

Public Assessment Report

Scientific discussion

**Palonosetron Fresenius Kabi 250 micrograms,
solution for injection**

**Palonosetron Fresenius Kabi 250 micrograms,
solution for injection in pre-filled syringe**

(palonosetron hydrochloride)

NL/H/3457/001-002/DC

Date: 21 April 2017

This module reflects the scientific discussion for the approval of Palonosetron Fresenius Kabi 250 micrograms, solution for injection and Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre-filled syringe. The procedure was finalised on 25 May 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for

Palonosetron Fresenius Kabi 250 micrograms, solution for injection and for Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre- filled syringe, indicated in adults for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy

Only Palonosetron Fresenius Kabi 250 micrograms, solution for injection is indicated in paediatric patients 1 month of age and older for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre-filled syringe has indications that are more limited compared to Aloxi as no indication in the paediatric population is proposed due to the specific pharmaceutical form. The limitation of the indication is considered acceptable.

This decentralised procedure concerns a generic/hybrid application claiming essential similarity with the innovator product Aloxi 0.25 mg/5 ml, solution for injection (EU/1/04/306/001) which has been centrally registered in the EEA by Helsinn Birex Pharmaceuticals Ltd since 22 March 2005.

For Palonosetron Fresenius Kabi 250 micrograms, solution for injection the marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

For Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre-filled syringe the marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. This concerns a hybrid application, as the pharmaceutical form of this product is different from the pharmaceutical form of the innovator product Aloxi, i.e. the solution for injection is supplied in a pre-filled syringe.

The concerned member states (CMS) involved in this procedure were: Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Ireland, Italy, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Sweden and the United Kingdom.

For Palonosetron Fresenius Kabi 250 microgram, solution for injection additional CMSs are Slovenia and Slovak Republic.

II. QUALITY ASPECTS

II.1 Introduction

Palonosetron Fresenius Kabi is a clear, colourless solution and free from visible particles. Each ml of solution contains 50 micrograms of palonosetron (as hydrochloride).

Each vial or pre-filled syringe of 5 ml of solution contains 250 micrograms palonosetron (as hydrochloride). The pH of the solution is between 4.7 - 5.3 and the osmolality between 270 – 330 mOsmol/kg.

- Palonosetron Fresenius Kabi 250 microgram, solution for injection is packed in Type I glass vial, closed with halobutyl rubber stopper and sealed with aluminium – plastic tear-off cap.
- Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre-filled syringe is packed in a pre-filled plastic syringe composed of a barrel of cyclo olefin copolymer material and a plunger and tip cap of halobutyl rubber.

The excipients are: mannitol (E421), disodium edetate dihydrate, sodium citrate dihydrate (E331), anhydrous citric acid (E330), sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

II.2 Drug Substance

The active substance is palonosetron hydrochloride, an established active substance, not described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white crystalline powder. Palonosetron hydrochloride is freely soluble in water, soluble in propylene glycol, slightly soluble in ethanol and 2-propanol. It has two chiral centres and the absolute configuration of its chiral centres is (S,S). The manufacturer produces one specific crystalline form.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The drug substance is manufactured in three main steps followed by some additional steps. The manufacturing process is described in sufficient detail. The proposed starting materials are considered acceptable. Adequate specifications are used for starting materials reagents and solvents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The limits for the identified impurities have been established and are considered acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for 10 batches. Six batches were stored at 25°C/60% RH (up to 36 months) and four batches at 40°C/75% RH (6 months) in accordance with applicable European guidelines. No clear changes or trend could be observed. Based on the data submitted, a retest period could be granted of 36 months when stored in the proposed packaging without specific storage temperature.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development data on equipment compatibility, filter compatibility and suitability are acceptable. The product in the glass vials as well as in the pre-filled syringes has the same pharmaceutical form and qualitative and quantitative in terms of the active substance as the reference product Aloxi.

