All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Idursulfase (Elaprase®)
Shire Human Genetic Therapies

Advice No: 1207 – October 2007

Recommendation of AWMSG

Idursulfase (Elaprase®) should not be recommended for use within NHS Wales for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

The clinical and cost effectiveness data presented was not sufficient for AWMSG to recommend its use.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

Date: 18th October 2007

The recommendation of AWMSG is:

Idursulfase (Elaprase®) should not be recommended for use within NHS Wales for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

The clinical and cost effectiveness data presented was not sufficient for AWMSG to recommend its use.

Key factors influencing recommendation:

- The data required to undertake a robust cost-effectiveness analysis of idursulfase (Elaprase®) is lacking. The inputs of the economic model submitted rely on a number of substantial assumptions which are inadequately justified e.g. utility values and survival benefit, and a likely underestimate of costs.

- Published evidence for idursulfase (Elaprase®) is limited to one year. Longer term data on overall survival is required to clarify the benefits of idursulfase.

- The Department of Health (DOH) guidance on idursulfase (Elaprase®) treatment, which is applicable in England, includes all patients under the age of five years, but the trial data submitted to AWMSG does not support this as children below this age were not included.

- There is a lack of comparative trial information available with regard to palliative outcome. This weakens the argument that idursulfase (Elaprase®) may alleviate the need for, or have superior efficacy to, palliative care treatment.

Additional note:

AWMSG will review this and other enzyme replacement therapies within three years.

2.0 PRODUCT DETAILS:

2.1 Licensed indication: Idursulfase (Elaprase®) is indicated for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II) [1].

2.2 Dosing:
Idursulfase (Elaprase®) is administered at a dose of 0.5 mg/kg body weight every week by intravenous infusion over a 3 hour period, which may be gradually reduced to 1 hour if no infusion-associated reactions are observed [1].
The dose for children and adolescents is 0.5 mg/kg body weight weekly.
There is no clinical experience in children under the age of 5 years, in heterozygous females, in patients over the age of 65 years or in patients with renal or hepatic insufficiency [1].

2.3 Market authorisation date: 8th January 2007 [2]

2.4 UK Launch date: 1st April 2007 [2]

3.0 DECISION CONTEXT

Hunter syndrome is a lysosomal storage disease caused by the missing or defective enzyme, iduronate-2-sulfatase (I2S), which acts to cleave O-linked sulfate moieties from two human glycosaminoglycans (GAG) known as dermatan sulfate and heparan sulfate. Insufficient levels of I2S lead to progressive accumulation of these GAG molecules in nearly all organs and body tissues [3].

The most common clinical signs and symptoms of GAG accumulation are slow mental development, enlarged tongue, coarse facial features, hearing loss, abnormal dentition, restrictive lung disease, hepatosplenomegaly, valvular heart disease, decreased joint range of motion, skeletal deformities, and severe short stature. In addition to their restrictive pulmonary disease, oropharyngeal and respiratory deposition of GAG leads to severe airway obstruction due to macroglossia, supraglottic narrowing, and tracheomalacia, further contributing to impaired pulmonary function and sleep apnoea[3].

In parallel with their loss of ability to perform activities requiring physical endurance, Hunter syndrome patients also lose much of their ability to perform even simple activities of daily living. Over time, the increasing size and protuberance of the tongue causes difficulty with swallowing and also may impair their ability to speak clearly. The progressive decrease in joint mobility and their broad, claw-like short fingers may prevent patients from independently performing many self-care activities including self-dressing, toilet care, and personal grooming. Hunter syndrome patients become entirely dependent on others for their continued survival at an early age [3].

Appendix 1; *Figure 1* – indicates the prevalence of Hunter syndrome and the age of symptomatic development.

Despite the heterogeneity in the disease progression, onset of signs and symptoms typically occurs between 2.5 to 4.5 years of age. An earlier appearance of clinical symptoms generally, but not always, predicts a more severe clinical course. Although the syndrome varies from mild to severe, most patients die in their second or third decade of life from respiratory and/or cardiac failure. In the more severe cases patients die within the first or second decade[4]. The issue of whether or not to treat patients with significant cognitive impairment is a difficult one, as if there is little evidence to suggest that a treatment does not cross the blood-brain barrier, it is likely to have little or no

impact on cognitive decline once it sets in. However, in young children it can be very difficult to predict later cognitive decline[5].

MPS II is an "ultra-orphan" disease with an incidence of just 1 in 166,000 births[6]. There are two known MPS II patients in Wales[7], but neither has been treated during the clinical trials for idursulfase; they currently receive palliative treatment only[4].

The current treatment of Hunter syndrome is palliative and focused on clinical symptoms e.g. surgery to reduce airway obstruction and continuous positive airway pressure (CPAP) has been used to treat sleep apnoea[3]. Haematopoietic stem cell transplant (HSCT) has been suggested as a way of providing donor cells capable of expressing I2S, but long-term results are limited. Bone marrow transplantation has also been attempted in a small number of cases with mixed results. However, this procedure is very risky and is not recommended as routine care for patients with Hunter syndrome[3]. As the scientific concept underpinning enzyme replacement therapy has already been established in other lysosomal storage diseases e.g. Gaucher and Fabry disease, there is a likelihood that enzyme replacement therapy (ERT) would also benefit Hunter syndrome patients[3].

Treatment guidelines have been developed by clinicians from specialist centres in Cambridge, Manchester and London. These centres are designated as National Specialist Commissioning Advisory Group (NSCAG) centres for the diagnosis and management of ERT disorders and the guidelines have been adopted by the Department of Health (DOH). They indicate that any patients over five years of age should only be offered treatment at the discretion of the specialist if there is evidence of progressive and significant decline [5].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Idursulfase is an ultra-orphan drug licensed for the long-term treatment of Hunter syndrome. Although the volume and quality of data available for any ultra orphan disease is likely to be limited, the patient population studied needs to be representative of the disease. In the clinical studies, the data are supportive of efficacy for the weekly 0.5 mg/kg dose in comparison to the every other week (EOW) dosage. However the EMEA have requested further information on the appropriate dose, dose schedule and infusion time as they considered the submitted dose finding study to be inconclusive.

