



**Clinical Commissioning Policy:  
Elosulfase alphafor  
Mucopolysaccharidosis IV Type A**

Reference: NHS England xxx/x/x

# **Clinical Commissioning Policy: Elosulfase alpha for Mucopolysaccharidosis IV Type A**

**Prepared by NHS England Specialised Services Clinical Reference Group for Metabolic Disorders**

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## **Policy Statement**

NHS England will commission in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

## **Equality Statement**

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

## **Plain Language Summary**

Mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA) is an ultra-rare, severely debilitating, multiple organ and tissue inherited lysosomal storage disorder, which progressively leads to significant morbidities and multisystem clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality.

Elosulfase alfa is the only enzyme replacement treatment option for MPS IVA patients. It is a form of the enzyme deficient in MPS IVA patients, and is identical to the naturally occurring human enzyme.

The efficacy of elosulfase alfa in patients with MPS IVA has been studied in an extensive clinical development program consisting of over 250 patients across multiple countries.

## 1. Introduction

Mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA) is an ultra-rare, severely debilitating, multiple organ and tissue inherited lysosomal storage disorder, which progressively leads to significant morbidities and multisystem clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality (Harmatz et al. 2013, Bank et al. 2009).

To date over 185 mutations in the GALNS gene causing MPS IVA have been identified. Because of the large number of mutations that can cause MPS IVA, clinical manifestations of the disease are heterogeneous. Clinical presentations of the disease range from a rapidly progressing phenotype to a slowly progressing phenotype. Onset of disease symptoms commonly occurs prior to 1 year of age in rapidly progressing patients or as late as the second decade of life in slowly progressing patients (Montaño et al. 2007).

UK Standard operating procedures on the management of MPS IVA recommends that affected individuals should be managed by a multidisciplinary team of health care providers with oversight provided by a geneticist or metabolic specialist experienced in the treatment of patients with lysosomal storage disorders. Regular comprehensive assessments are also recommended, with the frequency tailored to meet the individual needs of each patient.

Elosulfase alfa at a proposed marketed dose of 2.0 mg/kg/week is the only enzyme replacement treatment option for MPS IVA patients. It is a recombinant form of human N-acetylgalactosamine-6-sulfatase (rhGALNS) enzyme deficient in MPS IVA patients, and is identical to the naturally occurring human enzyme in terms of the amino acid sequence and N-linked glycosylation.

The efficacy of elosulfase alfa in patients with MPS IVA has been studied in an extensive clinical development program consisting of 7 clinical trials with over 250 patients across multiple countries.

## 2. Definitions

**Mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA)** is an ultra-rare, severely debilitating, multiple organ and tissue inherited lysosomal storage disorder, which progressively leads to significant morbidities and multisystem clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality

**Elosulfase alpha** is a recombinant form of human N-acetylgalactosamine-6-sulfatase (rhGALNS) enzyme deficient in MPS IVA patients, and is identical to the naturally occurring human enzyme in terms of the amino acid sequence and N-linked glycosylation.

## 3. Aim and objectives

This policy aims to set out the conditions under which patients with MPS IVA will receive treatment with Elosulfase alpha

The objectives are to:

- Establish the background to the policy

- Set out the clinical evidence that supports the policy
- Set out the criteria under which patients with MPS IVA will be treated with Elosulfase alpha
- Set out the expected outcomes for patients with MPS IVA being treated with Elosulfase alpha
- Set out the circumstances under which treatment with Elosulfase alpha will be stopped.

#### 4. Epidemiology and needs assessment

Using available U.S. incidence figures (1 in 200,000 to 1 in 300,000 live births), and based on an annual birth rate of approximately 695,000 live births per year in England (ONS, 2012), an estimate for the incidence of MPS IVA in England, would be approximately 2 - 4 births each year. Based on an approximate average lifespan of 25 years for MPS IVA patients (Lavery and Hendriksz 2014, in publication), the calculated prevalence of MPS IVA in England would be approximately 50 -100 patients which is in line with the number of patients currently identified in England (87 patients).

Current patient numbers across England are 87 (as identified by MPS Society and centres treating patients with MPS IVA). On average, 3 children are diagnosed per annum and 1 person dies, so it is anticipated that patient numbers will steadily increase.

