

# **Public Assessment Report**

## **Scientific discussion**

**Granisetron Claris 1 mg/ml,  
solution for injection**

**(granisetron hydrochloride)**

**NL/H/2942/001/DC**

**Date: 10 November 2014**

This module reflects the scientific discussion for the approval of Granisetron Claris 1 mg/ml, solution for injection. The procedure was finalised on 13 May 2014. For information on changes after this date please refer to the module 'Update'.

## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Granisetron Claris 1 mg/ml, solution for injection from Claris Lifesciences UK Limited.

The product is indicated in adults for the prevention and treatment of

- Acute nausea and vomiting associated with chemotherapy and radiotherapy.
- Post-operative nausea and vomiting.
- Prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.
- In children aged 2 years and above for the prevention and treatment of acute nausea and vomiting associated with chemotherapy.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Kytril 1 mg = 1 ml solution for injection (NL License RVG 20958), which was first registered in the Netherlands by Roche Nederland B.V. on 31 July 1997 through mutual recognition procedure IT/H/0300/003. Kytril solution for injection is no longer registered in the Netherlands. The reference product is marketed under different trade names across Europe, including Kevatriil®.

The concerned member states (CMS) involved in this procedure were Germany, Finland and Portugal.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

## II. QUALITY ASPECTS

### II.1 Introduction

Granisetron Claris 1 mg/ml is a clear, colourless solution, free from visible particles, with Osmolarity of 270 to 350 mOsmol/L and pH between 4.00 and 6.00. Each ml of solution for injection contains 1 mg granisetron (as hydrochloride).

The solution is packed in colourless glass ampoules with 1 ml and 3 ml fill volume. Each 1 ml ampoule contains 1 mg granisetron and each 3 ml ampoule contains 3 mg granisetron.

The excipients are: water for injections, sodium chloride, citric acid monohydrate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment).

### II.2 Drug Substance

The active substance is granisetron hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder which is freely soluble in water. The drug product is a solution for injection, hence particle size and polymorphic form of the drug substance are not deemed critical.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

#### Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

#### Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. monograph. Additional requirements for residual solvents, and microbial quality are included. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full-scale batch.

#### Stability of drug substance

The active substance is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

### **II.3 Medicinal Product**

#### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The development studies were aimed at obtaining a product essentially similar to the innovator product. Comparative studies were performed, showing the similarity with the originator product. The qualitative composition of the proposed drug products is the same as that of Kevatril. The packaging is usual and suitable for the product at issue. The manufacturing process is standard, and proof was provided that terminal sterilization can be performed. The pharmaceutical development of the product has been adequately performed.

#### Manufacturing process

The solution for injection is prepared by weighing the components and dissolving in water for injections. The pH is measured and if necessary adjusted. The volume is adjusted to final volume with water for injections. The solution is filtered before filling. The solution is filled in depyrogenised ampoules. After filling the ampoules are terminally sterilized, followed by 100% leak testing of the ampoules. Subsequently the ampoules are visually inspected, labelled and packed in secondary containers. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial-scale batches for both ampoule volumes. The product is manufactured using conventional manufacturing techniques.

#### Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

#### Microbiological Attributes

The product is terminally sterilized, intended for single dose use and does not contain any microbial preservatives. Suitability of the Ph.Eur. Type I containers is well established for sterile products.

#### Quality control of drug product

The product specification includes tests for appearance, degree of coloration, identity, extractable volume, pH, assays, related substances, bacterial endotoxins, sterility and osmolarity. Except for pH the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods are compendial procedures, or have been presented and adequately validated. Batch analytical data from the proposed production site have been provided on three batches for both fill volumes. The batch analysis results demonstrate compliance with the proposed release specifications.

#### Stability of drug product

Stability data on the product have been provided for six commercial-scale batches: three batches packed in 1 mL clear glass ampoules and three batches packed in 3 mL clear glass ampoules. These batches were stored at 25°C/60% RH (12 months), 30°C/65%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. All batches comply with the proposed set of specifications, at all temperatures tested. No up or downward trends in any parameter are observed under all conditions. The control tests and specifications for drug product are adequately drawn up. Photostability of the drug product was examined. Results show that the drug product is sensitive to light.

The proposed shelf-life of 24 months and the storage conditions of “do not store above 30°C; do not refrigerate or freeze; keep container in the outer carton in order to protect from light” are justified. An in-use physicochemical stability study of the drug product was carried out, by storing opened containers (ampoules) for 24 h at 25°C ± 2°C. The drug product was shown to be chemically stable during this period.

#### Compatibility

Compatibility studies were carried out in order to ascertain the possibilities of reaction of the chemical entities in the diluents or injection with the active ingredient, which could affect the purity or stability of the Drug Product. Diluent compatibility studies were performed with the following diluents, at 20°C to 25°C:

1. Sodium Chloride Injection BP (0.9% w/v)
2. Glucose Injection BP (5% w/v)
3. Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Injection BP
4. Hartmann's solution for Injection BP (Compound Sodium Lactate Injection BP)
5. Sodium Lactate Injection BP
6. Mannitol Injection BP (10% w/v)

In none of the studies any significant change was observed at any time point. Compatibility is demonstrated.

#### 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 Granisetron Claris 1 mg/ml, solution for injection has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to perform process validation for the first three maximum scale batches.
- The MAH committed to continue the stability study for the on going three exhibit batches until the approved shelf-life.
- The MAH committed to add one batch of the finished product per year to the stability testing program.

## **III. NON-CLINICAL ASPECTS**

### **III.1 Ecotoxicity/environmental risk assessment (ERA)**

Since Granisetron Claris is intended for generic substitution, 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**

This product is a generic formulation of Kytril solution for injection, 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

Granisetron 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

#### Biowaiver

Granisetron Claris 1 mg/ml, solution for injection is an aqueous parenteral formulation and therefore fulfils 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Granisetron Claris 1 mg/ml is entirely the same as the originator. Therefore, it 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 product 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 Granisetron Claris.

- Summary table of safety concerns as approved in RMP

Important identified risks	QT prolongation, Torsades de Pointes Other cardiac arrhythmias Hypersensitivity reaction
Important potential risks	Use in patients with - pre-existing arrhythmias - pre-existing cardiac disorders
Missing information	Use in paediatric population (Post-operative nausea and vomiting (PONV)) Use during pregnancy/lactation Effects on fertility in a human situation
Safety concern relating to the active substance	None
Safety concerns related to the route of administration	None
Safety concerns relating to the target population	None

The member states agree that no additional pharmacovigilance activities are required. The MAH committed to bring the RMP more in line with the applicable ‘Good pharmacovigilance practices’ in the future updates.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Granisetron Claris 1 mg/ml, solution for injection. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Both rounds of testing showed that, for each question, at least 90% of participants were able to find the correct information, and at least 90% of participants were able to answer the questions correctly. 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

Granisetron Claris 1 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is generic form of Kytril 1 mg = 1ml solution for injection. Kytril 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 Granisetron Claris 1 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 May 2014.

**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