Intrathecal idursulfase (Elaprase) for Hunter syndrome (mucopolysaccharidosis type II)

LAY SUMMARY

Hunter syndrome is a rare disorder which generally only affects males. It is caused by a deficiency in an enzyme called iduronate-2-sulfatase. This enzyme is essential for breaking down molecules in the body called glycosaminoglycans. These molecules stay stored in cells in the body and cause damage to organs. This can slow mental and physical development.

Intrathecal idursulfase is a new drug for the treatment of Hunter syndrome injected directly into the spinal canal once every month. A different formulation of this drug is already used, and is given as weekly injections into the bloodstream. However, this method of giving idursulfase does not slow the effects of Hunter syndrome on the brain. Some studies have suggested that intrathecal idursulfase may be helpful for patients with mild to moderate disease who have learning and behavioural difficulties.

If intrathecal idursulfase is licensed for use in the UK, it could be a new treatment option for patients with Hunter syndrome who have learning difficulties.

NIHR HSRIC ID: 10241
TARGET GROUP

- Hunter syndrome (mucopolysaccharidosis type II): mild to moderate disease in paediatric patients aged ≤18 years with cognitive impairment – in combination with intravenous (IV) idursulfase.

TECHNOLOGY

DESCRIPTION

Intrathecal idursulfase (idursulfase-IT; Elaprase; recombinant human iduronate-2-sulfatase; GC-1111; HGT2310; I2S; SHP-609) is an enzyme replacement therapy intended for the treatment of Hunter syndrome (mucopolysaccharidosis type II), a disease resulting from the deficiency of the iduronate-2-sulfatase enzyme. Idursulfase-IT is administered as a 10mg intrathecal injection once a month for 52 weeks, in combination with IV idursulfase administered at a dose of 0.5mg/kg once a week.

The IV formulation of idursulfase (as Elaprase) is already licensed in the EU for the treatment of patients with Hunter syndrome. Very common (>10%) adverse reactions reported include headache, hypertension, flushing, wheezing, dyspnoea, abdominal pain, nausea, dyspepsia, diarrhoea, vomiting, urticaria, rash, pruritus, pyrexia, chest pain, infusion site swelling and infusion-related reactions.

INNOVATION and/or ADVANTAGES

If licensed, intrathecal idursulfase will offer an additional long-term treatment option for paediatric patients with Hunter syndrome who have cognitive impairment.

DEVELOPER

Shire Pharmaceutical Contracts Ltd.

AVAILABILITY, LAUNCH OR MARKETING

The IV formulation of idursulfase is a designated orphan drug in the EU and USA.

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Hunter syndrome, or mucopolysaccharidosis type II (MPSII), is a rare, X-linked recessive disorder caused by a deficiency of the lysosomal enzyme iduronate-2-sulfatase, which catalyses a step in the catabolism of glycosaminoglycans. Incomplete breakdown of glycosaminoglycans leads to progressive accumulation of these substances in many tissues throughout the body, affecting multiple organs and physiological systems.

The clinical manifestations of Hunter syndrome vary considerably from patient to patient and there is a broad range of clinical severity and phenotypical involvement. Severely affected
patients have profound neurological involvement, with progressive learning difficulties and behavioural abnormalities, as well as disturbed motor function. In patients with central nervous system (CNS) involvement, disease progression is usually more predictable than in patients without CNS involvement. Onset typically occurs between 2 to 4 years of age, but in severe disease signs are often obvious in the first 12-15 months of life. Cognitive development plateau is usually evident by the second year of life. The most commonly reported symptoms of severe disease are accelerated growth, enlarged liver and spleen, ear, nose and throat problems, deafness, and hernia. An earlier appearance of clinical symptoms generally, but not always, predicts a more severe clinical course. The average age of diagnosis of patients with Hunter syndrome with progressive CNS involvement is 2 years and 2 months of age.

The most common general clinical signs and symptoms of Hunter syndrome include slow mental development, enlarged tongue, coarse facial features, hearing loss, abnormal dentition, restrictive lung disease, valvular heart disease, decreased joint range of motion, skeletal deformities, and severe short stature. In the attenuated form of Hunter disease, currently treated with IV enzyme replacement therapy, there is much more variability of height and physical disease progression; life expectancy can be up to 50-60 years of age. In this cohort of patients normal cognitive ability is usual.

Expert opinion suggests that approximately 50-60% of patients with Hunter Syndrome have progressive neurological involvement. A recent survey of 41 patients with Hunter syndrome showed 25 had confirmed progressive CNS involvement. In patients with CNS involvement, epileptic seizures are common and death usually occurs in the second decade of life. The average age of death is 13 years of age.

