NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Contract Variation Agreement No. 1 to the Managed Access Agreement for Asfotase alfa (Strensiq®) for treating paediatric-onset hypophosphatasia

Contract/Variation Reference: On 02 August 2017, NHS England and NHS Improvement (NHSE&I), Alexion Pharma UK Ltd., NICE together with two other parties (collectively the “Parties” and each a “Party”) entered into the “Managed Access Agreement for Asfotase alfa (Strensiq®) for treating paediatric-onset hypophosphatasia (the “MAA”).
IN WITNESS OF WHICH the Parties have signed this Variation Agreement No.1 on the date(s) shown below

<table>
<thead>
<tr>
<th>Date of agreement</th>
<th>12 August 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHS England and NHS Improvement</strong></td>
<td>Signed</td>
</tr>
<tr>
<td>........................................................</td>
<td>John Stewart</td>
</tr>
<tr>
<td>........................................................</td>
<td>National Director,</td>
</tr>
<tr>
<td>........................................................</td>
<td>Specialised Commissioning,</td>
</tr>
<tr>
<td>........................................................</td>
<td>NHS England and NHS Improvement</td>
</tr>
<tr>
<td><strong>Alexion Pharma UK Ltd.</strong></td>
<td>Signed</td>
</tr>
<tr>
<td>........................................................</td>
<td>Sean Richardson</td>
</tr>
<tr>
<td>........................................................</td>
<td>Vice President, General Manager UK &amp; Ireland</td>
</tr>
<tr>
<td><strong>Clinical Expert</strong></td>
<td>Signed</td>
</tr>
<tr>
<td>........................................................</td>
<td>Professor Nick Shaw, Consultant Paediatric Endocrinologist, University of Birmingham, Birmingham children’s hospital, also on behalf of Professor Nick Bishop and Professor Zulf Mughal</td>
</tr>
<tr>
<td><strong>Patient Organisation</strong></td>
<td>Signed</td>
</tr>
<tr>
<td>........................................................</td>
<td>Helen Morris, Patient Communities Manager, Metabolic Support UK (formerly CLIMB)</td>
</tr>
<tr>
<td><strong>NICE</strong></td>
<td>Signed</td>
</tr>
<tr>
<td>........................................................</td>
<td>Brad Groves, Associate Director, Managed Access, NICE</td>
</tr>
</tbody>
</table>
Date of this Variation Agreement No.1: 12 August 2021

This variation agreement relates to the variation of the MAA as set out below (the “Variation Agreement No.1”).

Capitalised words and phrases in this Variation Agreement No.1 have the meanings given to them in the MAA.

In consideration of their respective obligations under the MAA (as varied by this Variation Agreement No.1) the Parties have agreed to the following variation to the MAA:

1. Clause 3.1 shall be deleted and replaced as follows:

   3.1 This MAA shall take effect on the date of publication (02 August 2017) by NICE of the first final Guidance for asfotase alfa (the Effective date). It will remain in force until the earlier of: (i) publication of new guidance following a subsequent NICE HST review of asfotase alfa or; (ii) a maximum of 5 years and 6 months from the Effective Date. For the avoidance of doubt, this MAA shall expire automatically 5 years and 6 months from the Effective Date if it has not expired earlier as a result of the publication of new guidance following a subsequent NICE HST review of asfotase alfa.

2. Appendix A of the Managed Access Agreement July 2017 shall be deleted in its entirety and replaced as set out in Appendix 1 of this Variation Agreement No.1

All other definitions terms and conditions contained in the MAA and its Appendices shall continue to apply in full force and effect.

The variations set out in this Variation Agreement No.1 take effect on 12 August 2021.
Appendix A:

Asfotase alfa (Strensiq®) for Treating Paediatric-onset Hypophosphatasia

Managed Access Patient Agreement and

Informed Assent Form

The National Institute for Health and Care Excellence (NICE) has approved asfotase alfa, brand name Strensiq®, for patients who have been diagnosed with childhood-onset hypophosphatasia (HPP) who meet the starting rules outlined in a Managed Access Agreement.

What is a Managed Access Agreement?

An MAA is a way that doctors and the NHS can assess the long term benefits of a new medicine by collecting agreed test results over a given period of time in patients who have certain symptoms of HPP. It is an agreement between NICE, NHS England, Alexion Pharma UK Ltd (the distributor of Strensiq® in the UK), doctors who are experts in treating HPP (HPP Specialists) and the patient organisation Metabolic Support UK (formerly CLIMB).

The MAA describes who can receive treatment with asfotase alfa and how information will be collected to understand how patients being treated with asfotase alfa respond to treatment in the same way that patients did in clinical trials. It allows patients to start being treated while at the same time allowing more information to be collected on how well the medicine works. An MAA is needed because NICE and NHS England need to understand more about the long term benefits of asfotase alfa. The MAA is managed by NHS England in consultation with selected HPP specialists.