Baseline data collected from more than 350 subjects with MPS IVA enrolled in a prospective natural history study (MorCAP) in 10 countries representing about 10% of the global population showed that very few MPS IVA patients survive beyond forty years and recent analysis of the death certificates from every known MPS IVA patient in the UK who died between 1975 and 2010, showed the mean age at death ( $\pm$  standard deviation) was  $25.30 \pm 17.43$  years, with respiratory failure the primary cause of death in nearly two-thirds of patients (63%).

All patients suffer a range of serious and debilitating morbidities across multiple domains including respiratory function, cardiac function, endurance, growth and neurological impairments. The most common clinical features of patients with MPS IVA are progressive skeletal dysplasia, motor dysfunction, short stature, frequent surgical procedures mostly related to musculoskeletal impairments, and a significant limitation in mobility, endurance, and respiratory function (Montano, 2007b Harmatz P, 2013). Additional symptoms include hearing loss, cataracts, corneal clouding, and dental abnormalities. (Milkes, 1997).

Patients with MPS IVA often require multiple surgeries throughout their lifetime. General anesthesia can also be problematic due to compromised respiratory function and cardiac abnormalities.

MPS IVA patients often report severe limitations in daily living activities. Such as washing, making a bed, and pouring liquids into a glass. Of patients in the MorCAP study, 41% could not cut their fingernails, 31% were unable to tie a shoelace, 22% could not tuck in shirts, and 22% were unable to open a jar (Harmatz, 2013).

Many patients with MPS IVA require the use of a wheelchair and other mobility aids by their early teen years. Use of a wheelchair greatly reduces their quality of life with

wheelchair-bound users reporting a Health-Related Quality of Life score just slightly above death (Orme, 2007; Kobelt, 2005 & 2006).

There is currently no standard treatment for MPS IVA. Supportive care includes both medications and surgical interventions. Nonsteroidal anti-inflammatory drugs have been administered for joint pain, antibiotics for pulmonary infection, and oxygen supplementation and CPAP/BiPAP for pulmonary compromise and obstructive sleep apnoea.

## 5. Evidence base

### Clinical trials

A multinational clinical development program was designed to examine outcomes across the full spectrum of age and disease severity in the diverse MPS IVA patient population, and to assess the efficacy and safety of Elosulfase alfa in this population. In addition to the longitudinal natural history study (MorCAP) discussed above, the clinical development program for Elosulfase alfa included 7 studies (2 completed studies - none of the studies are published and 5 on-going) involving 235 patients and representing the largest pre-license clinical trial program ever undertaken for an enzyme replacement therapy. The clinical studies are:

- The pivotal placebo-controlled Phase 3 study (MOR-004), plus its extension (MOR-005)
- The initial Phase 1/2 study (MOR-002), plus its extension (MOR-100)
- Three on-going Phase 2 studies (MOR-006, MOR-007, MOR-008) aimed at investigating the efficacy of Elosulfase alfa 2.0mg/kg/week in the following subgroup of patients:
  - i. MOR-006: limited ambulation patients (6MWT < 30m);
  - ii. MOR-007: children < 5 years of age at time of first infusion; and
  - iii. MOR-008: versus Elosulfase alfa 4.0mg/kg/week in patients  $\geq 7$  years of age with 6MWT  $\geq 200$ m respectively.

Data from five of these studies are included in this report. MOR-006 and MOR-008 was not included because of on-going enrolment and very limited subject exposure at the data cut-off time point.

#### MOR-004/005

The pivotal clinical trial was the largest lysosomal storage disorder Phase 3 trial conducted to date. It was a randomised, double-blind, placebo-controlled, multinational study (MOR-004) with 176 patients with MPS IVA. It compared the effects of 24 weeks of intravenous infusions of Elosulfase alfa at a dose of 2.0 mg/kg weekly (2.0mg/g/week) or every other week (2.0mg/kg/qow) versus placebo in patients ranging from 5 to 57 years of age. Patients who completed participation in MOR-004 were eligible to enroll into the extension study (MOR-005) aimed at evaluating the long-term efficacy and safety of Elosulfase alfa for up to 240 weeks. There was no placebo group in this study.

