



Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

**Pombiliti 105 mg powder for concentrate for
solution for infusion**

cipaglucoasidase alfa

PLGB 25823/0003

Amicus Therapeutics UK Limited

LAY SUMMARY

Pombiliti 105 mg powder for concentrate for solution for infusion cipaglucosidase alfa

This is a summary of the Public Assessment Report (PAR) for Pombiliti 105 mg powder for concentrate for solution for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Pombiliti in this lay summary for ease of reading.

This product has been authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 20 March 2023 (EMA/H/C/005703/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

For practical information about using Pombiliti, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Pombiliti and what is it used for?

Pombiliti is a type of 'enzyme-replacement therapy' (ERT) that is used in the treatment of late-onset Pompe disease in adults. Pombiliti is always used with another medicine called miglustat 65 mg hard capsules. It is very important that the patient also reads the package leaflet of miglustat 65 mg hard capsules.

How does Pombiliti work?

Pombiliti is a type of 'enzyme-replacement therapy' (ERT) that is used in the treatment of late-onset Pompe disease in adults.

People with Pompe disease have low levels of the enzyme acid alpha-glucosidase (GAA). This enzyme helps control levels of glycogen (a type of carbohydrate) in the body.

In Pompe disease, high levels of glycogen build up in the muscles of the body. This keeps muscles, such as the muscles that help a person walk, the muscles under the lungs that help a person breathe, and the heart muscle, from working properly.

Pombiliti enters the muscle cells that are affected by Pompe disease. When in the cells, the medicine works like GAA to help break down glycogen and control its levels.

How is Pombiliti used?

The pharmaceutical form of this medicine is powder for concentrate for solution for infusion and the route of administration is by intravenous infusion (given through a drip into a vein). The patient should talk to their doctor if they would like to be treated at home. The patient's doctor will decide upon evaluation if it is safe for the patient to have home infusion of Pombiliti. If the patient gets any side effects during an infusion of Pombiliti, their home

infusion staff member may stop the infusion and start appropriate medical treatment. Pombiliti should be used in conjunction with miglustat. The patient can only use miglustat 65 mg capsules with cipaglucosidase alfa. The patient should NOT use miglustat 100 mg capsules (different product).

The patient should follow their doctor's instructions and read the package leaflet of miglustat 65 mg hard capsules for their recommended dose.

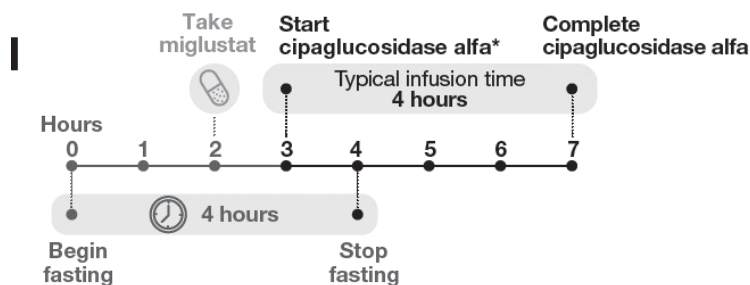
How much Pombiliti is given

The amount of medicine that the patient will be given is based on their weight. The recommended dose is 20 mg for each kg of body weight.

When and for how long Pombiliti is given

- The patient will be treated with Pombiliti once every other week. Miglustat 65 mg capsules are taken on the same day as Pombiliti. The patient should refer to the package leaflet of miglustat 65 mg hard capsules for information on how to take miglustat.
- The cipaglucosidase alfa infusion should start one hour after taking miglustat 65 mg hard capsules.
- In the event of a delay, the start of infusion should not exceed three hours from taking miglustat.
- The infusion of cipaglucosidase alfa lasts approximately four hours.

Figure 1. Dose timeline



* The cipaglucosidase alfa infusion should start one hour after taking miglustat capsules. In the event of infusion delay, the start of infusion should not exceed three hours from taking miglustat.

Switching from another enzyme replacement therapy (ERT)

If the patient is currently being treated with another ERT:

- The doctor will tell the patient when to stop the other ERT before starting Pombiliti.
- The patient should tell their doctor when they completed their last dose.

For further information on how Pombiliti is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the MHRA website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Pombiliti have been shown in studies?

A main study involving 125 patients showed that Pombiliti in combination with miglustat improved the physical abilities of patients with late-onset Pompe disease. The study looked at changes in the distance patients were able to walk before and after treatment. On average, patients treated with Pombiliti and miglustat for one year were able to walk 20 more metres in six minutes than they could before treatment.

What are the possible side effects of Pombiliti?

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at <https://yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Pombiliti approved?