Approximately 320 mutations of the causative gene, IDS, have been reported. It is seen almost exclusively in boys, but rare sporadic cases in females do occur. In the UK, four females have been diagnosed with Hunter syndrome in the past 20 years.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

Except in very rare cases, only males are affected by Hunter syndrome. The incidence of Hunter syndrome in Europe is estimated to be 1 in 100,000 male births. Over a 10 year period, between 1992 and 2002, 52 babies with Hunter syndrome were born in the UK.

Expert opinion suggests that 50-60% of patients with Hunter syndrome have progressive CNS disease and could therefore be eligible to receive treatment with intrathecal idursulfase.

---

a Patient group personal communication.
b Expert personal communication.
However a proportion of existing patients would not receive this therapy as the disease will have progressed too far for it to be of benefit\(^c\).

The impact of caring for a child with Hunter syndrome with progressive CNS involvement is hugely significant due to the lack of therapies available to address the neurological symptoms\(^d\). Research has suggested that children with CNS involvement require educational support by the age of 3-4 years\(^d\). Of the 19 of the 25 children over the age of 5 years with confirmed progressive CNS involvement, 10 are currently in special education and nine are currently in special educational units within mainstream schools or require 1:1 assistance\(^d\).

**PATIENT PATHWAY**

### RELEVANT GUIDANCE

**NICE Guidance**
- No relevant guidance identified.

**Other Guidance**
- OrphaNet. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. 2011\(^5\).

**CURRENT TREATMENT OPTIONS**

Until recently, the management of patients with Hunter syndrome was largely supportive, focusing on the treatment of signs and symptoms rather than addressing the underlying lysosomal enzyme deficiency\(^5\). Management requires a multidisciplinary approach, and patients require access to ENT\(^e\), respiratory, neurology and cardiology specialists, as well as physiotherapists, ophthalmologists and audiologists\(^5\). In severe neurologically impaired patients, management may include anticonvulsants and behaviour modifying medications\(^6\).

Enzyme replacement therapy with recombinant iduronate-2-sulfatase is now commonly used to treat patients with Hunter syndrome. Idursulfase (as Elaprase) is licensed in the EU for the long-term treatment of patients with Hunter syndrome\(^1\). However, as a large molecular protein, idursulfase is not expected to cross the blood brain barrier at therapeutic levels when administered intravenously\(^1\). It therefore is not thought to slow the progression of cognitive impairment in patients with CNS involvement\(^1\).

Alternatives such as stem cell transplantation using umbilical cord blood, peripheral blood haematopoietic cells or bone marrow have also been used, but they appear to offer limited clinical benefits in patients with this disease and have been associated with a serious risk of morbidity and mortality\(^5\). In the past three years in the UK, four patients diagnosed as infants with Hunter syndrome with CNS involvement have undergone haematopoietic stem cell transplantation\(^2\). Three of these patients were successfully transplanted and anecdotal evidence suggests the children are making progress cognitively\(^d\).

\(^c\) Expert personal communication.
\(^d\) Patient group personal communication.
\(^e\) Ear, nose and throat.
There is currently no new-born screening programme for Hunter disease, however early diagnosis is pivotal to optimum treatment outcomes particularly in patients with CNS involvement as neurological damage cannot be reversed. It has therefore been suggested that diagnosis remains the key gap in current care and services provisions.

### Efficacy and Safety

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Shire.</td>
<td>Shire.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
<td>Trial registry, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada, and other countries.</td>
<td>EU (incl UK), USA, Canada, and other countries.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=48 (planned); males; aged ≤18 yrs; Hunter syndrome; evidence of Hunter syndrome-related cognitive impairment; received and tolerated ≥4 mths of IV Elaprase; sufficient auditory capacity; no significant non-Hunter syndrome-related CNS involvement; no large chromosomal deletion or complex rearrangement that includes a deletion of the FMR1 and/or FMR2 genes; no significant medical or psychiatric comorbidities; no contraindications for performance of lumbar puncture such as musculoskeletal/spinal abnormalities or risk of abnormal bleeding; no history of complications from previous lumbar punctures; no opening CSF pressure upon lumbar puncture that exceeds 30.0cm H2O; no previously experienced infusion-related anaphylactoid event(s) or evidence of consistent severe adverse events (AEs) related to treatment with Elaprase; no history of poorly controlled seizure disorder.</td>
<td>n=42 (planned); males; aged ≤18 yrs; patients who have completed study HGT-HIT-094 and continued to receive Elaprase on a regular basis; no known hypersensitivity to any components of idursulfase-IT; no clinically relevant intracranial hypertension; no known or suspected hypersensitivity to anaesthesia; no condition that is contraindicated as described in the SOPH-A-PORT Mini S intrathecal drug delivery device instructions for use.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to idursulfase-IT 10mg intrathecal injection once every 28 days for 52 weeks in combination with IV Elaprase once per week; or standard of care treatment with IV Elaprase only once per week.</td>
<td>Idursulfase-IT 10mg intrathecal injection once every 28 days; in combination with IV Elaprase once per week.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 52 weeks.</td>
<td>Active treatment and follow-up 148 weeks.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Change from baseline in General Conceptual Ability score.</td>
<td>Change in physical and neurological examination, height and weight, head circumference, auditory capacity, vital signs and ECG recordings; pharmacokinetics; AEs.</td>
</tr>
</tbody>
</table>