Supportive evidence for the primary composite endpoint is provided by the reduction in hepatosplenomegaly and urinary GAG levels. On the current data available, these efficacy parameters do not appear to show any deterioration in the long term (1 year) [3]. There is little evidence to show that intravenous idursulfase crosses the blood-brain barrier. It is therefore likely to have little or no impact on cognitive decline once it is established and future cognitive decline is difficult to predict in young children under any circumstance. The main safety concerns with idursulfase appear to be infusion associated reactions (IARs) and immunogenicity. Administration is via a weekly three hour infusion, which may be gradually reduced if no IARs are observed. This administration needs to be initially carried out in an outpatient setting, which has associated implications such as transport for patients and their carers. AWMSG may wish to consider whether further safety evidence will be required from ongoing studies in order to support future home treatment. The company intends to address these concerns through the Hunter Outcome Survey (HOS) registry[4].

4.2 Review of the evidence on cost-effectiveness

The data required to undertake a robust cost-effectiveness analysis of idursulfase is lacking. The inputs of the economic model described in the company submission rely on a number of substantial assumptions that are likely to significantly bias the model in favour of idursulfase. These are inadequately justified, and introduce a large element of uncertainty that has not been addressed adequately. These include the adoption of utility values that are unrelated to the treatment of MPS II with idursulfase and are likely to be overoptimistic, and an assumed survival benefit that is not based on any evidence. In addition, the model does not adequately consider the full range of relevant costs associated with the use of idursulfase or the comparator (palliative care). Although improvements to the model would be possible, the cost-effectiveness estimate would be likely to remain as high, if not higher than that reported in the company submission.

AWMSG is mindful of the ultra-orphan drug status of idursulfase and the unmet clinical need of patients with MPS II. However, there is no evidence presented to suggest that idursulfase serves to bridge a gap to a "definitive" therapy, or that this "definitive" therapy is currently in development. AWMSG is of the opinion that the economic case for idursulfase has not been demonstrated.

5.0 LIMITATIONS OF DECISION CONTEXT:

- There are no other medicines licensed specifically for MPS II. Treatment to date has been palliative. However, the lack of information available for palliative outcomes does not support the fact that idursulfase may alleviate the need for palliative care treatments.
- Although the volume and quality of data available for any ultra-orphan disease are likely to be limited, the patient population studied needs to be representative of the disease.
- A recent Department of Health (DOH) update on nationally commissioned services in England highlighted that idursulfase seems to improve the physical condition of patients with MPS II but without preventing the cognitive decline that sometimes leads to early death [9]. Long-term data on overall survival is required to determine the effect of idursulfase in different patient sub-groups.
- The DOH guidelines for treatment include all patients under the age of five years, but the submitted trial data does not support this in terms of population inclusion [4, 5].
- Every other week (EOW) dosing has not shown demonstrable clinical benefit, but could be considered to slow progression of overt symptoms and disease and therefore reduce the overall long-term burden of associated disease palliative treatment. The EMEA have requested further information on dosage as they considered the submitted dose finding study to be inconclusive [3].
- From an immunological perspective, the effect of neutralising antibodies on safety and efficacy is still to be fully evaluated; therefore, no firm conclusions can be drawn [3].
- MPS II is a rare disease in females and there are currently no clinical trial data available for treatment of female patients.
- Published evidence for idursulfase is limited to one year and therefore the economic model relies on assumptions of survival benefit for which the data is not publicly available.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

Overall, the data included in the efficacy section of this submission is comprised from trials in 108 individual patients; 96 patients in the 12 month, Phase II/III pivotal study TKT024 [8], and 12 patients in the six month study TKT008 [10] (who subsequently enrolled into the Phase I/II open-label extension study, TKT018). A broad spectrum of disease manifestation was seen within the study participant population. Data from 24 months of treatment in an ongoing Phase I/II, open-label extension study (TKT018) has been excluded from the efficacy submission due to EOW dosing, but included in the safety section. TKT024EXT, the open-label extension of the TKT024 study, was ongoing with no efficacy data available at the time of submission.

The effects of idursulfase treatment have been demonstrated directly using clinical measurements e.g. Forced Expiratory Volume (FEV_1)% and indirectly using surrogate markers of the disease e.g. urinary GAG levels[4]. Efficacy was adequately demonstrated for the composite endpoint using the weekly dosage schedule, but it has not been shown for the EOW schedule where the evidence was weak with borderline significance. This was evident for the composite endpoint in the pivotal study, TKT024, which was driven only by one component, namely the six minute walk test (6MWT), with no clear evidence of any effect on pulmonary function by the EOW dose. Accordingly, the license is restricted to a weekly dosing for all patients with Hunter syndrome. Further outcome data are provided in this section. There is currently no data available for patients less than 5 years of age [4]. Study TKT038 and the HOS are intended to evaluate treatment within this age group [3].

6.1.1 Phase I/II study of idursulfase replacement in MPSII (TKT008) [10]

This was a double-blind, placebo-controlled, dose-escalating trial where 12 patients were randomised to receive one of three idursulfase doses (0.15mg/kg, 0.5mg/kg or 1.5mg/kg) by intravenous infusion EOW.

Three groups of four patients were enrolled sequentially to receive escalating idursulfase dose levels; within each group, three patients were randomised to receive idursulfase and one to placebo. For inclusion, patients had to be ≥ 5 years of age and co-operative with testing. The primary focus of the study was to assess the safety of idursulfase enzyme replacement therapy. Overall treatment was generally well tolerated and displayed a favourable safety profile. All 12 patients successfully completed the six month phase and elected to participate in the open-label extension phase (TKT018). Patients remained on their idursulfase dose level from the six-month study and placebo patients crossed over to idursulfase at the dose of their original treatment group (one patient at each dose level) [10].

The primary efficacy outcome was the extent of reduction in urinary GAG excretion[4].

Secondary efficacy outcomes included [4]:

- Liver and spleen size which were measured by magnetic resonance imaging (MRI). Hepatomegaly was defined as a liver volume (L) >3.5% of body weight (kg) in patients aged 5 to 12 years, >2.2% of body weight in patients aged 13 to 17 years, and >2.6% in patients more than 18 years old. Splenomegaly was defined as having a spleen volume greater than the 95th percentile of the normal distribution in children.

