CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Granisetron Hikma, 1 mg/ml solution for injection
Granisetron Hikma, 1 mg/ml concentrate for solution for injection
Hikma Farmacêutica S.A., Portugal

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/1872/001-002/MR
Registration number in the Netherlands: RVG 34915, 103103

16 June 2010

Pharmacotherapeutic group:	antiemetics and antinauseants, serotonin (5HT3) antagonists
ATC code:	A04AA02
Route of administration:	intravenous
Therapeutic indication:	prevention or treatment of acute nausea and vomiting induced by cytostatic therapy, administered on the day of treatment in adults and children older than 2 years of age; prevention and treatment of postoperative nausea and vomiting in gynaecological interventions
Prescription status:	prescription only
Date of first authorisation in NL:	16 October 2008
Concerned Member States:	Mutual recognition procedure with DE, IT, PT
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 Hikma, 1 mg/ml solution for injection (1 mg/1 ml) and Granisetron Hikma, 1 mg/ml concentrate for solution for injection (3 mg/3 ml), from Hikma Farmacêutica S.A.. The date of authorisation was on 16 October 2008 in the Netherlands.

The product is indicated for:
- the prevention or treatment of acute nausea and vomiting induced by cytostatic therapy (chemotherapy and radiotherapy) if administered on the day of treatment in adults and children older than 2 years of age,
- prevention and treatment of postoperative nausea and vomiting in gynaecological interventions.

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

Granisetron is a potent anti-emetic and highly selective 5-HT_3 receptor antagonist. Pharmacological studies have shown that granisetron is effective against nausea and vomiting induced by cytostatic therapy. Granisetron solution for injection is effective in the prophylaxis and treatment of postoperative nausea and vomiting in gynaecological interventions.
Radioligand studies have demonstrated that granisetron has negligible affinity for other receptor types, including the 5-HT_1, 5-HT_2, 5-HT_4 and dopamine D_2 receptors. Granisetron does not affect prolactin and aldosterone levels.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Kytril i.v. 1 mg=1ml, solution for injection (NL License RVG 20958) and Kytril i.v. 3mg=3ml, concentrate for solution for infusion (NL RVG 14791) which have been registered in the Netherlands by Roche Nederland B.V. since 31 July 1997 (1 mg/ml) and 5 September 1991 (3 mg/ml). In addition, reference is made to Kytril i.v. authorisations in the individual member states (reference product).
In the assessment these products are considered one product: Granisetron Hikma 1 mg/ml, as they both have the same quality with as only difference the volume presentation (1 mg = 1 ml and 3 mg = 3 ml).

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 Hikma, 1 mg/ml is a product for parenteral use in aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products 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 these products and no paediatric development programme has been submitted, as this is not required for a generic application.

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 these product types 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.*). The active substance is a white or almost white powder, which is soluble in water, sparingly soluble in methylene chloride and slightly soluble in methanol. The substance shows polymorphism.

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.

Manufacturing process
The manufacturing process has been adequately described. Additionally the MAH has clearly shown that only one polymorphic form is obtained.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur., with additional requirements for residual solvents, microbial endotoxins and microbial limits. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three consecutive full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25ºC/60%RH (18 months) and 40ºC/75%RH (6 months). The batches were adequately stored. Based on the results provided, the proposed storage period (2 years) and storage condition could be granted.

** 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 Hikma is a clear and colourless solution for injection with a pH of 4.0-6.0 and osmolality of 250-350 mOsmol/kg. The product is registered as an ampoule with 1 ml solution for injection (1 mg/1 ml) and as an ampoule with 3 ml concentrate for solution for infusion (3 mg/3 ml)

The solution for injection is packed in a colourless 1 ml type I glass ampoule with blue OPC.
The concentrate for solution for injection is packed in a colourless 3 ml type I glass ampoule with orange OPC.
OPC (one point cut) is to facilitate the breaking of the ampoule.

