IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Metaraminol
Metaraminol bitartrate
PA1968/024/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Metaraminol 0.5 mg/ml solution for injection in pre-filled syringe, from Laboratoire Aguettant for the treatment of acute hypotension due to loss of vasoconstrictor tone as may occur during spinal anaesthesia and as an adjunct to accepted remedial procedures in adults.

This national application is a hybrid application and was submitted in accordance with Article 10(3) of Directive 2001/83/RC, as amended.

The Applicant has not received scientific advice.

Metaraminol 0.5 mg/ml solution for injection in pre-filled syringe 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 www.hpra.ie.

Name of the product	Metaraminol 0.5 mg/ml solution for injection in pre-filled syringe
Name(s) of the active substance(s) (INN)	Metaraminol bitartrate
Pharmacotherapeutic classification (ATC Code)	C01CA09
Pharmaceutical form and strength(s)	0.5 mg/ml solution for injection in pre-filled syringe
Marketing Authorisation Number(s) in Ireland (PA)	PA1968/024/001
Marketing Authorisation Holder	Laboratoire Aguettant 1 rue Alexander Fleming Lyon 69007 France

II. QUALITY ASPECTS

II.1. Introduction

This application is for Metaraminol 0.5mg/ml solution for injection in pre-filled syringe.

II.2 Drug substance

The active substance is Metaraminol Bitartrate an established active substance described in the European/British 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 ml of solution for injection contains 0.5 mg of metaraminol (as tartrate).

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/*Ancillary Substances*)

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 parenteral preparations, 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./EU legislation for use with foodstuffs 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 have been provided, assuring consistent quality of Metaraminol 0.5 mg/ml solution for injection in pre-filled syringe.

III. NON-CLINICAL ASPECTS

This active substance has been available on the European/Irish market for several years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

IV. CLINICAL ASPECTS

IV.1 Introduction

Metaraminol 0.5 mg/mL solution for injection in pre-filled syringe contains the active ingredient metaraminol, as metaraminol tartrate. Metaraminol has a well-established efficacy and safety profile.

The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid medicinal product of the reference medicinal product Aramine 10 mg/mL solution for injection (PL 00025/5020R; Merck, Sharp & Dohme Limited) authorised in the UK in 1973. The reference medicinal product is not currently marketed in the UK or anywhere in the EU.

Compared with the reference medicinal product Aramine 10 mg/mL solution for injection, the hybrid formulation Metaraminol 0.5 mg/mL solution for injection in pre-filled syringe has a different presentation and strength.

No new clinical data were submitted however a Clinical Overview, outlining clinical pharmacokinetics, pharmacodynamics, efficacy and safety of metaraminol relevant to the proposed indications and posology based on a review of published scientific literature, was submitted to further support this application.

No bioequivalence study was submitted, and none are required in line with CHMP guidance on the demonstration of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). A biowaiver was therefore accepted.

The content of the SmPC approved during the national procedure is in accordance with the most recent version of the reference product and adapted relevant to the specificities of the formulation. It is also updated in the safety sections based on evolving scientific knowledge.

IV.2 Pharmacokinetics

Absorption
Metaraminol, when administered as an intravenous bolus in doses ranging from 0.5 to 5 mg, has a rapid onset of action within 1–2 minutes. Its peak effect occurs at around 10 minutes, and the duration of action lasts between 20 and 60 minutes.

Distribution
The medicine accumulates in organs rich in norepinephrine storage vesicles, such as the heart, spleen, and adrenal glands. Notably, metaraminol does not cross the blood-brain barrier.

Metabolism
Approximately 45% of metaraminol is bound to plasma proteins. It undergoes hepatic metabolism, indicating the liver plays a significant role in its biotransformation.

Elimination
Metaraminol is primarily excreted through the kidneys and bile, mostly in the form of metabolites. However, it remains unclear whether these metabolites retain pharmacological activity.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Adrenergic and dopaminergic agent, ATC code: C01CA09.

Metaraminol is a sympathomimetic agent with direct and indirect effects on adrenergic receptors. It has both alpha and beta-adrenergic activity, the former being predominant.

Metaraminol increases the force of myocardial contractions as well as having a peripheral vasoconstrictor action. It increases both systolic and diastolic blood pressures. The vasoconstrictor action of metaraminol is not affected by depletion of the tissue stores of noradrenaline.

Metaraminol is highly effective in displacing and replacing noradrenaline from the stores in adrenergic neurones and competitively inhibits noradrenaline uptake. The metaraminol that is taken up by the adrenergic neurones then acts as a false transmitter.

The overall effects of metaraminol are similar to those of noradrenaline but it is much less potent and has a more prolonged action. It can cause pulmonary vasoconstriction, and pulmonary blood pressure is elevated when cardiac output is reduced.

IV.4 Clinical Efficacy

Clinical evidence of efficacy of metaraminol in the proposed indications is well established considering its extensive clinical experience for more than 50 years.

No new efficacy data were submitted, and none were required.

IV.5 Clinical Safety

The safety profile of metaraminol is well established and primarily related to its α-adrenergic agonist activity.

No new safety data were submitted, and none were required.

A full list of undesirable effects associated with the use or metaraminol can be found in Section 4.8 of the SmPC.

The submitted Risk Management Plan, version 0.2 signed 19/Dec/2024 is considered acceptable. Routine pharmacovigilance and routine risk minimisation are considered sufficient. The Applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP

Important identified risks	none
Important potential risks	none
Missing information	none

The next PSUR should 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.

IV.6 Discussion on the clinical aspects

The clinical efficacy and safety profile of metaraminol is well known.

Compared with the reference medicinal product Aramine 10 mg/mL solution for injection, Metaraminol 0.5 mg/mL solution for injection in pre-filled syringe was developed as a ready to administer formulation.

A Risk Management Plan has been accepted, and safety updates are to follow the EURD schedule.

V. OVERALL CONCLUSIONS

Metaraminol is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence studies were not required for this application due the pharmaceutical form of the product, in line with the CHMP guidance documents. The SmPC is consistent with the most recent version of the reference product, Aramine 10 mg/mL solution for injection and adapted relevant to the specificities of the formulation. It is also updated in the safety sections based on evolving scientific knowledge.

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 Metaraminol 0.5 mg/ml solution for injection in pre-filled syringe demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	CRN00FFQZ	SmPC, IPAR and PIL	18/09/2026	17/09/2031