- 6MWT, subjects were instructed to walk back and forth between two marks that were 15 metres apart. An observer recorded the total distance covered in six minutes.
- Pulmonary function, which was assessed by spirometry to measure forced expiratory volume (FEV_1) in one second and Forced Vital Capacity (FVC). Three consecutive determinations of FVC and FEV_1 within 5% of each other were required for a successful measurement.
- Passive joint mobility, which was defined as the range of motion of neck, shoulder, elbow, wrist, hip, knee, and ankle joints as assessed by a physical therapist using a goniometer.
- Heart size and valve function, which were assessed by echocardiography. Estimates of heart size were made by a single investigator using standard formulae.
- Standard overnight sleep studies, which were performed in a Sleep Disorders Laboratory to measure the frequency of apnoeas, hypopnoeas, and oxygen desaturations.

The TKT008 study represents the first trial of ERT for the treatment of patients with MPS II and where the primary endpoint of a sustained reduction in urinary GAG excretion was achieved. Decreases in urinary GAG were seen two weeks after initiating idursulfase, with more rapid declines in the 0.5 and 1.5mg/kg groups. The mean decrease in urinary GAG for all patients (as well as the percent changes from baseline at each visit) were statistically significant (mean change, p=0.0092; percent change, p=0.0007). Urinary GAG levels did not change in patients treated with placebo during the double-blind phase. The reduction in urinary GAG levels was maintained through 48 weeks. The urine GAG level was reduced to near normal in the majority of patients, with two patients achieving levels within the normal range at six months [4,10].

Evidence of its biological activity was seen in the reduction in the size of the liver and spleen, and clinical benefit was suggested by the improvement in the 6MWT distance. Although not statistically significant, further clinical benefit was suggested from the observed changes in left ventricular hypertrophy and sleep apnoea [3].

Points to note

- The study population was small with 12 patients at different stages of disease progression [10].
- The primary efficacy endpoint of a sustained reduction in urinary GAG excretion was achieved.
- A statistically significant increase in the 6MWT distance was achieved over the 48 week period, although no other statistically significant benefits were seen with any of the other clinical parameters [4].
- No baseline weekly dosing data was available for this study, and it may therefore be that the dose selected was not optimal for this patient population. Selection of the dose was also based on pre-clinical data, in which a dose of 1.0 mg/kg/body weight was studied, this was not clinically evaluated [3].

6.1.2 Phase II/III study of idursulfase in MPS II (TKT024) [8]

This was a multi-centre, multinational, double-blind, randomised, placebo-controlled, 53-week, Phase II/III study of the efficacy and safety of idursulfase 0.5 mg/kg administered either weekly or EOW in 96 patients with Hunter syndrome.

The biochemical evidence of MPS II included a documented deficiency in the I2S enzyme activity of less than or equal to 10% of the lower limit of the normal range

measured in plasma, fibroblasts or leukocytes combined with a normal enzyme activity level of another sulfatase. All patients were required to reproducibly perform pulmonary function testing and have an abnormal FVC of less than 80% of predicted. Patients who had a tracheotomy or who had received a bone marrow or cord blood transplant were excluded from the study.

All 96 randomised patients were male between the ages of 4.9 and 30.9 years (5 patients were ≥ 26 years old). The mean age of patients in this study was 14.22 years old[3]. Nearly 45% of patients in the study were 5 to 11 years old and only 25% of patients were 19 years of age or older[3]. All patients were short in stature for their age [3].

The primary efficacy endpoint in the trial measured changes from baseline to week 53, combining FVC as a measure of respiratory function and the 6MWT as a measure of functional capacity [4].The 6MWT was conducted in accordance with American Thoracic Society guidelines [10]. In the primary composite areas, the efficacy endpoints were between the weekly treated group (n = 32) and the placebo group (n=32)

The secondary efficacy outcome [4] measurements were:
• Passive joint range of motion (JROM)
• Combined liver and spleen volume by MRI
• Urinary GAG levels
• Cardiac left ventricular mass (LVM) by echocardiography

All measurements were made at baseline, weeks 18, 36 and 53 [7].

Data were analysed by treatment group (32 idursulfase weekly; 32 idursulfase EOW; 32 placebo) with respect to demographic and baseline characteristics, clinical activity variables, safety variables, and pharmacokinetic (PK) measurements. Where applicable, each variable was quantified as a change from the baseline value [4].

When analysed on an intent-to-treat basis, weekly idursulfase was statistically significantly more effective than placebo on the primary two-component composite endpoint score (69.81 versus 50.86, p=0.0049) [7].

Appendix 1: Table 1 shows a summary of changes in secondary outcomes for MPS II (TKT024) [4]

Secondary outcome results were as follows [4,8]:

- Weekly idursulfase normalised liver volume in 20 of 25 patients (80%) who had hepatomegaly at baseline.
- Relatively few patients had an abnormally enlarged spleen volume at baseline. Three of the nine patients (33%) treated with idursulfase had normal spleen volumes by the end of treatment. In comparison, two of the 11 patients (18%) in the placebo group had normal spleen volumes by Week 53.
- The global JROM score did not show any improvement.
- Overall, 33 patients (34%) in the study had evidence of left ventricular hypertrophy (LVH) at baseline. The mean reductions in LVM seen with idursulfase fall within the range of 8% to 15%.
- All patients in this study had urinary GAG levels above the upper limit of the normal range (>126.6 micrograms GAG/mg creatinine) at baseline. By Week 53, idursulfase had normalised urinary GAG levels in 16 of 32 patients (50%). In contrast, none of the patients in the placebo group had normalised urinary GAG levels.

Physical function questionnaires were part of the tertiary outcome assessment. The Childhood Health Assessment Questionnaire (CHAQ) parent-assessed pain score showed a statistically significant improvement compared to placebo (p=0.0102). Other effects assessed e.g. satisfaction with physical ambulation, mobility, emotion, overall health, did not reach statistical significance [4].