The Elosulfase alfa 2.0 mg/kg/week dosing regimen demonstrated a statistically significant improvement at Week 24 in the 6 minute walk test (6MWT) compared with placebo. The modelled treatment effect versus placebo was 22.5 meters (95%

confidence interval [CI95], 4.0, 40.9;  $p=0.0174$ ). There was a 23.7 meter mean improvement in 6MWT at Week 12 in the weekly dosing regimen, with further improvement of a 36.5 meter mean change from baseline, at Week 24. The 2.0 mg/kg/qow regimen resulted in 6MWT distances comparable to placebo, with a Week 24 estimated treatment effect versus placebo of 0.5 m (CI95, -17.8, 18.9;  $P=0.9542$ ) (Figure 13).

Furthermore, additional efficacy findings from MOR004 showed numerical improvement across nearly all secondary and tertiary endpoints captured in the trial.

- 3 minute stair climb test (3MSCT) – Elosulfase alfa treated patients showed numerically greater performance compared to the placebo group but not statistically significant.
- Urinary Keratin Sulfate (urine KS) results – treatment with Elosulfase alfa led to a rapid and sustained reduction of urine KS in both treatment arms compared to placebo.
- Pulmonary Function Test. The Elosulfase alfa 2.0 mg/kg/week dosing regimen demonstrated improvement in the maximum voluntary ventilation (MVV) percentage change from baseline versus placebo at Week 24, with a trend toward statistical significance
- Anthropometric Results - for both Elosulfase alfa dosing regimens trended toward improvement in normalized standing height and growth rate z-scores in males  $\leq 18$  years and females  $\leq 15$  years at week 24. These findings suggest that Elosulfase alfa may slow the progressive negative deviation from normal growth rates and normal standing height in patients with MPS IVA who are still growing. However, the relatively short duration of the study (24 weeks) made it difficult to see statistically significant changes in anthropometric measure
- Activities of daily living results. Elosulfase alfa treatment was associated with a reduction in the extent of caregiver assistance and an improvement in mobility skills (dexterity, mobility, walking, stair climbing, and gross motor skills). Impact of treatment on activities of daily living was captured using the MPS health assessment questionnaire (HAQ) which assesses three domains: self-care (eating/drinking, dressing, bathing, grooming, tooth brushing, and toileting); mobility skills (dexterity, mobility, walking, stair climbing, and gross motor skills); and the extent of required caregiver assistance in the performance of these activities.
- Wheelchair use. None of the study's participants used a wheelchair at the beginning of the study. By week 24, 9% of the placebo group were using wheelchairs (as expected due to the progressive nature of MPS IVA) compared to none in both of the Elosulfase alfa groups. The lack of a similar increase in wheelchair use amongst subjects on active treatment is notable and may be clinically relevant in light of the progressive nature of MPS IVA.

In order to provide an overall test of the treatment effect a pre-specified O'Brien rank sum test of significance was performed on the clinical and functional endpoints captured in MOR-004. The cumulative improvement across all outcomes for Elosulfase treated patients was statistically significant when compared to placebo treated patients.



## MOR 005 results

72 week results from the ongoing open-label Phase 3 extension study (MOR-005) showed that improvements observed in MOR-004 were sustained.

- Patients treated with Elosulfase alfa 2.0mg/kg/week experienced stable and sustained improvements in 6MWT and 3MSCT, as well as sustained reduction in the pharmacologic marker of urinary KS
- Wheelchair use. Reported use of wheelchairs by patients treated with Elosulfase alfa after 72 weeks was better when compared to untreated natural history patient after 52 weeks follow-up. These results suggest that Elosulfase alfa reduces disease progression and improvements in endurance would translate into reduced wheelchair reliance leading to potential increases in patients quality of life and greater independence.
- Orthopaedic surgery results. During Study MOR-005, when surgical procedures were allowed, there have been fewer orthopedic surgeries in subjects receiving continuous weekly infusions of Elosulfase alfa from the beginning of study MOR-004 compared to subjects randomized to the placebo group in MOR-004. Additionally, subjects in the placebo group had surgeries earlier in the course of MOR-005 than the weekly dosed Elosulfase alfa subjects, including some procedures that occurred during MOR-004, indicating possible urgency for some interventions (planned major surgery during the 24-week treatment period was an exclusion criterion for MOR-004). These data suggest that Elosulfase alfa treatment may reduce or delay the need for orthopedic surgeries in patients with MPS IVA.