Pompe disease is a rare and debilitating disease, with patients having life-threatening heart and respiratory problems. Studies show that, when given in combination with miglustat, Pombiliti is effective at improving or stabilising the physical abilities of patients with late-onset Pompe disease. The side effects of Pombiliti, which are mostly mild to moderate, are considered manageable. The MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Pombiliti has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Pombiliti?"

Pombiliti has been authorised as a GB Orphan medicine. Orphan medicines are intended for use against rare conditions that are life-threatening or chronically debilitating. To qualify as an orphan medicine, certain criteria, for example concerning the rarity of the disease and the lack of currently available treatments, must be fulfilled.

What measures are being taken to ensure the safe and effective use of Pombiliti?

As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Pombiliti. The RMP details the important risks of Pombiliti, how these risks can be minimised, any uncertainties about Pombiliti (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Pombiliti:

Important identified risks	Infusion-associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies Comment: No difference between the GB annex and EU-RMP.
Important potential risks	- Immune complex related reaction - Medication error in home infusion setting - Use in pregnant and lactating women Comment: “Use in pregnant and lactating women” was added as a GB-specific important potential risk. This topic was classified as missing information in the EU-RMP. However, given that there is no anticipated usage in this patient population and there are no reasonable grounds to collect further data in this patient population, this safety concern was re-evaluated by the Applicant and revised for GB from missing information to an important potential risk.
Missing information	Long-term use (> 24 months) Comment: “Use in pregnant and lactating women” was removed from missing information. As described above, this safety concern was re-evaluated by the Applicant and revised for GB from missing information to an important potential risk.

Abbreviations: EU-RMP = European Union Risk Management Plan; GB = Great Britain; IgE = immunoglobulin E; IgG = immunoglobulin G.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Pombiliti are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to the safety information provided in the Pombiliti product information, the Marketing Authorisation Holder (MAH) has committed to:

- (1) additional pharmacovigilance activities through the provision of effectiveness and safety data derived from long-term follow-up studies and a prospective observational registry of patients with Pompe disease to further evaluate the long-term effectiveness and safety of Pombiliti.
- (2) additional risk minimisation measures through the provision of educational material for healthcare professionals and patients, in the form of (i) a prescriber guide on pregnancy and home infusion (ii) a patient reminder card on pregnancy and (iii) a patient/caregiver’s home infusion guide including an infusion diary.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Pombiliti

A marketing authorisation was granted in Great Britain on 30 June 2023.

The full PAR for Pombiliti follows this summary.

This summary was last updated in November 2023.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Pombiliti 105 mg powder for concentrate for solution for infusion (PLGB 25823/0003) could be approved.

The product is approved for the following indications:

Pombiliti is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α -glucosidase [GAA] deficiency).

The active substance in the product is cipaglucosidase alfa. Pompe disease is caused by a deficiency of acid alpha-glucosidase (GAA) that degrades glycogen to glucose in the lysosome. Cipaglucosidase alfa is intended to replace the absent or impaired endogenous enzyme.

Cipaglucosidase alfa is stabilised by miglustat minimising the loss of enzyme activity in the blood during infusion of this hydrolytic glycogen-specific enzyme enriched with bis-M6P N-glycans for high affinity cation-independent mannose 6-phosphate receptor (CI-MPR) binding. After binding, it is internalised in the lysosome where it undergoes proteolytic cleavage and N-glycan trimming which are both required to yield the most mature and active form of the GAA enzyme. Cipaglucosidase alfa then exerts enzymatic activity in cleaving glycogen and reducing intramuscular glycogen and ameliorating tissue damage.

This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 20 March 2023 (EMA/H/C/005703/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

This application was evaluated for fulfilment of orphan designation criteria and was examined by the Commission on Human Medicines (CHM) on 27 April 2023. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was satisfactorily demonstrated. Please see Annex 1 for a summary of the orphan approval.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (MHRA-100129-PIP01-21-M01).

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted on 30 June 2023.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPC is in line with current guidelines and was satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

The MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

IV. NON-CLINICAL ASPECTS

The MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS

The MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance and risk minimisation measures have been proposed:

Table 1: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern (GB-specific information)