Points to note

- TK024 is a pivotal trial in 96 Hunter syndrome patients which constitutes the largest, longest and most comprehensive trial conducted for a lysosomal storage disorder.
- The study did not include patients under the age of 5, over the age of 31 or females. The study was essentially carried out in males due to the X-linked recessive nature of the disease which is reflective of the fact that Hunter syndrome has rarely been reported in females. Idursulfase is not indicated in women of childbearing potential, this is reflected in the SPC. The company has committed to a study in patients under the age of 5 years [4].
- In trial TKT024, the adjusted changes from baseline in the primary endpoint were always lower for all treatment groups than the unadjusted changes, and therefore did not seem to reflect the experience of patients in the trial. Accordingly, the company supplied the recalculated marginally weighted adjusted means for the primary and other endpoints (absolute changes in FVC, changes in urine GAG levels, liver and spleen volumes) to the EMEA, including them in the SPC [3].
- With respect to neurological development progress and bioavailability of the enzyme in the CNS, idursulfase was not expected to have any effect on CNS disease, if present [3].
- Long-term data on relevant clinical end-points and safety was also requested by the EMEA, with comparison to historical data, through establishment of a patient registry. The company has made a commitment to continue to analyse such data for at least the first 10 years through the HOS [3].
- 6MWT and % predicted FVC have also been used to test enzyme replacement effectiveness in MPS I which is a closely related condition to Hunter syndrome[3].
- This study included patients from the UK [4].

6.1.3 Phase I/II, open-label maintenance extension study (TKT018) [9]

At completion of the Phase I/II study (TKT008), all twelve patients consented to participate in an ongoing, open-label, extension study, in which all patients received idursulfase, including those randomised to placebo in TKT008. Upon final analysis of the results from TKT008, all patients were transitioned to a common dose of 0.5mg/kg, which they continue to receive. The study endpoints and patient assessments evaluated in TKT008 were also evaluated in TKT018, so that the long-term clinical benefit of idursulfase therapy could be assessed [4]. All 12 patients have remained on active study drug for approximately three and a half years. There are no currently available data from this extension study.

6.1.4 TKT024EXT, an open-label extension of TKT024, currently ongoing.

94 of the original 96 patients elected to continue treatment in an open-label follow-up study in year two. All UK patients completed their year two visits in January 2007. Shire expects that the clinical results from this extension study will be available at the end of 2007. Subsequently, this study is likely to be reported towards the end of 2007 or early in 2008 [3, 4].

6.1.5 Hunter outcome survey (HOS)

Patients with MPS II, whether treated or not treated with idursulfase, are enrolled into the Hunter Outcome Survey (HOS), which is an international, multicentre, long-term observational study. This HOS survey is intended to improve the understanding of treated and untreated patients with MPS II [4].

HOS is a long-term observational study with the following objectives:

1. To collect data on the long-term follow-up of treated and untreated patients with MPS II.
2. To describe the population of patients affected with this disease.
3. To enhance the understanding of its natural history, including intra and interfamilial variations.
4. To monitor the safety and efficacy of idursulfase (I2S replacement therapy).
5. To provide a basis for the development of clinical management guidelines for MPS II.

This survey is not linked to the registration of the product and the final protocol is now available [4]. Data collection started in the UK in March 2006 and currently more than 160 patients worldwide (over 60 UK patients) are entered into the HOS survey. Shire anticipates that data publication will be on an ongoing basis. The survey is physician driven with regard to scientific direction and publications [4].

6.2 Safety:

Overall, therapy with idursulfase was generally well tolerated at a dose level of 0.5mg/kg administered both weekly and every other week [3]. No patient was reported to withdraw from a study due to an adverse event related to idursulfase. The overall incidence of adverse events, including those reported most commonly (10% of patients in any treatment group), were similar across treatment groups within the trial TKT024 (***Appendix 1*** *–Table 2*) [3,7].

The main safety concerns with idursulfase appear to be infusion associated reactions (IARs) and immunogenicity. IARs appear to be related to the dose and the frequency of administration as they were more common in the weekly schedules compared to EOW, and no IARs were reported in patients on the lower dose of 0.15 mg/kg body weight. The frequency of IARs seemed greatest during the first 6-12 months of treatment and decreased over time. Infusion-related adverse events were also frequently reported in the placebo group. Across all studies, serious adverse reactions to idursulfase 0.5mg/kg body weight weekly or EOW were reported in a total of five patients. Four patients experienced a hypoxic episode during one or several infusions, which necessitated oxygen therapy in three patients with severe underlying obstructive airway disease. Caution should be exerted in patients with decreased respiratory function, and a slower infusion rate and administration of pre-infusion treatment e.g.low-dose steroids, antihistamine, and beta-agonist nebulisation is recommended [4].

Although numbers are limited, antibody positive patients appeared to have an increased number of adverse events compared to those who were negative. Across all studies, 53/108 patients (49%) developed anti-idursulfase IgG antibodies at some point. Six of these patients also tested positive for IgM antibodies, and one patient tested positive for IgA antibodies. There were no reported episodes consistent with anaphylactic reaction to idursulfase and no patient developed IgE antibodies [3].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:
To date, treatment of the underlying disease has not been possible, hence the focus of care has been on palliative management of the clinical symptoms.
Other interventions such as bone marrow transplantation and HSCT have been used, although long term data is very limited [4].

7.2 Comparative effectiveness:
There are no available comparative data. The lack of comparative information available for palliative outcomes does not support the fact that idursulfase may alleviate the need for, or have superior efficacy to, palliative care treatment.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider
The key economic issue for AWMSG to consider is whether the additional benefits offered by idursulfase over the relevant comparator (palliative care) justify the additional costs.

8.2 Review of published evidence on cost-effectiveness
No relevant published economic evidence in the treatment of MPS II has been provided by the company or identified by standard literature searches conducted by WMP. A HTA systematic review of the clinical and cost-effectiveness of ERT in patients with MPS I was conducted in 2006. However, the authors felt that the cost-effectiveness of ERT in MPS I could not be estimated [12].

8.3 Review of company submission on cost-effectiveness
8.3.1 Summary of the evidence
The company submission[4] provides a brief description of a pharmacoeconomic model that was constructed to estimate the incremental cost per QALY of idursulfase versus palliative care. Details of the actual structure of the model are lacking and it is assumed that a simple decision-analytic model was constructed. As the company has not provided the model, verification of the model outputs is not possible. There is no indication that the model, nor any of the inputs, has been externally validated.

