Enclosure No:	**X**/AWMSG/0000
Agenda Item No:	Review of the process for appraising orphan and ultra-orphan medicines and medicines developed specifically for rare diseases
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Action for AWMSG:

Consider the findings of the review of the process for appraising orphan and ultra-orphan medicines and medicines developed specifically for rare diseases.

Purpose:

- Report on how the policy for the appraisal of orphan and ultra-orphan medicines and medicines developed specifically for rare diseases has been implemented.
- Describe the impact the policy has had on access to medicines for rare diseases.

Summary:

This paper reports on the impact of the AWMSG policy on orphan and ultra-orphan medicines and medicines developed specifically for rare diseases since its introduction in September 2015.

Definitions

Orphan medicine: a medicine with a European Medicines Agency (EMA) designated orphan status and is used to treat a condition with a prevalence of not more than five in 10,000 people.

Ultra-orphan medicine: 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 people or fewer in the UK (or 60 patients in Wales). By definition, ultra-orphan medicines are a subset of orphan medicines.

Orphan/Ultra-orphan equivalent medicine: a medicine developed specifically to treat a condition with a prevalence equivalent to either an orphan or ultra-orphan medicine, irrespective of whether it is designated by the EMA as an orphan medicine.

For all medicines the definitions above will apply to the full population of the licensed indication(s).

Background:

In response to the findings of an independent external review requested by Welsh Government in 2014 for the appraisal of orphan and ultra-orphan medicines[1], AWMSG introduced a new policy in September 2015 for appraising medicines indicated for the treatment of rare diseases. The main changes were:

- Specific inclusion in the new policy of all authorised medicines that have European Medicines Agency (EMA) designated orphan status. The previous AWMSG policy only applied to medicines that were considered by AWMSG to be ultra-orphan medicines (a small sub-set of orphan medicines).
- Inclusion of medicines which are not EMA designated orphan medicines but have a prevalence in Wales for the full licensed indication equivalent to an orphan medicine (≤ 5 in 10,000) or an ultra-orphan medicine (≤ 1 in 50,000). These are referred to in this report as orphan equivalent and ultra-orphan equivalent medicines.
- Additional criteria to be considered when appraising medicines for rare diseases to enable a wider societal perspective to be considered by AWMSG where the cost per quality-adjusted life year was above the normally accepted thresholds.
- Addition of a stage in the AWMSG appraisal process to strengthen the patient and clinician voice. A clinician and patient involvement group (CAPIG) could be convened following a negative recommendation at the preliminary recommendation stage to discuss in more detail the additional benefit of a medicine from a clinician, patient and societal perspective.

Assessment

Results are reported for the period September 2015 to December 2017.

Numbers of medicines appraised

Between September 2015 and December 2017, there were 79 appraisals by AWMSG. Twenty (25%) met the criteria to be appraised under the updated policy. There was an equal number of appraisals that were considered to be orphan/orphan equivalent and ultra-orphan/ultra-orphan equivalent.

Fourteen of the twenty appraisals (70%) were for a medicine that would not have met the criteria to be considered under the previous AWMSG ultra-orphan policy due to being either an orphan or orphan equivalent medicine (n = 10), or having a prevalence equivalent to an ultra-orphan medicine but not having EMA designated orphan status (n = 4).

An analysis of data for AWMSG appraisals between September 2015 and December 2017 shows that the recommendation rate for all medicines appraised by AWMSG was high, irrespective of whether a medicine was indicated for a rare or non-rare disease (see Table 1).

Table 1: AWMSG recommendation rate for medicines appraised between September 2015 and December 2017

Type of Appraisal	Number of appraisals recommended in full or given a restricted recommendation (%)
All appraisals	71/79 (90%)
Appraisals for medicines not indicated for a rare disease	53/59 (90%)
Appraisals for medicines for a rare disease	18/20 (90%)
Orphan/orphan equivalent appraisals (excluding subgroup of ultra-orphan medicines)	10/10 (100%)
Ultra-orphan/ultra-orphan equivalent appraisals	8/10 (80%)

Cost-effectiveness estimates reported for medicines for rare diseases

AWMSG is aligned with the National Institute for Health and Care Excellence (NICE) in adopting a cost-effectiveness threshold of £20,000 to £30,000 per quality-adjusted life year for appraised medicines. It is, however, recognised that there is the requirement for flexibility in the incremental cost-effectiveness ratio (ICER) threshold for some medicines, for example those medicines that are used towards the end of life or are used to treat a rare disease. AWMSG does not currently specify an upper ICER threshold for these medicines. The base case ICER was provided for 11 out of 20 submissions for medicines which met the criteria for consideration under the new policy. An ICER was not included in the other submissions due to: the medicine being dominant (more effective and less costly) (n = 1); a cost minimisation analysis being submitted (n = 5); the submission being for a limited submission, which does not include cost-effectiveness information (n = 2); and the medicine being appraised on publically available information, as the company did not provide cost-effectiveness information (n = 1). The base case ICER for the appraisals that received a positive recommendation (n = 10) ranged from [commercial in confidence information removed]. For the two medicines not recommended by AWMSG, the base case ICER was [commercial in confidence information removed] for one medicine, and was not reported for the other medicine as no cost-effectiveness information was provided by the company.

Patient access schemes (PAS)

Patient access schemes (PAS) are intended to improve the cost-effectiveness of a medicine by offering a discount, rebate or other variation from the list price of a medicine. Fifteen of the twenty (75%) appraisals that were considered under the new policy were associated with a PAS. All appraisals for medicines used to treat a rare disease that were associated with a PAS were recommended by AWMSG.

Clinician and Patient Involvement Group (CAPIG) meetings

There were five CAPIG meetings convened between September 2015 and December 2017. Of the five CAPIG meetings held, three subsequently resulted in a positive recommendation from AWMSG and two received a non-recommendation. Three CAPIG meetings were

convened following a preliminary non-recommendation from the New Medicines Group (NMG). Two appraisals were recommended by NMG and subsequently not recommended by AWMSG. Following requests for an independent review, CAPIG meetings were convened and the medicines reconsidered by AWMSG to include information from the CAPIG meeting. In both cases, the reappraisal of the medicines at AWMSG resulted in positive recommendations. All CAPIG meetings were convened between 7–11 weeks after the decision to hold a meeting.

Discussion

There was an increase in the number of medicines that could be considered by AWMSG under the updated policy. Twelve medicines that were appraised and subsequently given a positive recommendation would not have been eligible for consideration under the previous AWMSG ultra-orphan policy. One medicine that had received a non-recommendation from AWMSG on two occasions before the introduction of the new policy was re-appraised and recommended for use within NHS Wales.

The recommendation rate for medicines for rare diseases was high (90%) and was the same as the recommendation rate for medicines that were not indicated for a rare disease. This is in contrast to a previous analysis, conducted between 2002 and 2014, where only 20 of 34 (59%) orphan medicines (including the subset of ultra-orphan medicines) were recommended by AWMSG. There was a marked increase (100% compared with 52% in the previous analysis) in the recommendation rate of orphan/orphan-equivalent medicines (excluding ultra-orphan medicines). The recommendation rate for medicines that were considered to be ultra-orphan or ultra-orphan equivalent was numerically higher after the introduction of the updated policy than previously reported for ultra-orphan medicines (80% and 73%, respectively). These early findings suggest that the policy has enabled greater access to medicines for rare diseases by allowing additional considerations to be taken into account, particularly where the ICER is above the normally accepted threshold.

It did not appear that the recommendation rate correlated with the base case ICER, suggesting that cost-effectiveness may not be the only criterion for approval. The number of medicines not recommended was too small to infer any relationship between the ICER value and the likelihood of a non-recommendation.

Three medicines recommended by AWMSG were subsequently superseded by published NICE advice. All three received a positive recommendation from NICE.

There were two medicines that met the criteria to be considered as a medicine for the treatment of a rare disease but were not recommended by AWMSG. One medicine, Respreeza® to slow the progression of emphysema in adults with documented severe alpha 1-proteinase inhibitor deficiency, was not recommended due to uncertainty in both the clinical effectiveness and cost-effectiveness evidence. No cost-effectiveness information was provided for the other medicine, vismodegib for the treatment of adult patients with symptomatic metastatic basal cell carcinoma, or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy. As of May 2018, neither medicine has been approved by NICE or the Scottish Medicines Consortium (SMC).

Five CAPIG meetings were held between September 2015 and December 2017. Two medicines (pasireotide and two appraisals for ivacaftor) were approved following a CAPIG meeting being held.

Convening a CAPIG meeting added up to eleven weeks to the AWMSG appraisal process. As clinicians need a minimum of six weeks to re-arrange clinical commitments, the time taken to convene a CAPIG meeting was considered reasonable and was within the 8–12 week timeframe included in the policy. Feedback received from AWMSG members and from clinicians, patient organisations and applicant companies who attended the CAPIG meeting was favourable.

Conclusion

Since the introduction of the new policy for the appraisal of medicines for rare diseases, there has been an increase in the number of medicines considered and recommended by AWMSG for both orphan/orphan equivalent medicines, and ultra-orphan/ultra-orphan equivalent medicines. The new policy enables greater consideration of the clinical expert and patient organisation view in a transparent manner.

For future consideration

1. Following the introduction of ICER thresholds by NICE for highly specialised therapies, consideration should be given to whether ICER thresholds should be introduced for orphan and ultra-orphan medicines appraised by AWMSG

2. Give consideration to the benefits of introducing cost-consequence analysis as part of the CAPIG process

3. Consider amending the process to enable a CAPIG meeting to be convened for eligible medicines after an NMG or an AWMSG non recommendation.

References

1. Buss P, Evans S, and Phillips C. Review of the appraisal of orphan and ultra-orphan medicines in Wales. Report for the Minister of Health and Social Care. Oct 2013. Data on file.