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Infusion-associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies	Routine risk minimisation measures: - SmPC Sections 4.2, 4.3, 4.4, and 4.8; - PL Sections 2 and 4; - As stated in the SmPC (Section 4.3) and PL (Section 2), treatment is contraindicated in patients with history of life-threatening IARs (eg, anaphylaxis and severe cutaneous reactions) to the active substance or any of the excipients when rechallenge was unsuccessful; - As stated in the SmPC (Section 4.2), premedication used for patients that have switched from another ERT to Pombiliti in combination with miglustat should be continued when starting Pombiliti; - As stated in the PL (Section 2), patients are instructed to tell their doctor if they notice any signs of IARs or allergic events and such signs are listed in Section 4; - Recommendations for managing IARs including hypersensitivity and anaphylactic reactions are provided in the SmPC, including rate reduction or stoppage of infusion, guidance on resumption or re-initiating, recommendations regarding corrective treatment and premedications, and cardiopulmonary resuscitation equipment. Other routine risk minimisation measures beyond the Product Information: - Prescription only. Additional risk minimisation measures: - Prescriber guide on pregnancy and home infusion; - Patient/caregiver's home infusion guide including an infusion diary.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - None. Additional pharmacovigilance activities: - ATB200-02;ATB200-07; - Prospective observational registry.

Table 1: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern (GB-specific information)

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Medication error in home infusion setting	Routine risk minimisation measures: - SmPC Sections 4.2, 4.4, and 6.6; - PL Section 3; - As stated in the SmPC (Section 4.2), treatment should be supervised by healthcare professionals experienced in the management of Pompe disease; - As stated in the SmPC (Section 4.2), home infusions may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months, and recommendations regarding a decision to move to home infusions are described in the SmPC (Section 4.2); - As stated in the SmPC (Section 4.4), for patients who experience anaphylaxis or severe allergic reactions in the home setting, if they continue on treatment, their next infusions must occur in a clinical setting equipped to deal with such medical emergencies; - The SmPC (Section 6.6) contains detailed instruction regarding preparation of the medicinal product (including calculating the dose, activities before reconstitution, reconstituting the lyophilised cake/powder, dilution and preparation of the infusion bag, and preparing for administration); - Recommendations for managing IARs including hypersensitivity and anaphylactic reactions are provided in the SmPC. Other routine risk minimisation measures beyond the Product Information: - Prescription only. Additional risk minimisation measures: - Prescriber guide on pregnancy and home infusion; - Patient/caregiver's home infusion guide including an infusion diary.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - None. Additional pharmacovigilance activities: - ATB200-02; - ATB200-07; - Prospective observational registry.

Table 1: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern (GB-specific information)

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Important potential risk: Use in pregnant and lactating women	Routine risk minimisation measures: • SmPC Sections 4.6 and 5.3; • PL Section 2; • Recommendations regarding use in pregnant women and use in breastfeeding women are provided in the SmPC (Section 4.6) and PL (Section 2); • As stated in the SmPC (Section 4.6) and PL (Section 2), female patients of childbearing potential are advised to maintain reliable contraceptive methods prior, during, and for 4 weeks after stopping Pombiliti in combination with miglustat; • As stated in the PL (Section 2), Pombiliti in combination with miglustat should not be used during pregnancy, and patients are instructed to tell their doctor if they are pregnant, may be pregnant, or are planning to become pregnant; • As stated in the PL (Section 2), Pombiliti in combination with miglustat should not be used in breastfeeding women, and patients are instructed to tell their doctor if they are breastfeeding. Other routine risk minimisation measures beyond the Product Information: • Prescription only. Additional risk minimisation measures: • Prescriber guide on pregnancy and home infusion; • Patient reminder card on pregnancy.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • Prospective observational registry.
Refer to the EU-RMP for a summary of the risk minimisation activities and pharmacovigilance activities for the other safety concerns.		

Abbreviations: EU-RMP = European Union Risk Management Plan; GB = Great Britain; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; PL = package leaflet; SmPC = Summary of Product Characteristics.

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product as a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α -glucosidase [GAA] deficiency).

The SmPC, PIL and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

ANNEX 1**Summary of fulfilment of the criteria for orphan drug designation**

Product: Pombiliti 105 mg powder for concentrate for solution for infusion
Active substance: Cipaglucosidase alfa
Orphan Designation Number: PLGB/25823/0003/OD1

Background:

This application was evaluated for fulfilment of orphan designation criteria by the Commission on Human Medicines (CHM) and the designation criteria were considered fulfilled.

Evaluation:**Orphan condition**

The orphan condition is glycogen storage disease type II (Pompe's disease). This is acceptable and in line with the guidance on what constitutes a valid condition.

Orphan indication

The orphan indication is long-term enzyme replacement therapy (ERT) used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α -glucosidase [GAA] deficiency).

Life threatening/debilitating condition

The condition is life-threatening or seriously debilitating. In infantile-onset Pompe disease (IOPD), most babies die from cardiac or respiratory complications before their first birthday. In late-onset Pompe disease (LOPD), muscle weakness leads to progressive limitations of motor activities of daily living and ultimately death from respiratory failure after several years.

The proposed indication is acceptable, and it falls entirely within the orphan condition.