None of the clinical inputs of the model for the base case analysis are derived from the clinical trial data for idursulfase. Those that are used significantly bias the model in favour of idursulfase. Although utility values were estimated in the pivotal phase II/III trial, the model does not use these in the base case analysis. Instead, utility values have been adopted from a systematic review of ERT in Fabry's disease. Not only do these utility values relate to a different disease being treated by different agents, they were also assumed in the systematic review of ERT for Fabry's disease, rather than being based on actual measured values [12].

The survival data used in the economic model is based on a modelled estimate of survival in untreated patients, which was then adjusted by a factor to generate improved survival with idursulfase versus palliative care. No justification is provided for the modelled survival benefits for idursulfase, and the methods used for the modelling are inappropriate.

The model considers only the direct drug cost of idursulfase. No consideration is given to the costs/resources associated with administration of idursulfase, which involves weekly intravenous infusion (over three hours, at least initially). Further, the model assumes that idursulfase removes the need for any other care. As it is unlikely that idursulfase will remove the need for all other forms of care, this would have the effect of biasing the model in favour of idursulfase. Palliative care costs are not considered in the base case and no personal and social service costs/resources are incorporated due to a lack of data. These could feasibly be substantial for this patient group.

One-way sensitivity analysis has been conducted on the parameters of mortality, discount rate, palliative care resource use, the time horizon and utility values. The model appears to be relatively insensitive to the range of parameter values explored, with the significant exception of utility values. However, this insensitivity does not imply that the model is robust as the alternative input values for the key parameters tested have not been adequately justified.

8.3.2 Summary of the key findings

Over a 15 year time horizon, the model estimates the incremental cost per QALY of idursulfase over palliative care to be £564,692 [4]. This is based on (discounted) incremental costs of £3.366million and a gain of 5.962 QALYs per hypothetical patient. However, this estimate is highly sensitive to the assumed utility vales and survival estimates. Returning the utility vales to those actually estimated in the pivotal phase II/III study results in the estimated incremental cost per QALY more than doubling to £1,174,342.

8.4 Review of evidence on budget impact:

8.4.1 Summary of the evidence

The manufacturer's submission includes a budget impact analysis which assessed the likely costs of idursulfase over the next five years. The model is populated with data on the incidence and prevalence of MPS II. Only idursulfase drug costs are included in the analysis, which was conducted from the perspective of NHS Wales[4].

The company submission claims that, by extrapolating data from the UK, there would be 2.5 patients with MPS II expected to be born in Wales over the next 10 years, which would be equivalent to around one patient every three or four years[4]. There are thought to be two patients with MPS II in Wales[3]. There is some uncertainty in these estimates but, given the generally very low incidence rates of MPS II, these figures are likely of the correct order of magnitude.

Based on the two known patients in Wales and discussions with clinical experts, only one patient is currently expected to be eligible for treatment with idursulfase as the second patient has advanced disease. However, it is assumed that all subsequent patients would be eligible (from birth) for treatment with idursulfase[4]. There are no other licensed medicines specifically for MPS II. Other medicines are likely to be used in the palliative care of patients, e.g. oxygen therapy. However, data on what palliative care treatments are provided to patients is not available and the extent to which idursulfase may alleviate the need for palliative care treatment is unclear. No consideration is given to palliative care in the budget impact model.

8.4.2 Summary of the key findings

The budget impact analysis assumes that, in each of the years from 2007 to 2011, the number of patients with MPS II will remain constant at two (due to an assumed incidence of one case every four years and one death occurring over the next five years). It assumes that only one patient will be eligible for treatment in 2007 and 2008, but in 2009 this will increase to two patients (due to the death of the one existing patient who is not eligible for treatment and the birth of one new patient who would be eligible for treatment).

The acquisition cost of idursulfase is stated as £1,985 per 6mg vial and the drug is administered at a dose of 0.5mg/kg body weight/week. Based on the claimed average weight of patients obtained from trial and database data (33.4kg), the annual drug cost of idursulfase has been estimated as £309,660 per patient (single use vials only)[1,d] 2008, the budget impact is therefore expected to be £309,660 per year (assuming only one patient eligible for treatment). In each year 2009 to 2011, the annual drug cost is estimated as £619,320 (assuming two patients are eligible).

This does not take into account the lower body weight of newly diagnosed patients or the possibly increasing body weight of patients as they age. If idursulfase is found to be associated with a survival advantage, the number of patients treated with idursulfase, and the associated costs, may beyond 2011.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- As published trial data with idursulfase are limited to one year, mortality data for treated patients is limited. Data collection for all clinical parameters is essential to monitor the effectiveness and safety of treatment. It is intended that the observational HOS will inform on many objectives in order to improve the understanding of the disease process in treated and untreated patients [3].
- Idursulfase would not be suitable for a shared-care agreement with a non-specialist. Treatment initiation, monitoring and supervision should be retained under Specialist care.

9.2 Related advice:

- A recent DOH update on nationally commissioned services in England highlighted that idursulfase seems to improve the physical condition of patients with MPS II but without preventing the cognitive decline that can lead to early death [9]. However it must be noted that the main causes of mortality for Hunter syndrome patients are cardiovascular and pulmonary disease.
- DOH guidelines for the investigation and management of MPS II endorse the use of idursulfase in patients under the age of five years[5].

