CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Granisetron Mylan 1 mg, film-coated tablets
Granisetron Mylan 2 mg, film-coated tablets
Mylan B.V., the Netherlands

granisetron 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/0817/001-002/MR
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Pharmacotherapeutic group:	antiemetics and antinauseants; setotonin ($5HT_3$) antagonists
ATC code:	A04AA02
Route of administration:	oral
Therapeutic indication:	prevention of acute nausea and vomiting induced by cytostatic therapy (chemotherapy and radiotherapy) when administered on the day of treatment.
Prescription status:	prescription only
Date of authorisation in NL:	26 January 2005
Concerned Member States:	Mutual recognition procedure with BE, CZ, DE, HU, IT, SI and SK
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 concerned member states have granted a marketing authorisation for Granisetron Mylan 1 mg, film-coated tablets and Granisetron Mylan 2 mg, film-coated tablets, from Mylan B.V. The date of authorisation was on 26 January 2005 in the Netherlands. The product is indicated for prevention of acute nausea and vomiting induced by cytostatic therapy (chemotherapy and radiotherapy) when administered on the day of treatment.

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

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT_3) receptors. Pharmacological studies have demonstrated that granisetron is effective against nausea and vomiting as a result of cytostatic therapy. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types, including 5-HT_1, 5-HT_2, 5-HT_4 and dopamine D_2 binding sites.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Kytril® 1 mg and 2 mg (NL License RVG 16285 and 19203), containing 1 mg and 2 mg granisetron HCl respectively, which have been registered in Denmark by Roche a/s since 1991. 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. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Kytril® 1 mg, registered in the United Kingdom and Kevatril® 2 mg, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic 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 these products.

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 and excipients
The active substance is granisetron HCl, an established active substance described in a draft monograph the European Pharmacopoeia (Ph.Eur.*). It is a white to off-white crystalline powder, which is freely soluble in water, sparingly soluble in methylene chloride and slightly soluble in methanol. The manufacturing process development has been adequately described.

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.

Granisetron is synthesised in one reaction steps followed by purification. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents. The active substance specification is considered adequate to control the quality and meets the requirements of the draft monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 6 production scale batches.

Stability data on the active substance have been provided for 6 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 60 months. Based on the data submitted, a retest period could be granted of 5 years when stored in the original package, which protects the material from light, moisture and air (oxygen).

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

** 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 1 Mylan film-coated tablets contain as active substance 1.12 mg granisetron hydrochloride, corresponding to 1 mg granisetron, and are white or whitish tablets marked "GS" on one side and with no marking on the other side.
Granisetron 2 Mylan film-coated tablets contain as active substance 2.24 mg granisetron hydrochloride, corresponding to 2 mg granisetron, and are white or whitish tablets marked "GS2" on one side and with no marking on the other side.

The tablets are packed in opaque PVC/PVdC-Aluminium foil blisters.

The excipients are: lactose monohydrate, microcrystalline cellulose (E460), hypromellose (hydroxypropylmethyl cellulose) (E464), sodium starch glycolate, magnesium stearate (E572), titanium

dioxide (E171), macrogol (polyethylene glycol) 400, polysorbate 80 (E433). The tablets have the same dose proportional composition.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Kytril.

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 1 batch of each strength in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product is based on the monograph for tablets in the Ph.Eur. and includes tests for appearance, identification, uniformity of mass, average mass, assay, content uniformity, related substances, dissolution rate, hardness, loss on drying, disintegration time and microbiological impurity. 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 of each strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 6 batches of the 1 mg product in accordance with applicable European guidelines demonstrating the stability of the product over 36 months. Stability data on the product have been provided for 3 batches of the 2 mg product in accordance with applicable European guidelines demonstrating the stability of the product over 36 months and 3 batches of the 2 mg product demonstrating the stability of the product for 48 months. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are*: "No special temperature for storage, store in original container."*

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a generic formulation of Kytril, 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 HCl 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 HCl is a well-known active substance with established efficacy and tolerability.

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 Nederland.

For this generic application, the MAH has submitted 2 bioequivalence studies under fasted conditions In one bioequivalence study the pharmacokinetic profile of the 1 mg strength of the test product, Granisetron 1 Mylan, is compared with the pharmacokinetic profile of the reference product Kytril® 1 mg, United Kingdom. The second bioequivalence study compared the test product Granisetron 2 mg with the pharmacokinetic profile of the reference product Kevatril® 2 mg, registered in Germany. Kevatril is the name for the innovator product in Germany.

The choice of the reference products from Germany and the United Kingdom in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states.