## Phase 1/2 Dose Exploration Trial: MOR-002 and Extension MOR-100

The MOR-002/100 Phase 1/2 clinical study examined the safety, PK, and efficacy of weekly infusions of ascending doses of Elosulfase alfa in 20 patients aged 5-18 years old with MPS IVA. The aim of the study was to find the optimal dose of Elosulfase alfa. This study was performed entirely in the United Kingdom.

Elosulfase alfa was given every 12 weeks at 3 dose levels (0.1 mg/kg/week [Weeks 1-12], 1.0 mg/kg/week [Weeks 13-24], and 2.0 mg/kg/week [Weeks 25-36]). Key efficacy measures included 6MWT, 3MSCT, and respiratory function tests (FVC and MVV). Pharmacokinetic, pharmacodynamic (urine KS), and safety (adverse events [AEs], antibody response) profiles were also assessed.

- 6MWT and 3MSCT results. The 6MWT distance increased at Weeks 24 and 36 of the Dose-Escalation Period in conjunction with increasing dose of Elosulfase alfa, with the initial increase coming 12 weeks after the dose was changed from 0.1 mg/kg/week to 1 mg/kg/week and concomitant with the increase in dose to 2.0 mg/kg/week. After decreasing the dose in the Continuation Period, the mean change from Baseline at Week 72 was 4.0 meters

Similarly the 3MSCT mean stair climb rate minimally changed from Baseline at end of Week 12, then increased by 6.1 stairs/min at the end of Week 24, and then by 7.8 stairs/min at the end of Week 36. After decreasing the dose in the Continuation Period, the mean change from Baseline at Week 72 was 9.7 stairs/min.

- Pulmonary function test results. Respiratory function test (RFT) means increased

from Baseline during the 36-week Dose-Escalation Period, with continued increase through the Continuation Period (Week 72).

- Anthropometric results. Mean anthropometric measurements at Week 72 all increased from Baseline: length by 5.3 cm; sitting and standing height by 2.3 cm; right knee mean height by 1.5 cm and left knee mean height by 1.7 cm; and weight by 2.6 kg.

MOR-100 is an ongoing open-label extension study that is designed to evaluate the long-term efficacy and safety of elosulfase alfa. Patients who completed participation in study MOR-002 were eligible to enroll and receive elosulfase alfa at a dose of 2.0 mg/kg/week. In addition to assessments of long-term safety and efficacy, the study is evaluating changes in biochemical markers of inflammation and bone and cartilage metabolism. 17 patients took part in this study.

Patients in MOR-100 were no longer restricted from surgical procedures (as they were in MOR-002) and results need to be considered within the possible impact of surgical procedures on efficacy measures.

- 6MWT and 3MSCT. Improvements in results from the MOR-002 study were seen at weeks 12, 24, 36, 48 and 60. 6 subjects had reportable data at 84 weeks and also showed improvement. Similar results were seen in the 3MSCT. A decline was seen at week 72, prior to which 4 patients underwent orthopaedic surgery.
- Pulmonary function test results. After 72 weeks of treatment in the MOR-100 extension, forced vital capacity (FVC) showed continuing improvement, with a mean 15.8% increase from baseline.

#### MOR-007 Clinical Trial (Paediatric Children < 5 years)

MOR-007 is an ongoing Phase 2, open-label, multinational study to evaluate the safety and efficacy of BMN 110 in paediatric subjects less than 5 years of age with MPS IVA. In addition to safety and tolerability, normalized urine KS, anthropometric measurements, and other characteristics of MPS IVA are evaluated in this young population.

Enrolled patients are receiving 52 weeks of intravenous infusions of Elosulfase alfa at a dose of 2.0 mg/kg/week. After the primary treatment phase, patients will continue into the extension treatment phase for up to an additional 156 weeks of dosing plus 1 week of final assessments (up to a total of 209 weeks in the study).

As of the last data cut-off, 15 patients (0.8 – 4.9 years of age) had been enrolled into the trial. The mean ( $\pm$ SD) total duration of Elosulfase alfa exposure of these patients was 24.8 ( $\pm$ 9.12) weeks (range, 8 44 weeks).

