

National Institute for Health and Clinical Excellence

Appraising Orphan Drugs

1. Introduction

1.1 The Institute was invited, by the Department of Health, to indicate how it might meet ministerial requests to appraise so-called “orphan drugs”. This paper represents the Institute’s formal response.

2. Background

2.1 It has been recognised for many years that, because of the costs, special incentives are required if pharmaceutical manufacturers are to be encouraged to develop and market treatments for rare diseases. In both the US, and the EU, legislation has been put in place to promote the development of treatments for rare diseases. Comparable measures have also been introduced in Australia, Japan and Singapore.

2.2 The term “orphan drug” is used in both US and EU legislation to describe a drug indicated for a rare disease (“orphan disease”). The definition of an orphan disease varies, slightly, in the two jurisdictions: in the US it is one with a prevalence of less than 200,000 affected persons; in the EU it is one with a prevalence of less than 5 per 10,000 of the population. Under both schemes, a potential product can be granted “orphan drug status” if it is proposed for use to treat an orphan disease.

2.3 Orphan drug status in both the US and the EU gives manufacturers various benefits (eg waiver of licensing fees, extended patent protection). The US also offers tax relief on development costs.

2.4 Decisions about whether a product should be granted “orphan drug status” are taken by the relevant drug regulatory authorities (ie the Food and Drugs Administration in the US, and the European Medicines Agency in the EU). The number of disorders encompassed in both the US and EU definitions of an “orphan disease” is extensive.

2.5 The wide range of conditions that fall within the definition of “orphan diseases” has led to the emergence of an informal subcategory – called ultra-orphan diseases – to describe extremely rare conditions. The term has no formal

legal definition but treatments for these very rare – ultra-orphan diseases – have become known as “ultra-orphan drugs”.

3. NICE’s Orphan Drugs Projects

3.1 In order to respond to the question of how NICE might appraise orphan drugs the Institute organised, and participated in, a number of events:

3.1.1 An internal NICE workshop in March 2004 with invitees from National Specialist Commissioning Advisory Group and the Royal College of Physicians.

3.1.2 A conference, in September 2004, on “Managing rare diseases” jointly with the Royal College of Physicians of London

3.1.3 A meeting of the Institute’s Citizens Council, in November 2004, when it was asked: *Should the NHS be prepared to pay premium prices for drugs to treat very rare diseases?*

3.1.4 A workshop for patient organisations with a special interest in very rare diseases, in March 2005, jointly with the Royal College of Physicians,.

3.1.5 A feasibility study of the appraisal of Cerezyme (a product falling under the definition of an ultra-orphan drug as defined by the Institute), for the treatment of Gaucher’s disease, by a group drawn from NICE’s appraisal committee.

3.2 The Institute has also had access to the report from the Horizon Scanning Unit, on orphan drugs in development’ prepared at the request of the Department of Health.

4. NICE’s findings

4.1 From its existing experience, and the results of its discussions, the Institute concludes as follows:

4.1.14.1.1 A number of drugs which can be categorised as ‘orphan drugs’ have been referred to NICE and appraised successfully suggesting that for these drugs it was possible to apply NICE methodology (see Appendix 1).

4.1.2 No particular scientific or technical problems have arisen during the Institute’s appraisals of those orphan drugs that have been referred to it. Many, however, have had incremental cost effectiveness ratios (ICERs) at the “high”

end of what NICE and its appraisal committee consider to be cost effective within the NHS. One group (the beta-interferons and glatiramer acetate for the treatment of multiple sclerosis) exceeded this by a wide margin (up to £700,000 per QALY).

4.1.3 The Institute does not consider, therefore, that any changes to its processes are needed for the appraisal of conventional “orphan drugs” with a prevalence of greater than 1 in 50,000.