9.3 Previous AWMSG/NICE advice

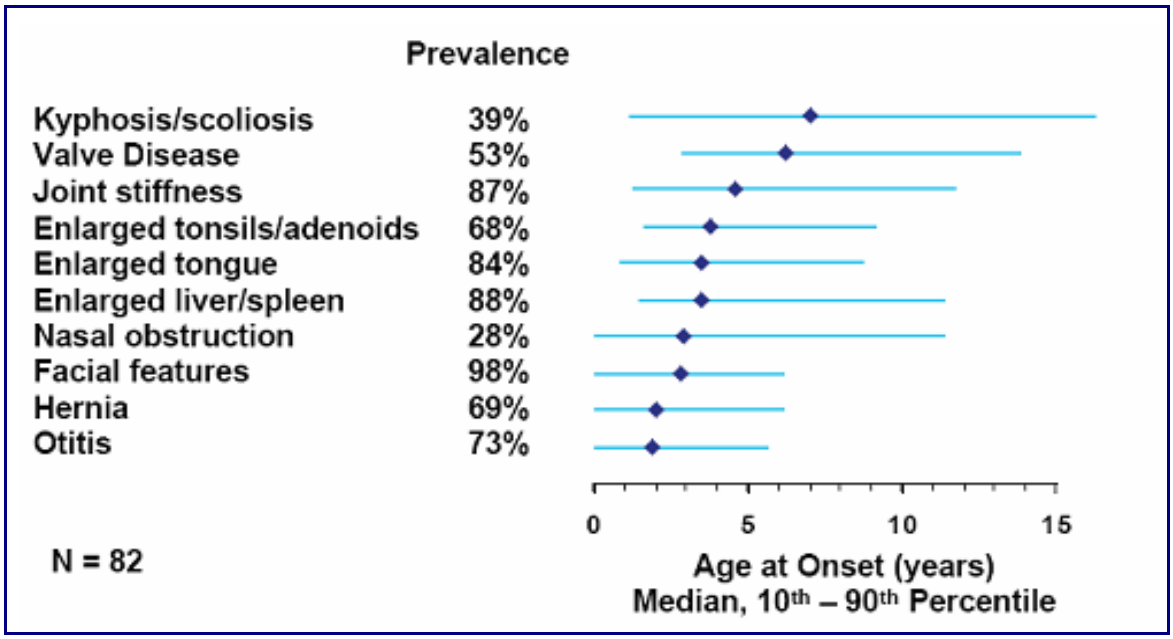
None

References

1. Elaprase®. Summary of Product Characteristics. Shire HGT UK Ltd. January 2007
2. Form A: Initial appraisal information. Shire HGT UK Ltd. May 2007
3. European Public Assessment Report. Elaprase®. January 2007. Available at: http://www.emea.europa.eu (accessed June 2007).
4. Form B: Detailed appraisal information: idursulfase (Elaprase®). Shire HGT UK Ltd. May 2007.
5. Department of Health. Guidelines for the Investigation and Management of Mucopolysaccharidosis type II, February 2007. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_073341 (accessed June 2007)
6. Society for Mucopolysaccharide diseases Available at: http://www.mpssociety.co.uk/incidence.htm (accessed June 2007)
7. MPS Society,UK. Data for mortality based on all MPS society patients registered with the MPS society. Mortality database contains data from 1950 to October 2006.
8. Muenzer J, Wraith JE, Beck M et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 2006; 8(8): 485-73
9. Department of Health. Changes to the portfolio of nationally commissioned services from April 2007. Gateway reference 7600, January 2007. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_064200 (accessed June 2007).
10. Muenzer J, Gucsavas-Calikoglu M, McCandless SE et al. A phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). Molecular Genetics and Metabolism (2006), doi:10.1016/j.ymgme.2006.09.001
11. ATS statement: guidelines for the six-minute walk test. American Journal Respiratory Critical Care Medicine 2002;166:111–7
12. Connock M, Juarez-Garcia A, Frew E. et al. A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1. Health Technology Assessment 2006; 10 (20).

APPENDIX 1. Additional clinical information

Figure 1 **: Prevalence and age at onset of clinical features of MPS II** [4]



Poster presented at 3rd Annual WORLD Symposium 2006 by Beck M et al, Lysosomal Disease Network, December 7-9, 2006 (Orlando, Florida, USA). (The HOS Global Advisory Board).

Table 1**: Summary of changes in secondary outcomes for MPS II (TKT024)** [4]

Endpoint	Mean (Standard error, SE) Adjusted Change from Baseline	Adjusted Mean (SE) Difference Compared to Placebo	p-value[a] (compared to placebo)
Number	32		
Combined liver and spleen Volumes (% change)	-25.8 (1.4)	-26.4 (2.2)	<0.0001
Liver Volume	-25.6 (1.7)	-25.2 (2.2)	<0.0001
Spleen Volume	-25.1 (3.5)	-33.2 (4.8)	<0.0001

[a] p-value based on adjusted mean change from the ANCOVA model (ITT population)

When compared with placebo, weekly idursulfase reduced liver volume from baseline to Week 53 by adjusted means of 25.2% (p<0.0001).

***Table 2*: Summary of selected treatment-emergent adverse events (TKT024)**[4]

Adverse event		Number (%) of Patients		
		Placebo	Idursulfase0.5mg/kg	
		n=32	EOW* n=32	Weekly n=32
Psychiatric Disorders	Anxiety	0	4 (13)	2 (6)
Nervous System Disorders	Headache	14 (44)	21 (66)	19 (59)
Respiratory, Thoracic and Mediastinal Disorders	Nasopharyngitis	15 (47)	19 (59)	17 (53)
Gastrointestinal Disorders	Abdominal Pain	13 (41)	19 (59)	16 (50)
	Dyspepsia	0	4 (13)	4 (13)
Skin and Subcutaneous Tissue Disorders	Pruritus	5 (16)	6 (19)	10 (31)
	Rash Pruritic	0	5 (16)	5 (16)
	Urticaria	0	4 (13)	5 (16)
Musculoskeletal and Connective	Arthralgia	9 (28)	14 (44)	10 (31)
Tissue Disorders	Chest Wall Pain	0	0	4 (13)
General Disorders and Administration Site Conditions	Infusion Site Swelling	1 (3)	4 (13)	4 (13)

*EOW=every other week. This is not the licensed or approved dose.

Note: Patients experiencing pharyngitis and nasopharyngitis or abdominal pain upper and abdominal pain are combined.

APPENDIX 2. Health Economic Review

Company submission - economic evidence

1. Description and critique of company submission

The company submission[3] provides a brief description of a pharmacoeconomic model that was constructed to estimate the incremental cost per QALY of idursulfase versus palliative care. Details of the actual structure of the model are lacking and it is assumed that a simple decision-analytic model was constructed. As the company has not provided the model, verification of the model outputs is not possible. There is no indication that the model, nor any of the assumed inputs, has been externally validated.