- Urine KS results. As in other studies, in subjects who completed Week 26 (n=8), treatment with Elosulfase alfa (2.0mg/kg/week) led to sustained reductions in urine KS.
- Anthropometric results. Anthropometric increases were also seen in children under 5 years old in MOR-007. Treatment with Elosulfase alfa (2.0mg/kg/week) over 26 weeks resulted in an increase in mean standing height from Baseline to Week 26 by and an increase in mean body length from Baseline to Week 26. Although there is no control group for comparison, data from the literature suggest that these children experience growth failure in early childhood; thus it is

possible these subjects would have fallen even further below normal without intervention (Harmatz P, 2013, Montano, 2007b).

## **Safety**

In the clinical development program a total of 235 subjects were exposed to Elosulfase alfa across 6 clinical studies at doses of 0.1, 1.0, 2.0, or 4.0 mg/kg/week or 2.0 mg/kg every other week. Subjects were exposed for up to 169.7 weeks of continuous treatment (overall mean [SD] duration of exposure was 50.2 [ $\pm$ 37.03] weeks and included subjects between the ages of 0.8 and 57.4 years. A total of 222 subjects were exposed to Elosulfase alfa at the proposed dose of 2.0 mg/kg/week. Patients were administered antihistamine approximately 30 to 60 minutes before each study drug infusion to mitigate the risk for potential hypersensitivity reactions associated with the administration of Elosulfase alfa.

Adverse events experienced by patients were mostly mild to moderate, the most common of which were associated with infusions and included vomiting, pyrexia, and headache.

171 (77%) subjects receiving Elosulfase alfa at the proposed dose experienced an adverse event. The incidence of these events generally decreased with increasing duration of treatment. 71.2% of subjects receiving Elosulfase alfa at the proposed dose experienced at least one infusion-associated reaction (IAR), defined broadly as all adverse events that occurred within 1 day after infusion onset or infusion end depending on the clinical trial.

As of date, only 1 subject in the clinical program has permanently discontinued treatment due to an adverse event, and no deaths have occurred, and all of the patients with IAR went on to receive subsequent infusions.

Serious adverse events (SAEs) occurred infrequently and were reported in 17.6% of subjects receiving Elosulfase at the proposed dose of 2.0mg/kg/ week and generally consisted of MPS IVA-related symptoms and associated necessary medical/surgical procedures.

Hypersensitivity adverse events occurred in 64 (27.2%) of patients exposed to Elosulfase alfa (at any dose) and the rate of recurrence were infrequent. Of the patients receiving Elosulfase at the proposed dose of 2.0mg/kg/ week 36 (16.2%) subjects had hypersensitivity adverse events, of which 16 cases were consistent with NIAID/FAAN 2006 criteria for anaphylaxis (Sampson H et al, 2006). These reactions were successfully managed with infusion rate adjustments and/or medical intervention, and all but 2 subjects continue to receive subsequent Elosulfase alfa infusions. This rate of anaphylaxis is comparable to other enzyme replacement therapies.

The overall safety data reveal an acceptable safety profile consistent with other approved enzyme replacement therapies. Safety analyses over time show that short-term and long-term treatment with Elosulfase is well tolerated. Evaluation of safety data by duration of treatment showed that the subject-year adjusted incidence of adverse events (AEs) decreased over time

