AWMSG)

AWMSG has the remit to appraise newly licensed medicines, including license extensions and/or new formulations of existing medicines. Advice is based on clinical-effectiveness and cost-effectiveness, as well as the anticipated budgetary impact and broader societal and equity issues. AWMSG recommendations are provided to Welsh Government’s Minister for Health and Social Services, who will take account of AWMSG advice when making the final decision as to whether the medicine should be routinely available in NHS Wales. AWMSG considers the following:

- How well the medicine works
- Which patients would benefit from receiving the medicine
- How does it compare to currently used treatments
- How the medicine affects the quality of a patient’s life
- How much the medicine costs compared to the other treatment options

An assessment of the evidence provided by the holder of the marketing authorisation, as well as any other available information, is carried out by the All Wales Toxicology and Therapeutics Centre (AWTTC). The assessment report (ASAR) is considered initially by the New Medicines Group (NMG) which meets in private and considers only the scientific evidence. NMG’s preliminary recommendation (PAR), and the manufacturer’s response, is subsequently considered and discussed at the AWMSG meeting which is held in public and also takes account of budget impact and wider societal issues. AWTTC also gathers information from patients, patient organisations and support groups about how people are affected by the condition and the potential impact of the new medicine on patients and their family or carer. The evidence submitted by the manufacturer to support the use of the medicine within NHS Wales is presented and discussed at the NMG and AWMSG meetings. For more detailed information regarding the assessment process please see the website at: www.awmsg.com
What is CAPIG and when is it used?

The introduction of CAPIG allows for a new stage in the AWMSG appraisal process, in circumstances when, having reviewed the scientific evidence, NMG did ‘not recommend’ the routine use of a medicine within NHS Wales to treat a rare disease where the patient population is small, i.e. an orphan or ultra-orphan medicine. The aim of CAPIG is to identify and discuss in more detail any additional benefits of the medicine from both a clinician and patient perspective. The additional information gathered for CAPIG (the CAPIG report) will be presented to AWMSG and this will help AWMSG make a decision that takes greater account of the patient and clinician perspective.

How will the new process work?

In making a submission for appraisal by AWMSG, the pharmaceutical company will be asked to state whether the medicine should be considered as an orphan or ultra-orphan medicine, or medicine used to treat a rare disease, and will be asked to provide evidence to support this.

The medicine will be appraised by NMG and will make a preliminary appraisal recommendation (PAR) to AWMSG. If NMG’s recommendation is negative, i.e. NMG does not support use of the medicine within NHS Wales, the submitting company (i.e. the holder of the marketing authorisation) can ask that CAPIG be convened.

Who will take part in a CAPIG meeting?

Chairman
AWMSG Patient and Public Interest Group (PAPIG) representative
Patient organisation / patient support group representatives
Clinical experts (max 3 - normally nominated by the specialist advisory group)*
Public/Lay representative (normally nominated by Community Health Councils)
AWMSG Lay member and/or deputy
Applicant company representative in non-voting capacity**
AWTTC Appraisal Lead (non-voting capacity)
AWTTC Administrator/Medical Writer (non-voting capacity)
AWTTC Liaison Manager (non-voting capacity)

*Clinical exerts are likely to be consultant level doctors; however, when appropriate, they may be clinical nurse specialists or clinical pharmacists.

**The applicant company will be able to attend and present a short statement at the meeting. They may input into discussions but will leave the meeting prior to any voting, completion of the CAPIG report or agreement of the final statement.

Declarations of Interest and Confidentiality

Those who take part in the CAPIG meeting must declare any conflicts of interest and sign a confidentiality agreement as information provided for the CAPIG meeting must remain confidential.
What preparation is needed before a CAPIG meeting?

CAPIG will discuss how the medicine affects a patient’s quality of life and how it impacts on a patient’s family or carers. The group will also consider issues such as the severity of the condition, any unmet need, the added value of the medicine for the patient, the patient’s family or carers, where in the patient pathway the medicine could most appropriately be used, specific patient groups that may benefit more from the use of the medicine and any important considerations in relation to treatment delivery. It is important that evidence is gathered to support the above issues before the meeting takes place. In summary, discussion will focus on patient and carer quality of life issues such as:

1. The ability to continue work or education
2. The management of symptoms such as pain and extreme tiredness
3. Helping relieve psychological distress
4. Convenience of how and where the treatment is received
5. The ability to self-care or maintain independence and dignity

There may already be some patient organisation and clinician view evidence. However, prior to the meeting AWTTC will request a short statement highlighting any ‘additional’ key issues.

How much time will I have to prepare for the CAPIG meeting?

CAPIG meeting dates will be scheduled alongside NMG meetings dates. AWTTC will confirm whether a CAPIG has been requested following negative advice from NMG. After the submitting company has confirmed they wish AWTTC to convene a CAPIG meeting, you will have approximately one month to prepare for the meeting as written statements will be required two weeks prior to the meeting.

What happens during a CAPIG meeting?

The Chair will guide everyone through the meeting and there will be opportunity to discuss and consider the views of all participants. A summary of the key points of discussion will be compiled in the format of a template report and the content will be agreed by group members.

What happens after the CAPIG meeting?

The completed CAPIG report will be included in the AWMSG meeting papers along with the rest of the appraisal documentation and posted on the AWMSG website. It will be a major factor in determining whether AWMSG will recommend the use of the medicine within NHS Wales.

Definitions

**Orphan medicine:** A Medicine with a European Medicines Agency designated orphan status, which includes conditions affecting fewer than 2,500 people in a population of 5 million (or 1,500 patients in Wales where the population is 3 million).

In addition, AWMSG may apply the same process and principles of consideration to a medicine to treat an equivalent size population irrespective of whether it has designated orphan status.
**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 (or around 60 patients in Wales).

**Rare disease:** is defined by the European Union as one that affects less than 5 in 10,000 of the general population.

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

In the application of these principles, AWMSG will apply a degree of pragmatism to the appraisal of medicines used to treat rare diseases where the patient population is small.