\(^1\) Patient group personal communication.
<table>
<thead>
<tr>
<th><strong>Secondary outcomes</strong></th>
<th>Change from baseline in adaptive behaviour composite score, Adaptive Behaviour Composite score obtained by VABS-II testing, standard scores obtained by DAS-II testing, age equivalents, V-scale scores and observed maladaptive levels of the VABS-II Maladaptive Behaviour Index.</th>
<th>Change from baseline in cluster areas of Differential Ability Scales-II (DAS-II) score, Vineland Adaptive Behaviour Scales-II (VABS-II) domains, T-scores of DAS-II, maladaptive levels of the VABS-II Maladaptive Behaviours Index; brain structure volume.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expected reporting date</strong></td>
<td>Study completion date reported as Sept 2017.</td>
<td>Study completion date reported as June 2019.</td>
</tr>
<tr>
<td><strong>Trial</strong></td>
<td>NCT00920647, 2010-020048-36, HGT-HIT-045; idursulfase-IT vs no treatment; phase I/II.</td>
<td>NCT01506141, 2011-000212-25, HGT-HIT-046; idursulfase-IT; phase I/II extension.</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>Shire.</td>
<td>Shire.</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Published.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td><strong>Source of information</strong></td>
<td>Publication ³, trial registry ⁴, manufacturer.</td>
<td>Trials registry ⁵, manufacturer.</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>EU (incl UK) and USA.</td>
<td>EU (incl UK) and USA.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>n=16; aged 3-18 yrs; males; iduronate-2-sulfatase enzyme activity ≤10% the lower limit of the normal range; and a documented mutation in the iduronate-2-sulfatase gene, or a normal enzyme activity level of one other sulfatase; an intelligent quotient (IQ) ≤77; no significant non-Hunter syndrome-related CNS involvement; patient or patient’s family has no history of neuroleptic malignant syndrome, malignant hyperthermia, or other anaesthesia-related concerns.</td>
<td>n=20 (planned); aged 3-18 yrs; males; patient completed all study requirements and assessments for study HGT-HIT-045; patients received and tolerated ≥12 mths of treatment with weekly IV infusions of Elaprase; no adverse reaction to study drug in HGT-HIT-045 that contraindicates further treatment.</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>Randomised to idursulfase-IT once per month at 1mg, 10mg, or 30mg in combination with IV Elaprase once per week; or standard of care treatment with IV Elaprase only once per week.</td>
<td>Idursulfase-IT administered once every 28 days, continued at the dose used in study HGT-HIT-045.</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Active treatment for 6 months, follow-up 6 months.</td>
<td>Active treatment for 30 months.</td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td>Number of serious AEs; number of treatment emergent AEs; clinically significant ECG findings.</td>
<td>Type and severity of AEs; clinically significant ECG findings.</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td>Pharmacokinetics.</td>
<td>Pharmacokinetics.</td>
</tr>
<tr>
<td><strong>Key results</strong></td>
<td>At 6 months, mean cerebrospinal fluid glycosaminoglycan concentration was reduced by approximately 90% in the 10mg and 30mg groups, and by approximately 80% in the 1mg group.</td>
<td>-</td>
</tr>
<tr>
<td><strong>Adverse effects (AEs)</strong></td>
<td>Most treatment emergent AEs were mild to moderate (grades 1-2) in severity. 14 serious AEs were experienced by 7 of 12 (58.3%) treated patients. All serious AEs were so designated because hospitalisation was required.</td>
<td>-</td>
</tr>
</tbody>
</table>
Expected reporting date - Study completion date reported as Nov 2021.

ESTIMATED COST and IMPACT

COST

The IV formulation of idursulfase (as Elaprase) is already marketed in the UK for the treatment of patients with Hunter syndrome: a 3mL vial (2mg/mL) costs £1,985.0016.

IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other
- No impact identified

Impact on Health and Social Care Services
- Increased use of existing services: monthly intrathecal administrations. Expert opinion states that while IV weekly idursulfase infusions are given to patients at home by a nurse, there is no current system in place for intrathecal therapy to be delivered this way9.
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs: monthly intrathecal injections potentially requiring hospital attendance and anaesthesia.
- Other reduction in costs: if successful in slowing the progression of neurological involvement.
- Other
- None identified

Other Issues
- Clinical uncertainty or other research question identified
- None identified

REFERENCES


9 Expert personal communication.