2. Population

The model was designed to assess the cost-utility of the long term use of idursulfase in patients with mucopolysaccharidosis II (MPS II). This reflects the licensed indication for idursulfase[2].

The characteristics of the hypothetical patient population are stated to be calculated from the population in the phase II/III trial (TKT024) and a Natural History database (data on file)[4]. The "average" age and weight of patients are calculated as 12.5 years and 33.4kg, respectively, and differ slightly from the values stated in the European Public Assessment Report (EPAR) for trial TKT024 (mean age 14.22 years and mean weight 36.02kg across all 96 patients)[3]. The Natural History database data are not actually presented, are referenced as data on file[4] and cannot be verified.

The patient population in study TKT024 ranged in age from 4.9 to 30.9 years at study entry and all were male[3]. It is likely that the patient population of the TKT024 study adequately reflects the patient population in Wales.

3. Perspective and time horizon

The model considers only the acquisition cost of idursulfase from the perspective of NHS Wales[4]. No consideration is given to any personal and social service costs/resources, which could feasibly be substantial for this patient group.

The base case analysis has a time horizon of 15 years, with the impact of 10 and 20 year time horizons explored in sensitivity analyses. Although the available clinical trial data is limited to three years[4], it is appropriate, when benefits are anticipated to continue beyond that time and /or when medicines increase life expectancy, to select a lifetime horizon.

4. Comparator

Palliative care is the comparator used in the model[4]. This is an appropriate comparator, as there are no other treatments licensed for use and care is typically symptomatic. However, palliative care costs/resources are not considered in the base case analysis (see section 6 Healthcare resource utilisation and cost section).

5. Clinical inputs

None of the clinical inputs of the model for the base case analysis are derived from the clinical trial data for idursulfase. Instead, utility values and mortality data have been obtained /derived from other sources and significant assumptions made in their application.

5.1. Utility values

Study TKT024, the pivotal phase II/III study of idursulfase, employed the Health Utilities Index Mark III (HUI3) questionnaire to estimate utility scores for treatment with idursulfase and placebo (palliative care). At week 1, utility scores were 0.575 and 0.501 for idursulfase and placebo, respectively (a difference of 0.074). The difference in the change in utility score between week 1 and week 53 for idursulfase (+0.064) and placebo (-0.003) was 0.067 [3]. Therefore, it can be seen that 52 weeks of treatment with idursulfase was not associated with an improvement in utility scores as measured by the HUI3.

The company submission states that the change in quality of life is underestimated by the HUI3 measure, as this is a generic questionnaire that may not be suited to MPS II. Therefore, alternative utility values were chosen for use in the base case analysis (0.94 for idursulfase-treated patients and 0.60 for placebo-treated patients). These alternative utility values were obtained from a HTA systematic review of clinical and cost-effectiveness of ERT for Fabry's disease[12].

There are several issues with such use of these alternative utility values. Not only do they relate to a different disease being treated by different agents, they were also stated within the systematic review of ERT for Fabry's disease, rather than being based on actual measured values[12]. In addition, the use of these alternative utility values assumes that patients receiving idursulfase regain immediate full health. The authors of the systematic review from which they were obtained acknowledge that this is unlikely and this assumption would bias the model in favour of ERT[12]

5.2. Mortality estimation

Mortality data on 106 patients with MPS II were obtained from the UK MPS Society database spanning from 1950 to 2006. These were used to generate a mortality curve for untreated patients, fitted with a cubic function which is inappropriate for this purpose as it results in a negative percentage of patients remaining alive at certain time points. It is unclear whether the legend for the abscissa is correct, as it is convention to present time since start of treatment, rather than age.

As treatment experience with idursulfase is limited to three years, mortality data for treated patients is limited. Therefore, a "best guess" for increased survival with idursulfase versus placebo was made. The gradient of the mortality curve for untreated patients was adjusted by three factors (0.4, 0.5, 0.66) to model three scenarios of improved survival with idursulfase. These scaling factors are not based on any evidence, and no justification is provided for their choice other than the middle factor being the "best guess" for use in the base case analysis.

The model implicitly assumes that there will be a survival advantage with idursulfase. After 30 years, approximately 53% of patients remain alive in the idursulfase group, compared with about 5% in the placebo control group. The evidence to support this survival advantage does not exist. A recent DOH update on nationally commissioned services in England highlighted that idursulfase seems to improve the physical condition of patients with MPS II but without preventing the cognitive decline that leads to early death[9]. Therefore, there are obvious issues with these assumptions of improved survival, although the main cause of mortality for Hunter syndrome patients are cardiovascular and pulmonary disease.

5.3. Adverse events

Adverse events are not considered in the economic model.

6. Healthcare resource utilisation and cost

The model considers only the acquisition cost of idursulfase. No consideration is given to the costs/resources associated with administration of idursulfase, which involves weekly intravenous injection (over three hours, at least initially). Further, the base case analysis does not consider palliative care treatment costs/resource use. This may have the effect of biasing the model against idursulfase (as it implicitly assumes that patients receiving idursulfase also consume the exact same resource use as those receiving palliative care, in addition to the costs of idursulfase). However, in the sensitivity analysis, the impact of palliative care costs of £10,000 per year is explored and the model assumes that idursulfase removes the need for any other care. As it is unlikely that idursulfase will remove the need for all forms of palliative care, this would have the effect of biasing the model in favour of idursulfase. No justification is provided for the figure of £10,000 for palliative care costs assumed in the sensitivity analysis.

No consideration is given to any personal and social service costs/resources, which is a limitation of the model as these could feasibly be substantial for this patient group.

7. Discounting

All costs and outcomes were discounted at 3.5% in the base case analysis, which is the preferred discount rate. The impact of discount rates of 0% and 7% were assessed in sensitivity analysis[4].

8. Results

8.1 Base-case

Over a 15 year time horizon, the model estimates the incremental cost per QALY of idursulfase over palliative care to be £564,692 [4]. This is based on (discounted) incremental costs of £3.366million and a gain of 5.962 QALYs per hypothetical patient.

8.2 Sub-group analysis

No sub-group analysis was conducted, and this is not likely to be applicable.