Granisetron HCl should be taken once (2 mg) or twice (1 mg) daily without reference to food intake. From the literature it is known that food does not interact with the absorption of granisetron. Therefore, a food interaction study is not deemed necessary. The bioequivalence studies under fasting conditions are in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioequivalence study I – 1 mg

For the first study an open-labeled, laboratory blind, single-dose, randomised, two-period cross-over, bioequivalence study was carried out under fasted conditions in 70 healthy subjects (43 males and 27 females), aged 18-55 years. For each subject there were 2 dosing periods of one of the two granisetron HCl formulations, separated by a washout period of 14 days. The tablets were orally administered with 240 ml water after an overnight fast. Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration. Four subjects were withdrawn from the study for adverse events which were unrelated to the drug treatment. Sixty-six subjects were eligible for pharmacokinetic analysis. The bioavailability of the test Granisetron 1 Mylan tablet was compared to the British reference product Kytril 1 mg, Roche UK.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of granisetron under fasted conditions.

Treatment N=66	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	59 ± 32	62 ± 34	6.0 ± 1.6	1.5 (1-3)	6.8 ± 3.0
Reference	60 ± 36	63 ± 38	6.0 ± 1.9	1.5 (0.5-6)	6.8 ± 3.1
***Ratio (90% CI)**	1.07 (0.98-1.17)	1.07 (0.98-1.17)	1.03 (0.98-1.09)	--	--
CV (%)	32	31	19	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. The other

pharmacokinetic variables were comparable between both products. Based on the pharmacokinetic parameters of granisetron under fasted conditions, it can be concluded that test Granisetron 1 Mylan tablet and the reference product Kytril 1 mg tablet, are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – 2 mg

For the second study an open-labeled, laboratory blind, single-dose, randomised, two-period cross-over, bioequivalence study was carried out under fasted conditions in 60 healthy subjects (45 males and 15 females), aged 18-55 years. For each subject there were 2 dosing periods of one of the two granisetron HCl formulations, separated by a washout period of at least 7 days. The tablet was orally administered with 240 ml water after an overnight fast. Blood samples were collected at pre-dose and at 0.5, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.5, 4, 5, 7, 9, 12, 16, 24, 36 and 48 hours after administration. Two subjects withdrew from the study, one with a reason not related to the treatment and one due to development of gastro-enteritis. Fourty subjects (30 males and 10 females), aged 18-48 years, were eligible for pharmacokinetic analysis. The bioavailability of the test Granisetron 2 Mylan tablet was compared to the German reference product Kevatril 2 mg, Hoffmann-La Roche AG.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of granisetron under fasted conditions.

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	87 ± 57	92 ± 60	10.5 ± 3.8	1.5 (0.5-3)	5.8 ± 2.9
Reference	88 ± 60	92 ± 63	10.5 ± 4.0	1.5 (0.5-5)	5.7 ± 2.8
***Ratio (90% CI)**	1.01 (0.91-1.12)	1.02 (0.92-1.12)	1.00 (0.94-1.05)	--	--
CV (%)	28	27	15	--	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

The study design was not optimal, or the analytical method was not sensitive enough to evaluate the $AUC_{0-\infty}$ of the metabolite 7-hydroxy-granisetron reliably. As the evaluation of the metabolite was only for exploratory purposes this is acceptable.

The 90% confidence intervals of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} calculated for granisetron, and AUC_{0-t} and C_{max} calculated for 7-hydroxy-granisetron are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. The other pharmacokinetic variables were comparable between both products. Based on the pharmacokinetic parameters of granisetron under fasted conditions, it can be concluded that test Granisetron 2 Mylan tablet and the reference product Kevatril 2 mg tablet, are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The formula and preparation of the bioequivalence batches are identical to the formula proposed for marketing.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan

Granisetron HCl 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 HCl can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation, 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.

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. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Granisetron 1 Mylan, film-coated tablets, 1 mg and Granisetron 2 Mylan, film-coated tablets, 2 mg have a proven chemical-pharmaceutical quality and are generic forms of Kytril 1 and 2 mg. Kytril is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SPC is consistent with that of the reference product.

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. Granisetron 1 Mylan, film-coated tablets, 1 mg and Granisetron 2 Mylan, film-coated tablets, 2 mg were authorised in the Netherlands on 26 January 2005.

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 bioequivalence has been demonstrated for Granisetron 1 Mylan and Granisetron 2 Mylan with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised on 1 August 2006.

The first PSUR has been submitted under the PSUR work-sharing project on assessment of PSURs and it covers a period from January 2005 till January 2008. Hereafter, PSURs will be submitted 3-yearly.

The date for the first renewal will be 26 January 2010.

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 Y/N
Change in the name and/or address of the MAH.	NL/H/0817 /001-002/ IA/001	IA	12-6-2008	22-7-2008	Approval	N
Change in the name of the medicinal product.	NL/H/0817 /001-002/ IB/002	IB	12-6-2008	20-8-2008	Approval	N
Change in the name of the medicinal product for BE only.	NL/H/0817 /001-002/ IA/003	IA	10-7-2009	24-7-2009	Approval	N
Change in pack size of the finished product; change in the number of units (e.g. tablets, ampoules, etc.) in a pack; change outside the range of the currently approved pack sizes.	NL/H/0817 /001/IB/ 004	IB	7-9-2009	6-9-2009	Approval	N