Medicines & Healthcare products Regulatory Agency

MHRA

# Public Assessment Report

# Decentralised Procedure

# Pyridostigmine Bromide 12 mg/ml Oral Solution

# (Pyridostigmine bromide)

# Product Licence Number: PL 50956/0001

# Procedure Number: UK/H/5255/01/DC

# Horizon Pharmaceuticals Ltd

# LAY SUMMARY

## Pyridostigmine Bromide 12mg/ml Oral Solution

## (Pyridostigmine bromide)

This is a summary of the Public Assessment Report (PAR) for Pyridostigmine Bromide 12mg/ml Oral Solution. It explains how Pyridostigmine Bromide 12mg/ml Oral Solution 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 Pyridostigmine Bromide 12mg/ml Oral Solution.

This product will be referred to as Pyridostigmine Bromide Oral Solution in this lay summary for ease of reading.

For practical information about using Pyridostigmine Bromide Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

**What is Pyridostigmine Bromide Oral Solution and what is it used for?**
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Mestinon® 60 mg tablets (Meda Pharmaceuticals Limited).

Pyridostigmine Bromide Oral Solution is used for the treatment of myasthenia gravis in adults and children, and also in adults to treat paralytic ileus (a rare form of constipation). In patients who suffer from myasthenia gravis, muscles quickly become tired and weak and, in severe cases, the muscles may become paralysed.

**How does Pyridostigmine Bromide Oral Solution work?**
Pyridostigmine Bromide 12mg/ml Oral Solution contains the active ingredient pyridostigmine bromide which belongs to a group of medicines known as cholinesterase inhibitors. This medicine stops Myasthenia gravis, which is caused by imbalance in activity of an enzyme in the body (cholinesterase). Pyridostigmine Bromide Oral Solution helps muscles to work properly.

**How is Pyridostigmine Bromide Oral Solution used?**
The pharmaceutical form of this medicine is oral solution and the route of administration is oral (by mouth).

**For myasthenia gravis**
This medicine takes 30 to 60 minutes to start working after the patient has taken it.
The effect of each dose should last about four hours during the day and about six hours at night.
The patient should try to take this medicine so that it can work when the patient's muscles are needed most, for example, when patients get up and about 30 to 60 minutes before a meal.

**Use in adults**

- The usual adult dose is 2.5 ml to 10 ml of solution to be taken five to six times daily, or higher doses if needed, as recommended by a doctor.

**Use in children**

- For children under 6 years, the usual starting dose is 2.5 ml of solution.
- For children aged 6 to 12 years, the usual starting dose is 5 ml of solution. A doctor will then gradually increase the dose until maximum improvement is seen. In children the total dose per day is usually 2.5 ml to 30 ml of solution.

**For paralytic ileus (constipation)**
**Use in adults**

- The usual adult dose is 5 to 20 ml of solution per day.

**Use in patients with a kidney or liver disorder**
The patient's doctor will decide at what dose to start the medicine and will increase the dose until maximum improvement is seen.

For further information on how Pyridostigmine Bromide Oral Solution is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

**What benefits of Pyridostigmine Bromide Oral Solution have been shown in studies?**
Pyridostigmine Bromide Oral Solution is a generic medicine that fulfils criteria meaning that no additional studies are required. Pyridostigmine Bromide Oral Solution has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics. Further information is provided in the main body of the Public Assessment Report (PAR).

**What are the possible side effects of Pyridostigmine Bromide Oral Solution?**
Because Pyridostigmine Bromide Oral Solution is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

**Why was Pyridostigmine Bromide Oral Solution approved?**
It was concluded that, in accordance with EU requirements, Pyridostigmine Bromide Oral Solution has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Pyridostigmine Bromide Oral Solution?**
A Risk Management Plan (RMP) has been developed to ensure that Pyridostigmine Bromide Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

## Other information about Pyridostigmine Bromide Oral Solution

A Marketing Authorisation was originally granted to Adeptio pharmaceuticals Limited (PL 40713/0001) on 03 April 2019. This application underwent a Change of Ownership procedure to the Marketing Authorisation Holder Horizon Pharmaceuticals Limited (PL 50956/0001) on 02 December 2019.

The full PAR for Pyridostigmine Bromide Oral Solution follows this summary.

This summary was last updated in February 2022.

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## Contents

# 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 Pyridostigmine Bromide 12 mg/ ml Oral Solution (PL 50956/0001) could be approved.

The product is indicated for the treatment of the following:
Adults:

- Myasthenia gravis and
- Paralytic ileus

Children:

- myasthenia gravis

The Reference Member State (RMS) for this procedure was the UK and the Concerned Member States (CMSs) were Germany, Italy and Spain.