The excipients are: sodium chloride, citric acid monohydrate (E330), hydrochloric acid for pH adjustment (E507), sodium hydroxide for pH adjustment (E524), water for injections.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main factors that were considered during product development are solubility of granisetron hydrochloride, stability in pH 4.0 – 6.0, osmolality contribution of the excipients, compliance of the drug substance to the Ph. Eur., protection to light, compatibility of the drug substance and the excipients, sterilisation and the packaging material. No overages are used. The method for sterilization was determined by testing the autoclave effect on the assay, pH, and related substances. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process involves dissolving sodium chloride and citric acid in water for injection, followed by dissolution of granisetron HCl and pH adjustment. The final solution is filtered in order to reduce bioburden. The solution is filled into clear glass ampoules type I ampoules and terminally sterilized using an autoclave. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product has been presented for three full-scale batches. The MAH committed to perform process validation on the first three industrial batches.

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

Quality control of drug product
The product specification includes tests for description, identification, volume in container, colour, clarity, pH, particulate matter, leak test, assay, related substances, bacterial endotoxins, sterility and osmolality. The end-of-shelf life specifications are similar to the release specifications, except for the exclusion of identification by UV-spectrum at the end-of-shelf life. This is acceptable. The analytical methods has been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot-scale batches per fill volume, demonstrating compliance with the release specification.

Microbiological attributes
According to the Ph. Eur. products, where feasible, should be sterilised in their final container. Granisetron is not sensitive to heat and it was therefore decided to perform the standard overkill autoclaving process. The solution is submitted to sterilizing filtration before filling to reduce the bioburden. The filters are tested for integrity before and after filtration.

Stability of drug product
Stability data on the product has been provided on three pilot scale batches per fill volume stored at 25ºC/60%RH (24 months) and 40ºC/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in glass I type ampoules. No clear trends or out of spec results are obtained during the months tested. No photostability study has been performed. The drug substance is however known to be susceptible to light. The proposed shelf life (2 years) and storage condition, (*Do not refrigerate or freeze, store in the original package in order to protect from light*) are acceptable.

Compatability/In-use stability
The composition of the drug product was based on the innovator product. Compatibility with different infusion fluids was studied immediately after dilution and 24 hours after dilution at room temperature. The diluents studied were 5% glucose, Hartmann's solution (a solution containing sodium chloride, potassium chloride, calcium chloride, and sodium lactate in distilled water) and 10% mannitol. No incompatibility was observed with the diluents tested.
The following diluents were not tested because they have common ingredients to the previously mentioned diluents: 0.9% sodium chloride, 0.18% sodium chloride, 4% glucose and sodium lactate. This is acceptable, also since the innovator is compatible with the same diluents as claimed by the MAH.
Diluted solutions are chemically stable for 24 hours when stored below 25ºC. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times

and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated 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., 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 Hikma, 1 mg/ml solution for injection and Granisetron Hikma, 1 mg/ml concentrate for solution for injection 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Granisetron Hikma, 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 products can be used instead of their reference products.

Risk management plan
Granisetron was first approved in 1991, 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 mutual recognition procedure is in accordance with that accepted for the reference product Kytril marketed by Roche.

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. Three rounds of testing including a pilot test were performed with a total of 23 participants. The questionnaire consisted of one general question and 19 product specific questions. Three additional questions requesting feedback of the participants on the

layout, design and user-friendliness of the PIL were also included. The question address the most relevant safety issues.

The result scores were very high. Both in the first and second round of testing, 100% of the participants were able to find the information “very easily” or “easily” and all of them (100%) were able to understand the information “very easily” or “easily”. As result of these high scores, no modifications were made to the PIL after either test round.

The responses to the three additional questions concerning the participants’ opinion on the layout, design and user-friendliness of the PIL resulted in some suggestions for improvement. The PIL was amended accordingly. The results are in general well presented, documented and discussed. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Granisetron Hikma, 1 mg/ml solution for injection and Granisetron Hikma, 1 mg/ml concentrate for solution for injection have a proven chemical-pharmaceutical quality and are generic forms of Kytril i.v. 1 mg=1ml, solution for injection and Kytril i.v. 3mg=3ml, concentrate for solution for infusion. Kytril i.v. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product; the SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Granisetron Hikma, 1 mg/ml solution for injection and 1 mg/ml concentrate for solution for injection were authorised in the Netherlands on 16 October 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Granisetron Hikma, 1 mg/ml solution for injection and 1 mg/ml concentrate for solution for injection with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 19 January 2010.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from January 2010 to January 2013.

The date for the first renewal will be: 19 January 2015.

The following post-approval commitment has been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to perform process validation on the first three industrial batches.

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
PIL	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