## **6. Rationale behind the policy statement**

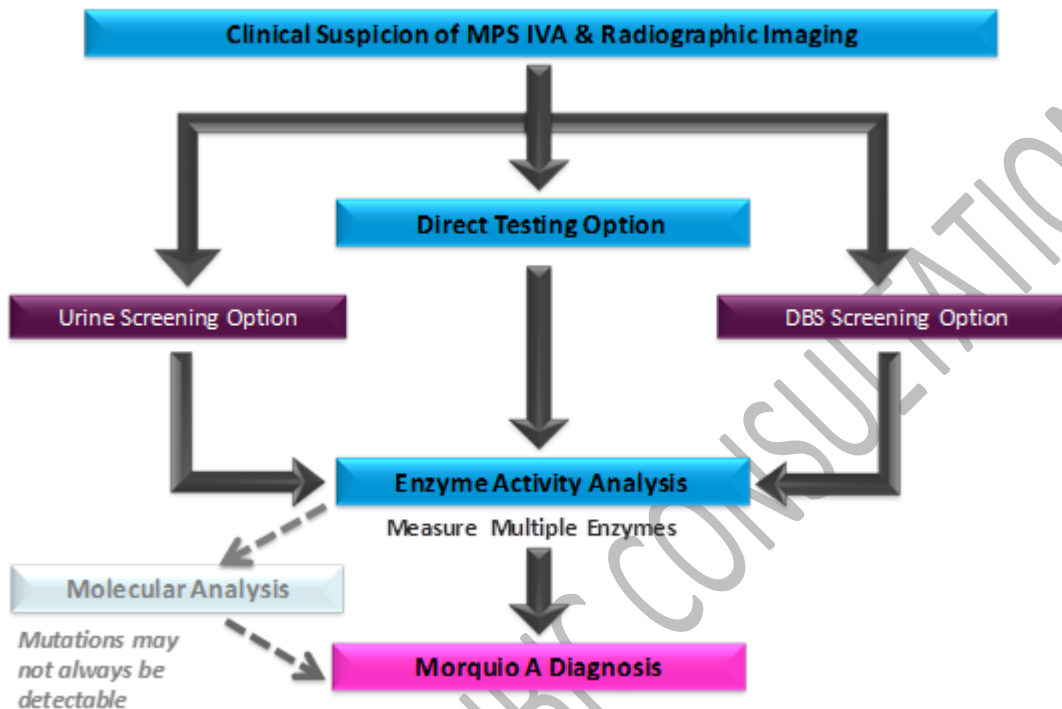
The policy sets out the criteria under which patients with MPS IVA will be treated

with Elosulfase alpha and the criteria for stopping treatment.

## 7. Criteria for commissioning

### Patient Criteria:

All patients with a confirmed diagnosis of MPS IVA following Enzyme Activity Testing and/or molecular testing following the pathway below.



All patients with a confirmed diagnosis of MPS IVA will be offered Elosulfase. In addition, as the dosage is based on a patient's weight, as the children receiving Elosulfase grow, the dosage will increase.

It is anticipated that not all patients will take up the offer of Elosulfase. 35 patients were on the clinical trial and it is understood that all will continue.

### Exclusion criteria:

- Patients without a confirmed diagnosis of MPS IVA
- Patients who would not benefit
  - Clinically determined (other disease processes)
  - Discussed with patient
- Patients to whom therapy would present too high risk
  - Other significant disease
  - Previous exposure to Elosulfase resulting in significant severe adverse reaction

**Patient pathway and administration:**

**Dosing regimen:** All patients will be on a dosing regimen of 2mg/kg per week as this was shown to be the most effective during clinical trials.

**Administration:** Administration of Elosulfase will be through infusion. The first 12 infusions will take place in a hospital setting and then providing safe and clinically appropriate, it is expected that infusion will be delivered through homecare.

Some patients will need to receive their infusion in a hospital setting after 12 weeks. Some patients may request to continue to have their infusion in a hospital setting and this will be discussed with their consultant with a view to the preferred option being homecare.

Some patients may require TIVAD insertion (standard for most paediatric patients) to enable long-term administration.