Pyridostigmine bromide is an anticholinesterase. As an antagonist to cholinesterase, the enzyme which normally destroys acetylcholine, the action of pyridostigmine bromide can briefly be described, therefore, as the potentiation of naturally occurring acetylcholine. Thus, it enhances the neuro muscular transmission in voluntary and involuntary muscles. Pyridostigmine bromide has a more prolonged action than Prostigmin (neostigmine) although it is somewhat slower to take effect (generally taking 30 to 60 minutes).

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended). The reference medicinal product is Mestinon® 60mg tablets, originally granted to Roche Products Limited on 07 August 1986. Following a change of ownership procedure on 01 March 1998, this license was transferred to Meda Pharmaceuticals Ltd (PL 15142/0006) as generic medicines of suitable originator medicinal products,

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

A two-part bioequivalence study has been provided comparing the test product Pyridostigmine Bromide 12 mg/ml Oral Solution and the reference product Pyridostigmine fast release 60 mg tablets (Mestinon®). The study was conducted according to the required Ethics and GCP procedures.

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.

The RMS and CMSs considered that the application could be approved at the end of procedure (Day 210) on 18 March 2019. A Marketing Authorisation was originally granted to Adeptio pharmaceuticals Limited (PL 40713/0001) on 03 April 2019. This application underwent a Change of Ownership procedure to the Marketing Authorisation Holder Horizon Pharmaceuticals Limited (PL 50956/0001) on 02 December 2019.

# II QUALITY ASPECTS

## II.1 Introduction

This product consists of a clear, slightly viscous solution.

In addition to pyridostigmine bromide, this product also contains the excipients acesulfame potassium (E950), citric acid anhydrous (E330), glycerol (E422), hydroxyethyl cellulose 250 HX, sodium benzoate (E211), trisodium citrate dihydrate (E331), sorbitol 70% solution (E420), purified water and raspberry flavour (contains propylene glycol (E1520)).

The finished product is packaged in an amber glass bottle with a tamper-evident, child-resistant, polypropylene closure with a low-density polyethylene (LDPE) liner containing 150ml of solution.

The bottle is contained within an outer cardboard carton. Each carton also contains a 5ml polyethylene oral dosing pipette. The pipette is marked with a scale with markings at every 1ml and intermediate marks at every 0.1ml.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

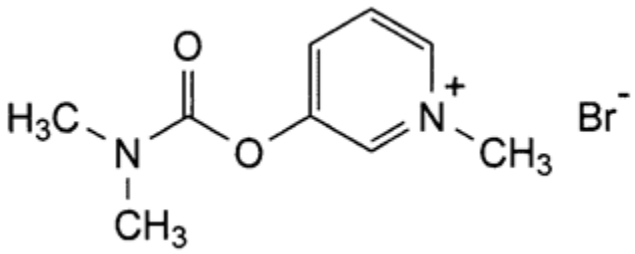
## II.2 ACTIVE SUBSTANCE

**rINN: Pyridostigmine bromide**

Chemical Name: BP) 3-(Dimethylcarbamoyloxy)-1-methylpyridinium bromide, 3-Hydroxy-1-methylpyridinium bromide dimethylcarbamate; 3- [[(dimethylamino)carbonyl]oxy]-1-methylpyridinium bromide

Molecular Formula: $C_9H_{13}BrN_2O_2$

Chemical Structure:




| | |
|---|---|
| Molecular Weight: | 261.1 g/mol |
| Appearance: | white or almost white crystalline, deliquescent powder. |
| Solubility: | Pyridostigmine bromide is very soluble in water and in ethanol (96 per cent). |

Pyridostigmine bromide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

## II.3 DRUG PRODUCT

**Pharmaceutical development**

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution has been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final product.

This product does not contain or consist of genetically modified organisms (GMO).

**Manufacture of the product**
A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years for unopened bottle, with the storage conditions “Store below 25°C and Keep the bottle in the outer carton in order to protect from light” are acceptable. Once the container is opened, the product must be used within 28 days.

### II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

## III NON-CLINICAL ASPECTS

### III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of pyridostigmine bromide are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

### III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

### III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

### III.4 Toxicology
No new toxicology data were provided and none were required for this application.

### III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

### III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

## IV CLINICAL ASPECTS

### IV.1 Introduction
The clinical pharmacology, efficacy and safety of pyridostigmine bromide are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

A two-part study was undertaken to investigate the pharmacokinetics of 2 proposed oral solutions of pyridostigmine bromide and to assess bioequivalence of the selected formulation [with or without sorbitol in the formulation] with the current marketed 60 mg oral tablet product, Mestinon®.

**The primary objectives of the study were:**
• To compare the pharmacokinetic (PK) profiles of 2 different pyridostigmine bromide (hereafter referred to as pyridostigmine) solution formulations with the marketed product (Mestinon®) (Part 1)

• To determine bioequivalence of a selected pyridostigmine solution formulation in comparison with the marketed product (Mestinon®) (Part 2)

The secondary objective of the study was to compare the safety and tolerability of the 2 solution formulations.

### IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following two part studies:

**Part 1 of the study**
This was a single centre, single dose, open-label, randomised 3-way crossover study in healthy subjects. Each subject received the following formulations in Part 1 after an overnight fast:

Regimen A: 60 mg pyridostigmine fast release tablet (Mestinon®)
Regimen B: 60 mg pyridostigmine oral solution (including sorbitol in the formulation)
Regimen C: 60 mg pyridostigmine oral solution (excluding sorbitol in the formulation)

This part of the study does not require further assessment here but the formulation including sorbitol was selected for the more relevant second part of the study, described below:

**Part 2 of the Study**
This is a single centre, single dose, open-label, randomised 2-way crossover study in 24 healthy adults. Each subject received the following formulations after an overnight fast:

Regimen D: 60 mg pyridostigmine fast release tablet (Mestinon®) (reference) and
Regimen E: 60 mg pyridostigmine oral solution (including sorbitol in the formulation as selected from the first part of the study) (test)

Subjects were screened for inclusion in the study in the 28 days before dosing. The subjects were admitted to the clinical unit on the evening of the day prior to dosing (Day-1), were

dosed on Day 1 and remained on site until 24 hours post-dose. Subjects returned to the clinical unit at 48 hours post-dose for a PK blood sample [completing 16 sampling points in all from 0 to 48 hours]. There was a minimum washout period of 7 days between each investigational medicinal product (IMP) administration in Parts 1 and 2.

## Result

**Pharmacokinetic parameters for pyridostigmine following a single oral dose of 60 mg are presented in the table below**

| **Regimen**<br>**Dose** | **D**<br>**60mg**<br>**N=24** | **E**<br>**60mg**<br>**N=23** |
|---|---|---|
| $T_{max}$ [h] | 2.00 (1.00–4.00) [n = 23] | 1.50 (0.50–3.00) |
| $C_{max}$ [ng/ml] | 36.3 (46.3%) [n = 23] | 36.7 (33.6%) |
| $AUC_{(0\text{-}last)}$ [ng.h/ml] | 186 (43.7%) [n = 23] | 185 (33.1%) |
| $AUC_{(0\text{-}inf)}$ [ng.h/ml] | 208 (43.9%) [n = 11] | 219 (26.9%) [n = 14] |
| $T_{1/2el}$ [h] | 4.86 (44.2%) [n = 11] | 5.25 (24.8%) [n = 14] |
| Frel [%] | NA | 99.4 (31.9%) |

Concentration–time profiles of pyridostigmine following administration of Regimen E (60 mg pyridostigmine oral solution including sorbitol) and Regimen D (60 mg pyridostigmine fast release tablet, Mestinon®) were consistent with extravascular dosing.

Following administration of Regimen E, the time taken to reach concentration maxima in individual subjects was similar to those reported following administration of Regimen D, with a median $T_{max}$ values of 1.500 and 2.000 hours, respectively.

There appeared to be negligible differences in systemic exposure following dosing of Regimen E when compared to Regimen D, reflected by a geometric mean Frel of 99.4%. Based on the 90% confidence intervals (CIs) for $C_{max}$ (88.37, 115.69) and $AUC_{(0\text{-}last)}$ (89.64, 110.97) bioequivalence of Regimen E and Regimen D was concluded.

Half-life values were similar for both treatments and the geometric mean $T_{1/2el}$ estimates were 4.86 hours for Regimen D and 5.25 hours for the Regimen E.

Peak concentrations occurred at similar times following administration of Regimens A (Mestinon®), B (60 mg pyridostigmine oral solution including sorbitol) and C (60 mg pyridostigmine oral solution excluding sorbitol) suggesting the rate of absorption was unaffected by dosage form.

Systemic exposure to pyridostigmine following administration of Regimen E (60 mg pyridostigmine oral solution including sorbitol) was similar compared to that observed following dosing of Regimen D (Mestinon®). It was concluded from the formal statistical analysis that Regimen D and Regimen E were bioequivalent with respect to $C_{max}$ and $AUC_{(0\text{-}last)}$.

Pyridostigmine was well tolerated when administered as a 60 mg oral solution including or excluding sorbitol in the formulation.

There were no serious or severe adverse events (AEs), although 1 subject was withdrawn as a result of moderate AEs that were possibly related to Mestinon®.

There were no clinically significant findings in any laboratory assessments, vital signs, Electrocardiograms (ECGs) or physical examinations.

### IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

### IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

### IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

### IV.6 Risk Management Plan (RMP)

The Applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

### IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

## V USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet 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.

## VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with pyridostigmine bromide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.

For use only as directed. Read enclosed leaflet. Replace cap firmly after each use and replace bottle in the outer carton.

Each ml contains 12mg pyridostigmine bromide. Contains sorbitol, propylene glycol, sodium benzoate, glycerol and sodium. See the leaflet for further information.

**Marketing Authorisation Holder**
Horizon Pharmaceuticals Limited
35 Grimwade Avenue
Croydon
CR0 5DJ, UK

PL 50956/0001

POM

# Pyridostigmine Bromide

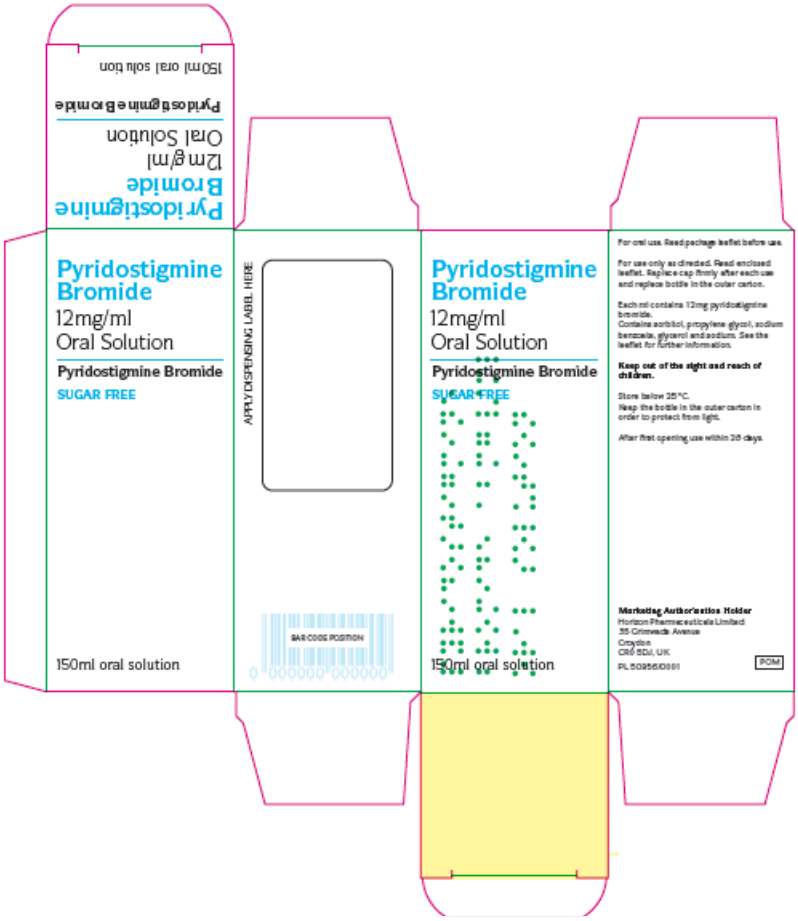
12mg/ml
Oral Solution

Pyridostigmine Bromide

**SUGAR FREE**

150ml oral solution

**Keep out of the sight and reach of children.**
For oral use. Read package leaflet before use.
Store below 25 °C. Keep the bottle in the outer carton in order to protect from light. After first opening use within 28 days.



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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 are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

| **Application type** | **Scope** | **Product information affected** | **Date of start of the procedure** | **Date of end of procedure** | **Outcome** | **Assessment report attached Y/N** |
|---|---|---|---|---|---|---|
| Type IB | To update section 4.2 of the SmPC to include administration of Pyridostigmine Bromide 12mg/ml Oral Solution via nasogastric gastric or percutaneous endoscopic gastrostomy feeding tubes to the SmPC. As a consequence, the PIL has been updated.<br>In addition, to correct typographical errors in section 4.2 and 4.8 of the SmPC. | SmPC and PIL | 19/10/2021 | 17/01/2022 | Approved | Y |

# Annex 1

**Reference:** PL 50956/0001-0010

**Product:** Pyridostigmine Bromide 12 mg/ ml Oral Solution

**Type of Procedure:** National

**Submission category:** Type IB Variation

**Reason**
To update section 4.2 of the SmPC to include administration of Pyridostigmine Bromide 12mg/ml Oral Solution via nasogastric gastric or percutaneous endoscopic gastrostomy feeding tubes to the SmPC. As a consequence, the PIL has been updated.
In addition, to correct typographical errors in section 4.2 and 4.8 of the SmPC.

**Supporting evidence**
The Company has submitted an updated SmPC and PIL.

**Evaluation**
To support the proposed change to the SmPC, the MAH has provided information on the compatibility of the product for the proposed update to include use with enteral feeding tubes,

The updated documents are satisfactory.

**Conclusion**
The proposed changes are acceptable.

In accordance with legal requirements, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

**Decision:** Grant

**Date:** 17 January 2022