4.2 There would, however, be problems in the appraisal of drugs for very rare diseases – “ultra-orphan drugs” – largely because of their high costs. The Institute recommends that this group be defined as conditions with a UK prevalence of less than 1 in 50,000. NICE’s advises the adoption of this definition for two reasons: first, it matches the prevalence criteria (less than 1000 persons in the UK) used by the National Specialist Commissioning Advisory Group in determining those conditions that should fall within its programmes; and, second, it encompasses all products that appear, both now and in the foreseeable future, to be particularly problematic.

4.3 Not all drugs with indications for ultra-orphan conditions (ie a prevalence of less than 1:50,000), pose problems. In the UK conditions such as leprosy and cholera are, very occasionally, seen but it would be inappropriate for these to be included. Treatments for ultra-orphan conditions that present special difficulties are characterised by all of the following features:

- high acquisition costs and correspondingly high ICERs;
- use solely for an ultra-orphan disease (ie not also indicated for non-ultra-orphan diseases);
- use in ultra-orphan diseases that are chronic, severely disabling, and/or life-threatening; and
- potentially for life-long use;
- Examples of ultra-orphan products filling the above criteria, and already marketed, are shown in Appendix 2.

4.4 The Institute’s feasibility study of the appraisal of Cerezyme (which fulfills all the criteria in 4.2 and 4.3 above) indicates that, in the assessment and interpretation of the data, the same principle can be applied as used currently for non-orphan drugs.. Despite limitations on the numbers of treated patients, as well as the duration of treatment, the Institute is confident that it is able to provide the NHS with robust and reliable advice on the clinical effectiveness of ultra-orphan drugs.

4.5 The Institute’s general approach to the economic evaluation of health technologies attempts to minimise their opportunity costs. This is usually undertaken by estimating the ICER either as the cost per QALY or the cost per life year gained. Where the ICER exceeds the range of £20,000 to £30,000

there must be increasingly strong reasons (usually based on equity) for the appraisal committee to recommend a product as “cost effective”. The appraisal committee has never considered, as cost effective, any technology with an ICER of more than £48,000 per QALY; and even in this instance (Glivec for blast phase chronic myeloid leukaemia) there were exceptional reasons.

4.6 The estimation of the cost effectiveness of ultra-orphan drugs (as defined in paragraphs 4.2 and 4.3 above), from estimates of their cost utility (ICER), would give rise to no particular technical difficulties. However, with annual treatment costs ranging from £50,000 to more than £300,000 per patient per year, estimates of the ICERs for ultra-orphan products will invariably give rise to values that would be considered cost ineffective under NICE’s conventional criteria. Under its current decision rules, therefore, the Institute would be most unlikely to ever recommend their use in the NHS.

4.7 NICE has considered whether the QALYs achieved with ultra-orphan drugs could be “weighted” so as to produce a final cost per QALY aligned to the Institute’s current approach to cost effectiveness. Although equity weighting has been discussed in the health economic literature, the technique has yet to reach maturity. For this reason the Institute, as a matter of general policy neither recommends, accepts, nor uses equity weighting in its current technical appraisal processes. Furthermore, NICE is unaware of any work that has attempted to develop equity weights in relation to ultra-orphan drugs. NICE does not therefore recommend this approach for the foreseeable future.

4.8 The conclusions of the Citizens Council, and the judgment of the board, suggests there is public support for the NHS to meet the reasonable treatment costs of expensive treatments for ultra-orphan conditions. This would accord with the NHS’s egalitarian principles.

4.9 If the Institute is to appraise ultra-orphan drugs, and be prepared to accept substantially higher ICERs than those hitherto considered to be cost effective, then separate decision rules (ie the range of ICERs considered “cost effective”) will need to be developed and adopted for these products. The Institute proposes that these ultra-orphan drug decision rules are based on the ICERs of those ultra-orphan drugs currently on the UK market. This will provide an implicit benchmark against which new ultra-orphan products can be evaluated. Some indication of the likely range of ICERs is shown in Table 2 but it should be emphasised that these are crude estimates, that further work will be necessary to provide more robust data, and that a final position on cost effective ICERs will need to be confirmed through wider consultation. The further work would determine a rationale for a new IOD threshold. However, it appears that at current prices indicative ICERs for ultra-orphan products are in the range of £200,000 to £300,000 per QALY (ie a ten-fold increase on the decision rules currently applied in conventional appraisals).