Since you will be treated with asfotase alfa, your information will need to be collected under the MAA. This is a condition of receiving treatment with asfotase alfa in England. Thanks to this information, the NICE guidance can be looked at again at the end of
the MAA, and a further decision can be made on whether NHS should continue to pay for patients to receive this medicine in England.

This Managed Access Patient Agreement sets out:

- Rules for starting and stopping treatment with asfotase alfa.
- An explanation of the MAA database and how it will work.

1. Patient Eligibility

- NICE, the HPP specialists and Metabolic Support UK agree that patients in England should be able to have asfotase alfa (Strensiq®) as long as they meet the starting rules that are described in the MAA and are being treated by a specialist in HPP in a specialist HPP centre. If a patient meets the starting rules, they will be required to go to their clinic appointments for tests at three months, six months and 12 months in the first year of treatment, and then at least every 6 months after that for a check-up.

- All patients (whether by themselves or through a parent or guardian) will need to sign up to this Managed Access Patient Agreement.

2. Access to treatment and data collection

- The starting rules and regular tests in this Managed Access Patient Agreement have been developed by the clinical experts in HPP together with representatives of a patient organisation and other interested groups.

- Children under the age of 5 may not be able to do some of the tests, but they should be tried at least once every 12 months until the age of 5 at which point, they must be done (see Appendix C).
• It is expected that all patients, who can have their medicine at home, will receive supply of asfotase alfa via home care delivery. Patients and parent/ guardians will get support to make sure that they are able to inject asfotase alfa safely and effectively at home.

3. Starting Rules

• All patients must have a diagnosis of childhood-onset HPP (regardless of their current age) confirmed by one of the national HPP specialist centres, according to national guidelines. Treatment with asfotase alfa must be started by the one of these centres.

• All patients who meet the starting rules for asfotase alfa will be discussed by a committee of HPP experts and a pain management expert from different hospitals before treatment is started, except in babies where HPP is needed urgently. In this situation the specialist may start treatment straight away. The committee will meet monthly by teleconference and face to face every 6 months.

• All patients, or their guardian (as applicable), must give their consent for their information needed for the MAA to be entered into the MAA database which is part of the HPP Global Registry. This is to allow the effect of the treatment to be measured.

• All patients, or their guardian (as applicable), must sign consent to keep to the rules of the Managed Access Agreement, including attending regular appointments and completing questionnaires.

Perinatal- and Infantile-onset HPP: Patients below 1 year of age with symptoms and signs of HPP should be initiated on asfotase alfa therapy as soon as is possible.
Other Patients with Childhood-Onset HPP who meet the starting rules for asfotase alfa therapy include:

1. **Children aged 1-4 with **ONE **of the following:**

   I. Have not achieved expected developmental gross motor milestones for age as demonstrated by the BAMF-Scale (Brief Assessment of Motor Function); OR

   II. Continuing or recurring musculoskeletal pain where there is **significant** pain that affects daily activities which:
       
       - Affects quality of life
       - Hasn’t got better with 2 different types of painkiller which have been recommended by a national pain specialist

2. **Children aged 5-18 with **ONE **of the following:**

   I. Continuing or recurring musculoskeletal pain where there is **significant** pain that affects daily activities which:
       
       - Affects quality of life
       - Hasn’t got better with 2 different types of painkiller which have been recommended by a national pain specialist

   OR

   II. Limited mobility assessed by a specialist according to the modified Bleck Ambulation Efficiency Scoring and with a Bleck score between 1-6:
3. Patients over the age of 18 years old with childhood-onset HPP who have two or more of the following:

I. Current fractures (commonly affected areas include feet, hip, spine, wrist and thigh bone) with a history of non-traumatic, recurrent or non-/poorly-healing fractures (e.g. inability to remove fixation devices due to risk of recurrent fracture).

II. Continuing or recurring musculoskeletal pain where there is significant pain that affects daily activities which:
   - Affects quality of life
   - Hasn’t got better with 2 different types of painkillers which have been recommended by a national pain specialist.

