CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Granisetron hameln 1 mg/ml concentrate for solution for injection or infusion
Hameln Pharma plus GmbH, Germany

granisetron (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1093/001/DC
Registration number in the Netherlands: RVG 100089

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Pharmacotherapeutic group:	antiemetics and antinauseants; serotonin (5-HT_3) antagonist
ATC code:	A04AA02
Route of administration:	parenteral use
Therapeutic indication:	prevention or treatment of nausea and vomiting induced by chemotherapy or radiotherapy in adults and children, 2 years of age and older.
Prescription status:	prescription only
Date of authorisation in NL:	16 September 2008
Concerned Member States:	Decentralised procedure with DE, DK, FI, PT, SE, UK
Application type/legal basis	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Granisetron hameln 1 mg/ml, concentrate for solution for intravenous injection or infusion, from Hameln Pharma plus GmbH, Germany. The date of authorisation was on 16 September 2008 in the Netherlands. The product is indicated for the prevention or treatment of nausea and vomiting induced by chemotherapy or radiotherapy in adults and children, 2 years of age and older.

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

Granisetron hameln 1 mg/ml is a highly selective antagonist of 5-hydroxytryptamine (5 HT_3) receptors and a potent anti-emetic . Radioligand binding studies have demonstrated that Granisetron hameln 1 mg/ml has negligible affinity for other receptor types including other 5 HT and dopamine D2 binding sites.
Granisetron hameln 1 mg/ml is effective after parenteral administration, either prophylactically or by intervention, in abolishing the retching and vomiting evoked by administration of cytotoxic drugs or by whole body X irradiation.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Kytril i.v. 1mg, solution for injection 1 mg/ml. The innovator product has been registered in the Netherlands by Roche Nederland B.V. since 31 July 1997 (NL License RVG 20958). In addition, reference is made to Kytril authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Granisetron hameln 1 mg/ml is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to this product.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is granisetron hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white powder, freely soluble in water, sparingly soluble in methylene chloride, slightly soluble in methanol. It contains no chiral centers. Granisetron hydrochloride is the endo-isomer. The exo-isomer is controlled as Ph.Eur. impurity F.

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/EMEA 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.

Quality control of drug substance
The drug substance specification and methods are in line with the Ph.Eur., with additional requirements for residual solvents. This specification is acceptable in view of the route of synthesis, the Ph.Eur. and ICH guidelines. Batch analytical data of 3 commercial batches, demonstrating compliance with the drug substance specification, have been provided.

Stability of drug substance
Stability data has been obtained during storage at 25°C/60%RH (24 months) and 40°C/75%RH (6 months) in accordance with applicable European guidelines. The drug substance was packaged in the commercial packaging, i.e. sealed colourless LDPE bag, placed in a black LDPE bag and put in a HDPE drum. The substance is sensitive to light. Based on the submitted results, the proposed retest period of 30 months has been approved when stored in the original package in order to protect from light.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Granisetron hameln 1 mg/ml contains as active substance 1.12 mg granisetron hydrochloride, equivalent to 1 mg granisetron. The product is a clear and colourless solution and packed in 1 or 3 ml colourless ampoules. The headspace of the ampoule concerns nitrogen. Pack sizes are 5 x 1 ml, 10 x 1 ml, 5 x 3 ml and 10 x 3 ml.

The excipients used are:
- Sodium chloride
- Citric acid monohydrate
- Sodium hydroxide (for pH adjustment)
- Water for injection

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packagings are usual and suitable for the product at issue.

Excipients
The excipients are common in the manufacture of parental formulations. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 pilot-scale batches in accordance with the relevant European guidelines. As the equipment is independent of the actual batch size this validation is also acceptable for production scale batches.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, pH, extractable volume, sub-visible particles, identity and assay of active substance, impurities, 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 the proposed production site(s) has been provided for 3 pilot-scale batches demonstrating compliance with the specification. The MAH committed to provide batch analytical data of the first 3 production batches.

Stability tests on the finished product
Stability data on the product haven been provided for 3 batches of 1 ml and 3 batches of 3 ml in accordance with applicable European guidelines, demonstrating the stability of the product over 18 months. On basis of the data submitted, a shelf life was granted of 30 months without specific temperature conditions. The labelled storage conditions are: "*Do not store above 25ºC; Do not freeze; Keep the ampoules in the outer carton in order to protect from light.*" The MAH committed to submit stability data covering the shelf-life period of 30 months.

In-use stability
Chemical and physical in-use stability data have been provided demonstrating that the reconstituted solution remains stable for 24 hours following reconstitution, when stored at 25˚C. From a microbiological point of view, the product should be used immediately. If to be stored, the dilutions should be prepared under appropriate aseptic conditions.

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.2 Non clinical aspects

This product is a generic formulation of Kytril i.v. 1 mg, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of granisetron released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Granisetron is a well-known active substance with established efficacy and tolerability.

Granisetron hameln 1 mg/ml is administered as an aqueous solution intended for intravenous injection containing the same active substance in the same concentration as the currently authorised reference medicinal product. As Granisetron hameln 1 mg/ml is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). Granisetron hameln 1 mg/ml is a generic of the reference product Kytril i.v. 1 mg, solution for injection 1 mg/ml, which is already on the European market. Thus, all data regarding to safety and efficacy available of the reference medicinal product also apply to this application.

Risk Management Plan
Granisetron was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of granisetron can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Kytril i.v. 1 mg, although more detailed and better formulated. The indication *'prevention and treatment of postoperative nausea and vomiting in gynaecological interventions'* mentioned in the SPC of Kytril i.v. 1 mg was not claimed for Granisetron hameln 1 mg/ml. Previously this was stated to be a patented indication of Hoffman-La Roche. The currently submitted SPC can be approved, however harmonisation with other granisetron registrations is advisable.

Readability Test
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. An initial test was performed with 2 participants, followed by two test rounds with 10 participants each. The distribution of age, gender and educational background was acceptable and the study population is deemed adequately representative of the target population. The results were considered supportive of the proposed package leaflet. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Granisetron hameln 1 mg/ml, concentrate for solution for injection or infusion, has a proven chemical-pharmaceutical quality and is a generic form of Kytril i.v. 1 mg, solution for injection 1 mg/ml. Kytril i.v. 1 mg 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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Kytril i.v. 1 mg, although more detailed and better formulated. The indication *'prevention and treatment of postoperative nausea and vomiting in gynaecological interventions'* in the SPC of Kytril i.v. 1 mg was not claimed for Granisetron hameln 1 mg/ml.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Granisetron hameln 1 mg/ml with the reference product, and have therefore granted a marketing authorization. The product was authorized in the Netherlands on 16 September 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during the written procedure.

A European harmonised birth date has been allocated (19 February 1991) and subsequently the first data lock point for granisetron is December 2008. The first PSUR is therefore expected in December 2011, after which a PSUR should be submitted every 3 years.

The date for the first renewal will be: 12 May 2013.

The following post-approval commitments have been made during the procedure:

Quality – Medicinal product

- The MAH committed to provide batch analytical data of the first 3 production batches.
- The MAH committed to submit stability data covering the shelf-life period of 30 months.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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