4.10 It is possible that even with these new, ultra-orphan, decision rules NICE will consider that some products to be cost ineffective. Under these circumstances, and on the recommendation of the Institute, it is proposed that the Department be given the opportunity to enter negotiations with manufacturers to investigate the possibility of a price reduction that would bring the ICER into line with NICE's ultra-orphan decision rules. If some price reduction were to be negotiated, the Department would then re-refer the product to the Institute for further evaluation.

4.11 Because of the differences that are proposed between conventional appraisals, and the evaluation of the clinical and cost effectiveness of ultra-orphan treatments, the Institute recommends that a new programme is developed. This would draw a clear distinction between the two programmes and their different decision rules. Important features of this new programme are that it should not be described as an "appraisal"; that a separate and distinct process would be developed and applied; and that advice should be developed by a new committee – the "Ultra-orphan Drugs Evaluation Committee" – under a chair who is not involved with the appraisal programme (although some members of the appraisal committees might be appointed to it).

4.12 From the report of the Horizon Scanning Unit, together with its own enquiries, the Institute estimates that about two new ultra-orphan products (as defined in paragraphs 4.2 and 4.3) are like to reach the market each year (at least over the next five years).

5. The Institute's proposal

5.1 NICE recommends that ministers refer ultra-orphan drugs with the request that the Institute prepares guidance, for the NHS. The referral might take the form of a *"request for an ultra-orphan evaluation of the clinical and cost effectiveness offor the treatment offor use in the NHS"*

5.2 The criteria for referral would comprise those currently used plus additional ones (paragraphs 4.2 and 4.3 above):

- the condition should have a UK prevalence of less than 1:50,000; and
- the product should only be indicated for an ultra-orphan condition; and
- where the product is indicated for more than one ultra-orphan condition, the combined prevalences should be less than 1:50,000; and
- the condition should be chronic, severely disabling, or life-threatening; and
- the product should be, potentially, for long-term use.

5.3 The Institute's would develop a process, based on the current appraisal programme. This would include the identification of consultees, a scoping meeting, and the preparation/evaluation of an assessment report. Consultees

would be invited to comment on the report before its consideration by the “Ultra-Orphan Drugs Evaluation Committee”.

5.3 The Ultra-Orphan Drugs Evaluation Committee would consider the report, as well as the submissions of consultees, and advise on use within the NHS. In developing its advice the committee would give particular attention to:

- Whether the product produced, or was reasonably likely to produce, significant health benefits (substantial reduction of disability, or increased longevity) in those receiving it;
- Whether only sub-groups of patients were likely to benefit and, if so, which ones;
- What monitoring arrangements should be recommended;
- The circumstances when treatment should be withdrawn for efficacy (or reasons of safety);
- The ICER.

5.4 The committee would prepare draft guidance, for consultation, before preparing (after considering the responses of consultees) final guidance. As with the appraisals, consultees would have rights of appeal.

5.5 Where the committee recommended against the use of a product on grounds of cost effectiveness, and where an appeal (if any) had been rejected) the Institute’s chief executive (on the advice of the Guidance Executive) would refer the results of the evaluation to the Department of Health with a view to discussing, with the manufacturer, a reduction in the acquisition price of the product. If a price reduction were to be agreed with the manufacturer, ministers would consider re-referring the topic to the Institute. The Ultra-Orphan Drugs Evaluation Committee would reconsider the product, in the light of the reduction in the ICER, and prepare its final advice. There would be no further consultation or appeal.

6. Next steps

6.1 Minister endorsement of this proposal has not yet been sought by DH officials, and they will discuss this further with ministers once they have our proposals. If ministers wish to proceed along the lines suggested in this report, the Institute would undertake the following.