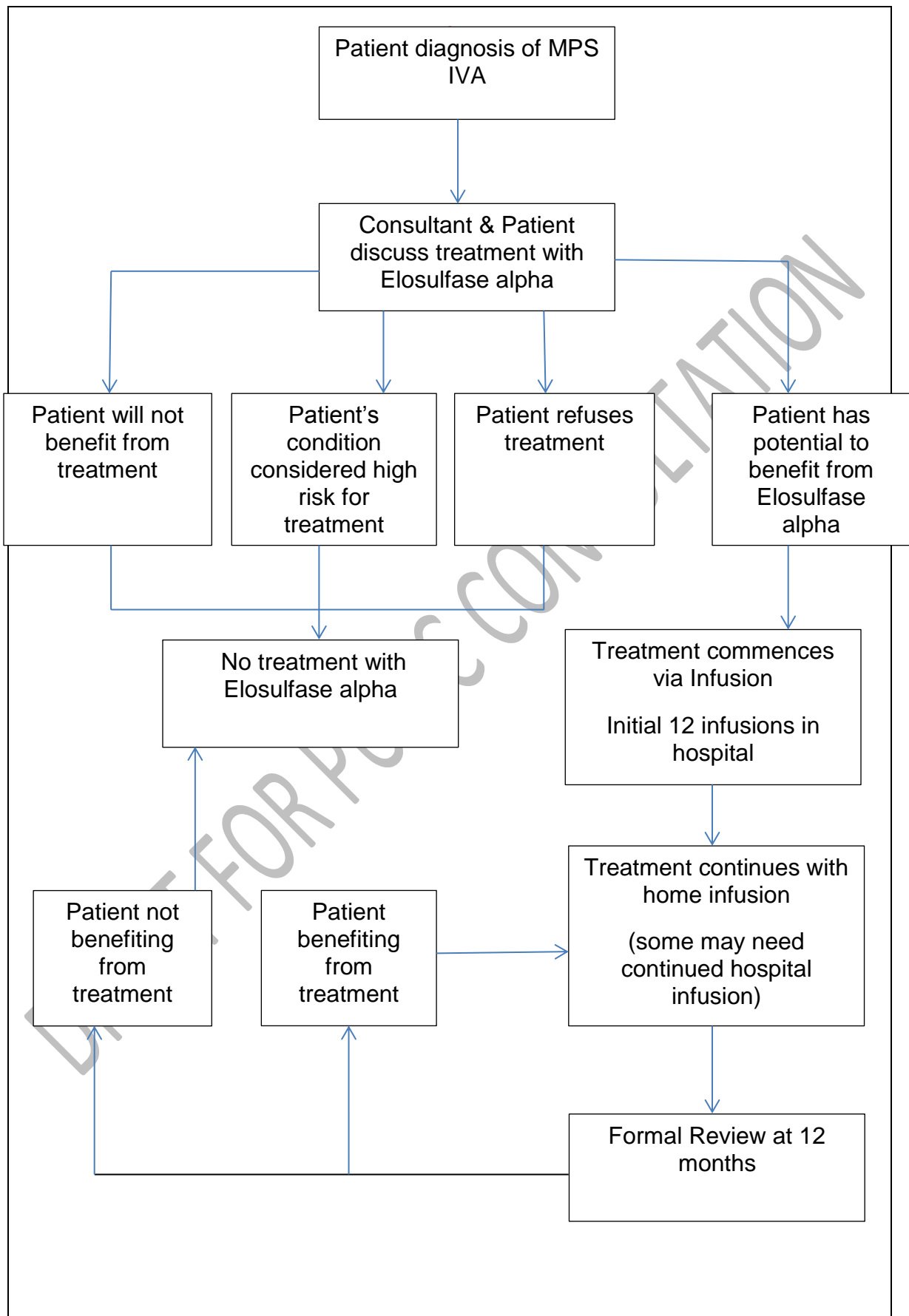
**Stopping Criteria:**

All patients will be regularly reviewed and assessed. Patients who show no clear benefit after 12 months will cease to receive Elosulfase. The expected benefits are measurable and based on those used in the clinical trials and include:

- Endurance – 6 minute walk test and 3 minute stair climb test
- Respiratory
  - Respiratory function
  - Sleep study assesment
- Cardiac Function
- Urinary GAG
- Activities of daily living – MPS health assesment questionnaire and/or EQ-5DL
- Compliance with treatment regime based on number of infusions missed (expected compliance is 85%).
- Significant adverse events

Patient choice – unable to comply with treatment regime and/or tolerate adverse side effects of treatment

## 8. Patient pathway



## **9. Governance arrangements**

All patients will be under the care of a specialised LSD centre and consultant.  
The first 12 infusions will take place in a hospital setting and then providing safe and clinically appropriate, it is expected that infusion will be delivered through homecare  
Some patients will require infusion in a hospital setting after 12 weeks.  
All patients will be monitored regularly and formally every 12 months.

## **10. Mechanism for funding**

Elosulfase alpha and homecare infusions will be commissioned and contracted by NHS England.

## **11. Audit requirements**

All Lysosomal Storage Disorder services are required to carry out an annual audit and report these to a national meeting of LSD centres.  
Regular audit of practice will be carried out to drive up standards of care and evidence based practice established to record patient outcomes.

## **12. Documents which have informed this policy**

Evidence Review : Elosulfase alfa (Vimizim) for the treatment of MPS IVA

## **13. Links to other policies**

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

## **14. Date of review**

This policy will be reviewed in April 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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