Prevalence of the Condition in Great Britain (GB)

Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the point prevalence for the condition is estimated to be 0.15 in 10,000 people in GB. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of treatment

The following methods have been identified:

- Myozyme (alglucosidase alfa) and Nexviadyme (avalglucosidase alfa) are authorised medicinal products in the applied for orphan indication.

These are therefore considered satisfactory methods and significant benefit must be demonstrated.

Justification of significant benefit

Methods for the treatment of the orphan condition already exist in GB. Suitable justification has been provided that cipaglucosidase alfa plus miglustat provides a significant benefit to those affected by the condition as specified in the orphan indication.

1. Significant benefit over alglucosidase alfa (Myozyme)

A direct randomised head-to-head comparison (PROPEL study) is available. Although the primary endpoint of PROPEL marginally failed to achieve statistical significance, if the data are considered overall there is clear evidence from multiple endpoints of additional benefit for cipaglucosidase alfa/miglustat compared to alglucosidase alfa, with almost all endpoints trending in a favourable direction and many achieving statistical significance. It is not considered plausible that this pattern would have been seen by chance if there was truly no difference.

The benefit was driven by the effect in the treatment experienced subgroup. In the ERT-experienced population, cipaglucosidase alfa/miglustat showed clinically meaningful and nominally statistically significant improvements for both the primary endpoint of 6-minute walk distance (6MWD) (difference in least squares [LS] means of 17 meters; $p = 0.047$) and the first key secondary endpoint of % predicted forced vital capacity (FVC) (difference in LS means of 3.5%; $p = 0.006$) compared to alglucosidase alfa.

Based on a large body of data from other neuromuscular and chronic respiratory diseases, especially idiopathic pulmonary fibrosis (IPF), 6MWD increases greater than 6% (range 3 to 11%) and FVC changes greater than 3% (range 2 to 6%) are considered clinically relevant. As shown by patient-level responder analyses using these thresholds for clinically meaningful changes in the ERT-experienced population, more than 3 times as many ERT-experienced subjects on cipaglucosidase alfa/miglustat demonstrated clinically meaningful improvement of $> 6\%$ for 6MWD versus alglucosidase alfa (~40% versus 13%), and ~28% of ERT experienced subjects on cipaglucosidase alfa/miglustat versus 0 subjects on alglucosidase alfa demonstrated clinically meaningful improvement of $> 3\%$ for FVC. Additionally, only about half as many subjects on cipaglucosidase alfa/miglustat demonstrated clinically meaningful worsening of $> 6\%$ for 6MWD versus alglucosidase alfa (17% versus 33%) or clinically meaningful worsening of FVC $> 3\%$ (29% versus 50%).

Therefore, it is considered that a significant benefit over Myozyme has been shown in ERT-experienced patients, who represent approximately 95% of symptomatic LOPD patients.

2. Significant benefit over avalglucosidase alfa (Nexviadyme)

There are no clinical study data available that directly compare cipaglucosidase alfa/miglustat versus avalglucosidase alfa.

The randomised controlled trial of avalglucosidase alfa compared to alglucosidase alfa (COMET) is in ERT-naïve patients, whereas PROPEL is mainly in ERT-experienced patients, so it is not appropriate to compare the overall results from these trials.

ERT-experienced patients (across study comparisons)

There are no data from randomised trials for avalglucosidase alfa in ERT-experienced patients, whereas in the PROPEL trial cipaglucosidase alfa/miglustat showed nominal statistically significant superiority over alglucosidase alfa for both 6MWT and FVC as noted previously. Therefore, benefit has been demonstrated in this population for cipaglucosidase

alfa/miglustat and has not been for avalglucosidase alfa providing additional confidence for using cipaglucosidase alfa/miglustat in ERT-experienced patients.

Furthermore, while acknowledging the limitations of cross-trial comparisons, the comparison of the single-arm data from ATB200-02 vs NEO-1/-EXT is suggestive of a long-term advantage for cipaglucosidase alfa/miglustat vs avalglucosidase alfa in ERT-experienced patients in both size of improvement and maintenance of effect.

ERT-naïve patients (across study comparisons)

Based on limited data from the trials previously mentioned and their inconsistent results, no significant benefit can be concluded for cipaglucosidase alfa/miglustat versus avalglucosidase alfa in the ERT-naïve population.

However, it is considered that overall significant benefit has been shown in terms of efficacy over both Myozyme and Nexviadyme in ERT-experienced patients. As these patients represent the majority (95%) of symptomatic LOPD patients, it is considered that significant benefit has been shown in the therapeutic indication.

Conclusion:**Conclusion on acceptability of orphan designation**

The applicant has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: 30 June 2023

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, is recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N