All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG appraisal process for a medicine for a rare disease

Background

AWMSG reviewed its process for appraising orphan and ultra-orphan medicines and medicines developed specifically for rare diseases, in July 2018. The process was updated in July 2019 to implement the recommendations from the review.

Introduction

The clinical and cost-effectiveness evidence for a medicine for a rare disease is usually based on small numbers of patients, and is therefore often associated with greater uncertainty than for other medicines. Medicines for a rare disease, particularly those for very rare conditions, are commonly associated with higher costs.

AWMSG acknowledges that the rarity of a disease is likely to affect the evidence available and the medicine's cost, and appreciates the need for innovation and research to meet the clinical needs of patients with a rare disease.

Patients with a rare disease should have the same opportunity to access medicines as other patients. Equity of access to medicines is an important consideration when appraising a medicine for a rare disease.

Greater uncertainty and higher costs can mean that medicines for rare diseases may not meet conventional standards for establishing clinical and cost effectiveness. AWMSG takes into account a broad range of considerations when appraising a medicine for a rare disease; the cost per quality-adjusted life-year (QALY) is considered as only part of a wider judgement of a medicine's value.

AWMSG considers how the incremental cost-effectiveness of the medicine being appraised relates to other medicines or treatments currently being used in the NHS to treat a disease, including those that AWMSG or NICE have appraised. AWMSG's appraisal process for medicines for rare diseases aligns with NICE's technology appraisal and highly specialised technologies (HST) programmes.

Definitions

AWMSG considers medicines for rare diseases as orphan, orphan-equivalent, ultra-orphan or ultra-orphan equivalent.

Orphan medicine (or orphan-equivalent)	A medicine with orphan status* (or a medicine without orphan status* with a prevalence** of ≤ 1 in 2,000 people in Wales [or the UK] for the full licensed population and meets the criteria for European Commission orphan status).
Ultra-orphan medicine (or ultra-orphan equivalent)	A subset of orphan medicines that have a prevalence** of ≤ 1 in 50,000 people in Wales (or the UK) for the full licensed population (or a medicine without orphan status* and a prevalence** of ≤1 in 50,000 people in Wales (or the UK) for the full licensed population and meets the criteria for European Commission orphan status).

*Medicines granted orphan status by the European Commission meet these criteria[1]:

- A medicine intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating.
- The prevalence of the disease or condition in the EU must be ≤ 1 in 2,000 people, or it must be unlikely that marketing the medicine would generate sufficient returns to justify the investment needed for its development.
- No satisfactory method of diagnosis, prevention or treatment of the disease or condition can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the disease or condition.

** Prevalence figures apply to the full population of the licensed indication/s and should be based on national published figures or by consulting clinical experts and prescribing data if published figures are not available.

Process for appraising a medicine for a rare disease

The appraisal process for medicines for a rare disease is aligned with AWMSG's process for all other medicines. However, there is an additional stage to further assess the benefits of the medicine from the perspective of clinicians and patients through the Clinician and Patient Involvement Group (CAPIG). A CAPIG meeting may be convened if a medicine for a rare disease receives a negative recommendation from the New Medicines Group (NMG), or if a positive recommendation from the NMG is followed by a negative recommendation from AWMSG.

Applicant companies should indicate in their submission to AWTTC if they consider a medicine to be a medicine for a rare disease. The AWMSG secretariat assessment report (ASAR) will state whether the medicine should be considered as a medicine for a rare disease, and the company has the opportunity to respond to this view in the company's response to the ASAR.

AWMSG members will be reminded of the broader considerations they should take into account when appraising a medicine for a rare disease.

Clinician and patient involvement group (CAPIG)

AWTTC seeks views from clinical experts and patient organisations for all medicines that AWMSG appraises. A CAPIG meeting aims to identify and consider in detail any additional issues related to the medicine for a rare disease from a patient, clinician and societal perspective. Companies have the option to submit supplementary cost-consequence analyses for the CAPIG meeting. Further information on CAPIG is available in the CAPIG information sheet and in the CAPIG terms of reference.

Timelines for appraising a medicine for a rare disease

The timelines for appraising a medicine for a rare disease are the same as for other medicines unless a CAPIG meeting is convened. A CAPIG meeting may add up to 12 weeks to the overall time for the appraisal by AWMSG.