III. Limited mobility assessed by a specialist according to the modified Bleck Ambulation Efficiency Scoring and with a Bleck score between 1-6.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Non-walker older than 2 years of age</td>
</tr>
<tr>
<td>2</td>
<td>Therapy walker with the use of crutches or sticks</td>
</tr>
<tr>
<td>3</td>
<td>Therapy walker without the use of crutches or sticks</td>
</tr>
<tr>
<td>4</td>
<td>Household walker with the use of crutches or sticks</td>
</tr>
<tr>
<td>5</td>
<td>Household walker without the use of crutches or sticks</td>
</tr>
<tr>
<td>6</td>
<td>Neighbourhood* walker with the use of crutches or sticks</td>
</tr>
</tbody>
</table>

*Neighbourhood walker defined as one who can walk no more than 300m.
4. Stopping Rules

Each year all test results will be looked at to see if asfotase alfa should be stopped by the HPP expert committee. The committee will decide to stop treatment if any of the following apply:

- Patient does not attend their appointments (misses more than one visit in any 18-month period with no attempts to rearrange; assessments missed due to medical reasons should be rescheduled as soon as possible).

- Patient is unable to tolerate asfotase alfa including continuing injection reactions which cannot be managed with usual medicines/measures and have a significant impact on quality of life.

- Asfotase alfa treatment is no longer helping the patient.

**Children, under the age of 18 years**, must reach **two out of the three** following non-responder rules before discontinuing:

- Loss of height or failure to maintain growth along centile lines following one year on a stable dose

- No improvement, or did not reach the expected cut off for the test of six minute walk test (6MWT) improvement of either <25m or <10% compared to test results before treatment or a fall in Bleck score of more than one level

- No reduction in pain: failure to achieve significant reduction in frequency of dose of analgesics (pain killers) or failure to see an improvement in quality of life as measured by PedsQL

**Adults, aged 18 years and over**, must reach **one of the three** following non-responder criteria before discontinuing:
• No improvement, or did not reach the expected cut off for the test of six minute walk test (6MWT) improvement of either <25m or <10% compared to test results before treatment or fall in in Bleck score of more than one level

• Continued fractures over a 3 year period

• No reduction in pain: failure to achieve significant reduction in frequency of dose of analgesics or failure to achieve improvement in quality of life as measured by Brief Pain Inventory and EQ5-D-5L

5. Expiry of the Managed Access Agreement

• At the end of Managed Access Agreement, NICE will look again at how well asfotase alfa works in patients such as yourself. If at the end of the Managed Access Agreement: (i) NICE no longer recommends asfotase alfa for NHS funding, NHS England funded treatment will need to stop; (ii) NICE recommends asfotase alfa for further NHS funding, then asfotase alfa will continue to be funded in England according to the arrangements between NICE and NHS England at that time.

• You understand that if NICE no longer recommends asfotase alfa for NHS funding, this could mean that your treatment with asfotase alfa will discontinue.

6. Acceptance and use of information

• You, or the parent(s)/guardian(s) of a child, must sign this Managed Access Patient Agreement to confirm that you accept and will comply with the requirements of the Managed Access Patient Agreement as part of the start criteria for treatment.

• Please note: By signing this document, you are agreeing to complete a Quality of Life questionnaire required as part of this Managed Access Patient
Agreement. The Quality of Life survey is a very short series of questions which allow you to say how you feel the treatment is helping your daily living. Your doctor or a team member will give you the questionnaire when needed, and help you fill out the answers. You will need to fill in this questionnaire about every 3 months.

- The information collected from your tests and clinic visits will be held in a Managed Access Agreement database. You as patient (or through your guardian) will need to sign a consent form agreeing to your information being entered into the MAA database. The information collected about you and your treatment will not identify you by name, address etc. This database is part of a larger database, the Global HPP Registry and your doctor will talk to you about whether you wish to take part in the separate registry study as well.

- Information collected under the MAA will be shared with NHS England, NICE and Alexion, and may be stored both inside and outside of the EU on static databases and portable devices (including being stored in the United States of America).
Informed Assent Form (Wording According to Patient Age)

To be signed by patient and/or parent or guardian AND clinician

I understand the conditions of the Managed Access Programme and the Managed Access Patient Agreement (including the circumstances in which NHS access to the treatment will cease)

Signature of Patient (if over 18) ______________

Date ______________

If patient is under 18 with informed assent

I have explained the details of the Managed Access Programme and the Managed Access Patient Agreement (including the circumstances in which NHS access to the treatment will cease) to (insert name) ______________ who understands the conditions and likely benefits of the treatment

Signature of parent or guardian ______________

Date ______________
I (insert name) _______________ understand the treatment and the conditions of the Managed Access Programme and the Managed Access Patient Agreement (including the circumstances in which NHS access to the treatment will cease) which my parents / guardian have explained to me.

Signature of Patient ______________

Date ______________

If patient is under 18 without informed assent

I understand the conditions of the Managed Access Programme and the Managed Access Patient Agreement (including the circumstances in which NHS access to the treatment will cease) and the likely benefits of treatment for my child.

Signature of parent or guardian______________

Date ______________

Name of Clinician: _______________

Signature of Clinician: ______________

Date_________________________