On both products the same leachable studies have been performed. Three conditions (25°C/40% RH, 30°C/35% RH, and 40°C/≤25% RH) have now been applied up to 12 months (intended are 36-36-6 months, respectively). The maximum amounts of the detected leachables are all at a considerably lower level than calculated based on the PDE for the substance involved and based on the maximum daily dose of 1500 µg palonosetron. Herewith the view is supported that for all leachables involved very high safety margins are applicable, and that the use of both container systems is safe.

A bioequivalence study between the reference product and Palonosetron Fresenius Kabi is not required since Palonosetron Fresenius Kabi is an aqueous solution intended for intravenous injection similar to the reference product Aloxi.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. A flow diagram of the process has been provided. It comprises standard steps of compounding, pH adjustment, pre-filtration, filtration, closing and crimping of the glass vials and closing of the syringes, terminal sterilisation, inspection of filled containers and labelling and packaging. Process validation data on the product have been presented for three batches per packaging form in accordance with the relevant European guidelines.

Control of excipients

For all excipients certificates of analysis are provided. All excipients comply with specifications of the Ph.Eur. These specifications are acceptable.

Microbiological attributes

Both pharmaceutical forms are terminally sterilised products, with a bacterial endotoxin limit of 0.5 IU/ml. The data provided on microbiological attributes are considered acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form including requirements for the bacterial endotoxins. The specification includes tests for description, pH, extractable volume, osmolality, identification, assay, content, related substances, (sub-)visible particles, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 3 batches per packaging from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches per packaging at 25°C/40-60% RH (24 months), 30°C/35-65% RH (24 months) and at 40°C/25-75% RH (6 months) in accordance with applicable European guidelines. No changes or trends have been observed except for one impurity, which will be controlled accordingly. The products are not sensitive to light. On basis of the data submitted, a shelf life could be granted of 36 months when stored in the proposed packaging. Upon opening of the vial or prefilled syringe, the solution should be used immediately and the unused solution should be discarded.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Palonosetron Fresenius Kabi 250 microgram, solution for injection and Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre-filled syringe have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Palonosetron Fresenius is intended for substitution of similar medicinal products on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

These products are generic and hybrid formulations of Aloxi which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Palonosetron is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Palonosetron Fresenius Kabi 250 microgram, solution for injection and Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre-filled syringe are parenteral formulations and therefore fulfil the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Palonosetron Fresenius Kabi 250 microgram, solution for injection and Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre-filled syringe is entirely the same as the originator. Therefore, they may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current products can be used instead of its reference product.

IV.3 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 Palonosetron Fresenius Kabi.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> - Severe constipation - Severe hypersensitivity reactions
Important potential risks	<ul style="list-style-type: none"> - QT/QTc prolongation - Convulsive events - Serotonin syndrome
Missing information	<ul style="list-style-type: none"> - Effect in pregnancy - Effect in lactating women - Effects on fertility - Use in paediatric population - Effects in patients with end stage renal disease undergoing haemodialysis

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Aloxi. No new clinical studies were conducted. Palonosetron Fresenius Kabi is a parenteral

formulation and fulfils the requirements for an exemption from bioequivalence studies. Risk management is adequately addressed. These generic and hybrid medicinal products can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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. Twenty-four participants were tested in total. Four participants were tested during the preliminary round of testing. Ten participants were tested in the first round and ten participants were tested in the second round. The 15 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. All the information presented is compliant to the standard of the latest QRD template and because all participants were able to easily locate the necessary information, no amendments were deemed necessary after both rounds. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Palonosetron Fresenius Kabi 250 microgram, solution for injection and Palonosetron Fresenius Kabi 250 micrograms, solution for injection in pre-filled syringe have a proven chemical-pharmaceutical quality and are generic and hybrid forms of Aloxi 0.25 mg/5 ml, solution for in injection. Aloxi is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Palonosetron Fresenius Kabi with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 May 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Replacement or addition of a site where batch control/testing takes place; additional site	NL/H/3457/1-2/IA/001	IA	27-03-2017	19-04-2017	Approved	No