Clinical effectiveness

The AWMSG document "Guidance on appraisal structure and evidence" outlines the process for assessing clinical effectiveness. The appraisal of a medicine for a rare disease is based on this document, and takes into account:

- The degree of severity of the disease as presently managed, in terms of survival and quality of life of patients and their carers.
- Whether the medicine addresses an unmet need.
- The innovative nature of the medicine considering the significance of improvement over existing therapies in areas such as efficacy, safety and convenience and if substantial health gains are generated over existing treatments (> 1 QALY).
- The broader societal impact and whether the medicine has an impact on non-health benefits that may not adequately be captured in the QALY (for example, the impact on families and carers, work and schooling), costs to sectors outside the National Health Service (NHS) and Personal Social Services (PSS) perspective, such as educational services, and productivity losses attributable to changes in health outcomes.

Additional criteria are also considered when appraising a medicine for a rare disease:

- Whether the medicine can reverse or cure, rather than stabilise the condition.
- Whether the medicine bridges a gap to a definitive therapy (for example, a gene therapy) and that the definitive therapy is currently being developed.

Cost effectiveness

Cost effectiveness is assessed based on the AWMSG document "Guidance on appraisal structure and evidence". AWMSG takes account of how recommendations may allow the more efficient use of available healthcare resources, and the implications for healthcare programmes for other patient groups that adopting the new medicine may displace. AWMSG takes into consideration these factors:

- the broad clinical priorities of Health and Social Services in Wales;
- the degree of clinical need of patients with the condition under consideration;
- the broad balance of benefits and costs; and
- the potential for long-term benefits to the NHS of innovation.

AWMSG doesn't use a fixed incremental cost-effectiveness ratio (ICER) threshold for approval of medicines. The ICERs for medicines for rare diseases will be included in the appraisal documents but the cost per QALY gained is only part of the judgement of the value

of a new medicine and wider societal issues are also an important consideration. Guidance on the ICER threshold per QALY gained that AWMSG usually considers cost effective is listed in Table 1.

Table 1: ICERs expressed as cost per QALY gained* usually considered cost effective by AWMSG (for guidance only)

Medicine type	ICER (cost per QALY gained)
All medicines	Below a most plausible ICER of £20,000 per QALY gained, the decision to recommend the use of a medicine is usually based on the cost-effectiveness estimate and the acceptability of a medicine as an effective use of NHS resources. Above £20,000 per QALY range, AWMSG's judgement about the acceptability of the medicine as an effective use of NHS resources should usually make explicit reference to factors concerning: the certainty about the calculation of ICERs; the innovative nature of the medicine; particular features of the disease or condition and people who will receive the medicine; and broader societal impacts.
Orphan medicine (or equivalent)	Below a most plausible ICER of £20,000 per QALY gained, the decision to recommend the use of a medicine is usually based on the estimated cost-effectiveness and the acceptability of a medicine as an effective use of NHS resources. Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the medicine as an effective use of NHS resources will acknowledge the likely uncertainty in the ICER, and specifically take account of the following factors: • innovative nature of the medicine (improvement on existing treatment and health gains generated over existing treatments for example, > 1 QALY); • features of the condition and population receiving the medicine (for example, the severity of the condition, in terms of baseline health-related quality of life [HRQL] and prognosis), recognising society's priority for expensive treatments for a serious condition over relatively inexpensive treatments for conditions with mild discomfort (which may be calculated to give an equivalent ICER); • broader equity and societal impacts; • impact on non-health benefits that are not captured in the QALY. If the ICER per QALY gained for a medicine increases in the £20,000 to £30,000 per QALY range, AWMSG's judgement about the acceptability of the medicine as an effective use of NHS resources should normally make explicit reference to the relevant factors listed above. Above an ICER of £30,000 per QALY gained, the case for supporting the medicine on these factors has to be increasingly strong.
Ultra-orphan medicine (or equivalent)	Equity and other broader considerations will allow AWMSG to operate a higher cost-effectiveness threshold, usually up to £100,000 per QALY gained. Above a plausible ICER of £100,000 per QALY gained, judgements take account of the size of the incremental therapeutic benefit, by considering the number of additional QALYs gained. There will need to be compelling evidence that the treatment offers significant QALY gains.
*The cost per QALY gained is only part of the judgement of the value of a new medicine	

If the plausible ICER is above £100,000 per QALY gained for ultra-orphan (or equivalent) medicines then the size of the incremental therapeutic improvement will be taken into account. The number of additional QALYs gained will be considered by AWMSG and this is aligned with NICE's HST interim programme[2] (Table 2).

Table 2. QALY gains for a plausible ICER of >£100,000 per QALY gained (in line with NICE's HST interim programme)[2]

Incremental QALYs gained (per patient, using lifetime horizon)	**Weight versus £100,000 per QALY**
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal increments)
Greater than or equal to 30	3

References

1. European Medicines Agency (March 2019) Orphan designation: overview. https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview
2. National Institute for Health and Care Excellence (April 2017) Interim process and methods of the Highly Specialised Technologies Programme updated to reflect 2017 changes. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf