IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

APO-go POD 5 mg/ml solution for infusion in cartridge
Apomorphine hydrochloride hemihydrate
PA0593/042/004

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for APO-go POD 5 mg/ml solution for infusion in cartridge, from Stada Arzneimittel AG on 13th November 2020 for the treatment of motor fluctuations ('on-off' phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication.

The submission has been made under Article 8(3) of Directive 2001/83/EC (as amended), with IE is the Reference Member State and AT, DE, DK, EL, ES, LU, NL, NO, PT, RO, SI, SE and UK are Concerned Member States in the decentralised procedure.

This abridged decentralised application concerns a line extension for drug substance (apomorphine hydrochloride) of the already approved originator product, APO-go PFS 5mg/ml (PA 0593/043/003; IE/H/658/3/MR) first authorised in the UK on 15/09/2004. The product is already approved with the same formulation using the
Pre-Filled Syringe (PFS) device, but in this marketing authorisation application the proposed commercial delivery mechanism is through the APO-go CARTRIDGE POD SYSTEM for continuous infusion.

In addition to the line extension application, new data was supplied to support updates to the posology with respect to administration via continuous subcutaneous infusion by minipump.

The product is subject to prescription which may not be renewed. The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at https://www.hpra.ie/homepage/medicines

Name of the product	APO-go POD 5 mg/ml solution for infusion in cartridge
Name(s) of the active substance(s) (INN)	Apomorphine hydrochloride hemihydrate
Pharmacotherapeutic classification (ATC code)	N04BC07 Apomorphine
Pharmaceutical form and strength(s)	5 mg/ml solution for infusion
Marketing Authorisation Number(s) in Ireland (PA)	PA0593/042/004
Marketing Authorisation Holder	Stada Arzneimittel AG
MRP/DCP No.	IE/H/0658/004/DC
Reference Member State	IE
Concerned Member State	AT DE DK EL ES LU NL NO PT RO SE SI UK

II. QUALITY ASPECTS

II.1. Introduction

This application is for APO-go POD 5 mg/ml solution for infusion in cartridge

II.2 Drug substance

The active substance is Apomorphine hydrochloride hemihydrate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each 20 ml cartridge contains 100 mg apomorphine hydrochloride hemihydrate

The excipients in the medicinal product are listed in section 6.1 of the SmPC. A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications. P.5 Control of Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for a solution for infusion and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC. Evidence has been provided that the packaging complies with Ph. Eur. requirements. P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of APO-go POD 5 mg/ml solution for infusion in cartridge.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacological actions of apomorphine hydrochloride and the rationale for its use in Parkinson's disease is amply supported by studies reported in the literature over many years, and nonclinical data is largely superseded by documented experience of clinical efficacy and safety. Therefore, the applicant presented a "mixed" nonclinical dossier consisting of bibliographic data that have been supplemented by sponsored studies. The non-clinical dossier has been written by Dr. Naghmeh Fouladi (Brittania Pharmaceuticals) and an appropriate signed statement (dated 23/10/2018) and CV have been provided as set out in Article 12 in accordance with Annex 1 of Directive 2001/83/EC. The assessment of this application was based on the nonclinical overview, written summaries and study reports.

The HPRA has been assured that Good Laboratory Practice (GLP) standards were followed in an appropriate manner in the studies conducted. GLP status cannot be verified for published studies referenced in support of this application.

III.2 Pharmacology

Apomorphine hydrochloride is a potent, direct-acting dopamine receptor agonist active at D1 and D2 receptors. Apomorphine has with full intrinsic activity at D2 receptors, and partial agonist activity at D1 receptors. D2-mediated actions of apomorphine include pituitary hormone release, dopamine autoreceptor regulation of dopamine synthesis and release or acetylcholine release in the striatum. Postsynaptic activation of dopamine receptors by apomorphine causes a cessation of neuronal firing of

pre-synaptic fibers through the activation of recurrent, negative feedback circuitry, to reduce motor fluctuations. The overview of preclinical pharmacology based on literature review is adequate.

III.3 Pharmacokinetics

Apomorphine hydrochloride is a widely used and well-known active substance. It is rapidly absorbed following subcutaneous administration in mice, rats and monkeys. Peak concentrations in the brain are achieved rapidly and decline rapidly. Apomorphine hydrochloride also distributes widely to the spleen, liver, kidney and large intestine. The metabolism of apomorphine hydrochloride in mice, rats and monkeys differs to the metabolism in humans. The relevance of nonclinical metabolism is limited. In humans multiple CYP enzymes (e.g. CYP2B6, CYP2C8 and CYP3A4/5) are involved in the metabolism of apomorphine. The major elimination route in animals was the urine, similar to humans. The overview of the nonclinical pharmacokinetics and supplementary studies are considered adequate.

III.4 Toxicology

In rats and monkeys repeated subcutaneous administration of apomorphine hydrochloride causes hyperactivity, disorientation and biting at high doses. These effects occur at exposures significantly higher than that seen in patients. Genotoxicity studies indicate that metabolites of apomorphine hydrochloride are mutagenic and clastogenic. Carcinogenicity studies in rats identified an increase in Leydig cell tumours; this is not believed to be relevant to humans due to differences in the endocrine system. Apomorphine hydrochloride was associated with reduced maternal care in rats and failure to breathe in newborn pups. Local toxicity studies in rabbits show that subcutaneous apomorphine hydrochloride is an irritant and the formulation of this product is the least irritating stable formulation. The toxicology studies conducted are considered acceptable.

III.5 Ecotoxicity/environmental risk assessment

As APO-go Cartridge 5 mg Solution for Infusion is intended for generic substitution, increased exposure to the environment is not anticipated. An Environmental Risk Assessment (ERA) was performed and apomorphine hydrochloride is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

Apomorphine hydrochloride is a widely used and well-known active substance. Literature review of nonclinical pharmacology and pharmacokinetics were supported by nonclinical pharmacokinetic and toxicology studies. Given the well-established clinical profile of apomorphine no further studies were required.

IV. CLINICAL ASPECTS

IV.1 Introduction
The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

The applicant has not conducted any new pharmacokinetic studies to support this application. The medicinal product is already approved in the same formulation, APO-go PFS 5mg/ml solution for infusion in pre-filled syringe (also referred to as APO-go PFS 5mg/ml), first authorised in the UK on 15/09/2004 and as such the pharmacokinetics are unlikely to differ.

<u>Absorption</u>
Apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4-12 minutes), and the brief duration of clinical action of the active substance (about 1 hour) is explained by its rapid clearance.

<u>Distribution</u>
After subcutaneous injection of apomorphine, its fate can be described by a two-compartment model, with a distribution half-life of 5 (±1.1) minutes.

<u>Biotransformation</u>

The metabolism of apomorphine is extensive and complex and involves enzymatic and non-enzymatic degradation pathways. Hepatic metabolism by glucuronidation and sulphonation occurs to at least ten per cent of the total. Extrahepatic metabolism involves intravascular oxidation, methylation and enteric sulfation.

Elimination
After subcutaneous injection of apomorphine, its fate can be described by a two-compartment model, with a distribution half-life of 5 (±1.1) min and an elimination half-life of 33 (±3.9) minutes.

Linearity/non-linearity
Apomorphine exhibits linear pharmacokinetics.

Pharmacokinetic/pharmacodynamic relationships
Clinical response correlates well with levels of apomorphine in the cerebrospinal fluid; the active substance distribution being best described by a two-compartment model.

IV.3 Pharmacodynamics

No new pharmacodynamics studies have been conducted by the applicant in support of this application. See the SmPC for more details.

Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties does not share transport or metabolic pathways with levodopa.

IV.4 Clinical Efficacy

The main clinical study supporting the efficacy of apomorphine as a continuous infusion was the TOLEDO study. This was a randomised, multiple-centre, parallel group, double-blind, placebo-controlled study conducted in 107 subjects with Parkinson's disease (PD) with motor complications not well controlled on their current medical treatment.

The approved originator product APO-go 5mg/ml PFS Solution is indicated in the same population as the Apo-go Cartridge delivery system. Some deviations to the posology have been made with the support of the TOLEDO study methods and results.

Results
For the primary efficacy endpoint of change in OFF time over 24 hours from baseline to Week 12, apomorphine continuous subcutaneous infusion was statistically superior to placebo with a LS mean (95% CI) difference of -1.87 (-3.15, -0.58) hours (p=0.0047).

The LS mean change (95% CI) in daily ON time without troublesome dyskinesia at Visit 10 (Week 12) for apomorphine-treated patients was an increase of 2.90 hours (2.07, 3.73) compared to 0.85 hours (-0.09, 1.78) for placebo-treated patients. The LS mean difference between the treatment groups was 2.05 hours (0.74, 3.36) (p=0.0022)

IV.5 Clinical Safety

Apomorphine is a well-known active substance with an established safety profile. This extension application concerns APO-go Cartridge 5 mg/ml Solution for Infusion, the formulation of which is identical to the authorised APO-go PFS 5 mg/ml Solution for Infusion.

The undesirable effects listed in the proposed APO-Go SmPC, 4.8 is the same as that contained in the SmPC, 4.8 of the identical formulation authorised as APO-go PFS 5 mg/ml Solution for Infusion.

Overall, no unexpected safety signals were detected in the TOLEDO study. The frequency and profile of AEs were consistent with the clinical course of the underlying condition and the known safety profiles of apomorphine and other anti-PD medications.

Training/education materials supplied to clinicians for the use of the proposed Apo-Go Cartridge device with respect to establishing the threshold dose, administration of intermittent bolus doses and the maintenance of dose were submitted during this application, these are comparable to the authorised APO-go PFS 5 mg/ml Solution for Infusion training and

educational materials. The SmPC also includes instructions on how to set up the infusion and references user guides for the pump and pod which are stated as for the healthcare professional's use.

Risk management plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to apomorphine.

Summary table of safety concerns as approved in the RMP

Summaryof safety concerns	
Important identified risks	None;
Important potential risks	Dopamine dysregulation syndrome; Punding; Dopamine agonist withdrawal syndrome; Use in pregnancy;
Missing information	Use in lactation;

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Assessor's overall conclusions on the Risk Management Plan
The revised risk management plan (version 1.1, date of final sign-off, 18 May 2020) is considered acceptable.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

Apomorphine continuous subcutaneous infusion was demonstrated as an effective treatment for PD in patients who have motor symptoms, by reducing mean OFF time compared to placebo by 1.87 hours, increasing on time without troublesome dyskinesia by 2.05 hours. The maintenance of treatment has been illustrated over a 64week period with reductions in OFF time sustained.

The adverse event profile of this active substance is established and well known. Overall, no unexpected safety signals were detected in the TOLEDO study. The frequency and profile of AEs were consistent with the clinical course of the underlying

condition and the known safety profiles of apomorphine and other anti-PD medications. Whilst the study population is small, the number of subjects and follow-up time is regarded as sufficient to make a safety assessment for this application.

V. OVERALL CONCLUSIONS

Benefits

The safety profile of the active substance apomorphine has been well established over many years' use in the treatment of patients with Parkinson's Disease. Continuous subcutaneous (s.c.) apomorphine was generally well tolerated on evaluation of safety in the TOLEDO study. The TOLEDO study demonstrated effect with use that represents real-world use, i.e. titration of dose as outlined in Section 4.2 and adjustment of maintenance dose according to efficacy and tolerability *"usuallyrange between4 mg/hrand6 mg/hr(0.8mland1.2ml).Somepatientsmayobtainadequatesymptomcontrolwithaslittleas2 mg/hr andotherswillrequireasmuchas8 mg/hr.*"Within the parameters set by the TOLEDO study, apomorphine continuous s.c infusion showed a significant effective for PD in patients who have motor symptoms, by reducing mean OFF time compared to placebo by 1.87 hours, increasing ON time without troublesome dyskinesia by 2.05 hours. The maintenance of treatment was illustrated over a 64-week period with reductions in OFF time sustained. The frequency and profile of treatment-related AEs were consistent with the known safety profile of apomorphine and no new safety signals were detected with the proposed posology.

Risks

The undesirable effects most commonly associated with the use of s.c. apomorphine are subcutaneous effects (e.g. injection/infusion site reactions) neuropsychiatric disturbances (hallucinations, somnolence, transient sedation, dizziness/light-headedness), nausea and vomiting. Uncommon effects include hypotension, dyskinaesias and blood disorders. Rare adverse reactions include impulse control disorders, aggression, agitation and allergic reactions (including anaphylaxis and bronchospasm). Adverse events are usually mild, non-serious and recover on discontinuation.

Integrateinformationon preclinicalandclinicalsafetyalongwithanypost-authorisationcommitmentsandelaborateon any"risk management"aspectsthatmayinfluencethebenefit-riskassessment,orareconsiderednecessaryto appropriatelymanageany identifiedoremergingsafetyconcerns.

ForapplicationsunderArticle8(3),10a,10ballfollowingstatementscanbeused:
The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that APO-go POD 5 mg/ml solution for infusion in cartridge demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

03 Feb 2026

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
C.I.4	IE/H/0658/004/II/107	SmPC sections 4.2, 6.3 & 6.6	16.11.2020	01.06.2022
C.I.4, C.I.3.a	IE/H/0658/004/II/123/G	SmPC section 4.2 PIL section 2 & 3.	02.02.2023	07.05.2023
New MR as RMS	IE/H/0658/004/E/001	PIL section 6	05.12.2025	03.02.2026