6.1.1 NICE would develop a detailed process along the principles described in section 5 (above). Following approval by the Board, the proposed scheme would go out for consultation.

6.1.2 The Institute will undertake further work to estimate, with greater confidence, the ICERs of the ultra-orphan products currently marketed. These

would form the basis of the decision rules used by the Ultra-Orphan Drugs Evaluation Committee in evaluating cost effectiveness.

6.1.3 The Institute are aware that at the time a new ultra-orphan product is marketed, significant numbers of UK patients will have been undergoing treatment as part of the manufacturer's prelicensing trials. The continuation of such treatment, at the NHS's expense, is an issue that NICE will discuss with officials. This will only become a problem, of course, if NICE decides against advising use in the NHS on grounds of cost ineffectiveness.

6.2 Care will need to be taken to ensure that manufacturers do not "game" the system. They could do so by gaining marketing authorisation for an ultra-orphan indication then, subsequently, obtaining marketing authorisation for a non-orphan indication with a premium price already established. One approach to avoiding this is for the Department to make it clear that additional indications would immediately trigger a referral to NICE for review under its conventional appraisal programme.

6.3 The Institute estimates that the resources it will require to evaluate an ultra-orphan product will be similar to those needed for a conventional appraisal. If ministers wish to proceed with the new programme that is described in this document, this will have resource implications, and that additional resources will be required if existing technology appraisal capacity is to be protected.

Appendix 1

Conditions for which orphan drug designation has been granted and for which NICE appraisals have been completed

Condition	Mid-range incremental cost effectiveness ratios (£)
Ovarian cancer refractory or resistant to standard chemotherapy (FDA & EMEA)	Topotecan = 32,500/LYG
Pancreatic cancer (FDA & EMEA)	Gemcitabine = 12,550/LYG
Metastatic colorectal adenocarcinoma (FDA)	Irinotecan /Oxaliplatin = 27,500/LYG (second line) = 29,000/LYG* (first line) Capecitabine Tegafur uracil
Malignant glioma FDA & EMEA)	Temozolomide = 35,000/LYG
Crohn's disease (FDA)	Eterncept = 27,500/QALY (severe) = 100,000/QALY* (fistulising)
Non-Hodgkin's lymphoma (FDA)	Rituximab = No ICER able to be calculated
Chronic myeloid leukaemia (FDA & EMEA)	Imatinib = 37,500 (second line) = 48,000 (blast phase)
Multiple sclerosis (FDA)	Beta interferons = 69,000/QALY (20 year projection) = 580,000/QALY (5 year perspective)
Juvenile rheumatoid arthritis (FDA)	Infliximab = 16,082/QALY
Motor neuron disease (FDA & EMEA)	Riluzole = 38,500/QALY
Idiopathic or organic growth hormone deficiency in children with growth failure (FDA)	Human growth hormone = 13,250/QALY
Short stature associated with Turner's syndrome (FDA)	Human growth hormone = 26,500/QALY
Growth hormone deficiency in adults after epiphyseal closure (FDA)	Human growth hormone = 35,000/QALY (moderate to severe only)
Gastrointestinal stromal tumours (GIST) (FDA)	Imatinib = 35,500/QALY

*Figures in bold italics show ICERs considered to be cost ineffective by NICE

Appendix 2

Some ultra-orphan drugs in current use

Product	Condition	Prevalence	Preliminary estimated ICER (£ per QALY)
Agalsidase beta (Fabrazyme)	Fabry's	200	203,009
Imiglucerase (Ceredase)	Gaucher's (types I and III)	270	391,244
Laronidase (Aldurazyme)	Mucopolysaccharidosis (type 1)	130	334,880
Miglustat (Zavesca)	Gaucher's (type I)	270	116,800
Nonacog alfa (BeneFIX)	Haemophilia B	350	172,500
Iloprost (Ventavis)	Primary pulmonary hypertension	100	23,324