9. Sensitivity analysis

One-way sensitivity analysis has been conducted on the parameters of mortality, discount rate, palliative care resource use, the time horizon and utility values. No probabilistic sensitivity analysis has been attempted.

Given the very high incremental cost per QALY calculated in the base case analysis, the model appears to be relatively insensitive to the range of parameter values explored, with the significant exception of utility values. However, this insensitivity does not imply that the model is robust. Sensitivity analysis around the mortality data is confined to the most optimistic and most pessimistic “best guess” adjustments to a modelled survival curve, with no justification provided for the adjustment made for the base case analysis and no consideration that survival may not be improved versus. palliative care. Also, sensitivity analysis around resource use was explored by assuming a palliative care cost of £10,000 per patient per year without any evidence to support this figure and making no allowance for the likely palliative care costs still required for patients receiving idursulfase.

Besides the assumed survival advantage, the greatest uncertainty in the model relates to the utility values. In the sensitivity analysis, the utility value for idursulfase recipients was set to 0.639 (as estimated at week 53 in study TKT024 using the HUI3 questionnaire) and the utility value for placebo was set to 0.575 (which curiously

appears to be the utility value in patients receiving idursulfase at week 1). This more than doubled the incremental cost per QALY to £1,174,342.

Summary of relevant published economic evidence

No relevant published economic evidence in the treatment of MPS II has been provided by the company or identified by standard literature searches conducted by WMP. A HTA systematic review of the clinical and cost-effectiveness of ERT in patients with MPS I was conducted in 2006 [12]

Company submission - budget impact analysis

1. Description and critique of company submission

The manufacturer's submission includes a budget impact analysis which assessed the likely costs of idursulfase over the next five years. The model is populated with data on the incidence and prevalence of MPS II. Only idursulfase drug costs are included in the analysis [3].

2. Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales, with a five year time horizon. Incidence data for the UK as a whole has been used and the prevalence of MPS II specifically in Wales is thought to be known [4]. There is no reason to suggest that this would not be appropriate data for estimating the incidence and prevalence of MPS II in Wales.

3. Data sources

3.1. Incident cases

Incidence data for the UK has been obtained from the MPS Society, which co-ordinates the European registry of MPS and related diseases [6] and various other sources. Collectively, these relate to incidence rates obtained from 1974–1991. The company submission claims that over a 11 year period 1992–2002, 52 babies with MPS II were born in the UK [4]. This is based on multiplying the average affected male live birth rate by the number of live births during the period. Extrapolating from this data, the company submission estimates that over the next 10 years, there would be 2.5 patients with MPS II expected to be born in Wales, which would be one patient every three or four years [4]. There is some uncertainty in these estimates but, given the generally very low incidence rates of MPS II, these figures are likely to be of the correct order of magnitude.

3.2. Prevalent cases

The company submission states that there are two known patients with MPS II in Wales, which it claims are consistent with previous prevalence estimates in Great Britain [4]. The company appears to have confirmed this with the MPS society.

3.3. Market share

There are no other licensed treatments for MPS II. Market share is not an issue with this product.

3.4. Rates of adoption

Based on the two known patients in Wales and discussions with clinical experts, only one patient is currently expected to be eligible for treatment with idursulfase as the second patient has advanced disease and is not considered suitable for treatment.

However, it is assumed that all subsequent patients would be eligible (from birth) for treatment with idursulfase [4].

3.5. Displaced medicine(s)

There are no other licensed medicines specifically for MPS II. Other medicines are likely to be used in the palliative care of patients, e.g. oxygen therapy. However, data on what palliative care treatments are provided to patients were not presented and it is unclear the extent to which idursulfase may alleviate the need for palliative care treatments. No consideration is given to palliative care in the budget impact model.

4. Results

4.1. Base-case

The budget impact analysis assumes that, in each of the years 2007 to 2011, the number of patients with MPS II will remain constant at two (due to an assumed incidence of one case every four years and one death occurring over the next five years). It assumes that only one patient will be eligible for treatment in 2007 and 2008, but in 2009 this will increase to two patients (due to the death of the one existing patient who is not eligible for treatment and the birth of one new patient who would be eligible for treatment).

The acquisition cost of idursulfase is stated as £1,985 per 6mg vial and the drug is administered at a dose of 0.5mg/kg/week. Based on the claimed average weight of patients obtained from trial and database data (33.4kg), the annual drug cost of idursulfase has been estimated as £309,660 per patient (single use vials only) [1,4].

In each of the years 2007 and 2008, the budget impact is therefore expected to be £309,660 per year (assuming only one patient eligible for treatment). In each of the years 2009 to 2011, the annual drug cost is estimated as £619,320 (assuming two patients are eligible).

This does not take into account the lower body weight of newly diagnosed patients or the possibly increasing body weight of patients as they age.

4.2. Sub-group analysis

No sub-group analysis has been conducted, and this is not likely to be appropriate.

5.0 Sensitivity analysis

No sensitivity analyses have been conducted around any of the assumptions.

Appendix 3

Summary of Medical expert opinion

- The National Specialist Commissioning Advisory Group (NSCAG) has prepared Department of Health (DOH) guidelines for MPS II (Hunter Syndrome). There is no equivalent programme for patients in Wales.

- Cambridge, Manchester and London are all dedicated NSCAG centres. The current LSD service at University Hospital of Wales is likely to play a major role within the near future.

- Enzyme Replacement Therapy (ERT) has led to spectacular advances in this disease area and not using them would be providing sub-optimal treatment.

- NSCAG have proposed the following inclusion criteria:

    1. A documented biochemical diagnosis of MPS II as above.
    2. All patients under the age of five (male and female).
    3. All patients over the age of five should also be offered treatment. However, if there is evidence of progressive and significant cognitive decline by this stage, then it is left to the discretion of the treating clinician, in discussion with the parents, to decide whether it is appropriate to commence treatment

.

- There are only three patients with Hunter's syndrome in Mid and South Wales. Due to their age they are not suitable for ERT but it would be desirable to be able to consider it for new patients.

Appendix 4. Patient Interest Group submission(s) - supplied as a separate document

Appendix 5. Company written response – supplied as a separate document