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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Rizatriptan Aurobindo 5 mg and 10 mg, tablets
Aurobindo Pharma B.V., the Netherlands

rizatriptan benzoate

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/2416/001-002/DC
Registration number in the Netherlands: RVG 110262 - 110263

22 January 2013

Pharmacotherapeutic group:	antimigraine preparations, selective serotonin (5HT1B/1D) agonists
ATC code:	N02CC04
Route of administration:	oral
Therapeutic indication:	Acute treatment of the headache phase of migraine attacks with or without aura in adults.
Prescription status:	prescription only
Date of authorisation in NL:	18 December 2012
Concerned Member States:	Decentralised procedure with DE, ES and FR
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 Rizatriptan Aurobindo 5 mg and 10 mg tablets, from Aurobindo Pharma B.V. The date of authorisation was on 18 December 2012 in the Netherlands.

The product is indicated for acute treatment of the headache phase of migraine attacks with or without aura in adults.

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

Rizatriptan binds selectively with high affinity to human 5-HT1B and 5-HT1D receptors and has little or no effect or pharmacological activity at 5-HT2, 5-HT3; adrenergic alpha1, alpha2 or beta; D1, D2, dopaminergic, histaminic H1; muscarinic; or benzodiazepine receptors.
The therapeutic activity of rizatriptan in treating migraine headache may be attributed to its agonist effects at 5-HT1B and 5-HT1D receptors on the extracerebral intracranial blood vessels that are thought to become dilated during an attack and on the trigeminal sensory nerves that innervate them. Activation of these 5-HT1B and 5-HT1D receptors may result in constriction of pain-producing intracranial blood vessels and inhibition of neuropeptide release that leads to decreased inflammation in sensitive tissues and reduced central trigeminal pain signal transmission.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Maxalt 5 mg and 10 mg tablets (NL License RVG 21815, 21816) which has been registered in the Netherlands by Merck Sharp and Dohme B.V. since 11 February 1998. The Netherlands is RMS for the MRP procedure under which Maxalt is processed, procedure number NL/H/0144, in which the UK is concerned member state in this procedure. Therefore, the NL and UK marketed product are considered the same. In addition, reference is made to Maxalt authorisations in the individual member states.

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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Maxalt 10 mg tablets, registered in the United Kingdom. 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 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 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 rizatriptan, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder or crystals, which is slightly hygroscopic. It is soluble in water, sparingly soluble in ethanol and practically insoluble in methylene chloride. The active substance does not have a chiral center.
Polymorphs of rizatriptan benzoate are known in the literature. However, the basic patent process in crystallizing rizatriptan benzoate, which yields the polymorphic form, is followed and identical to the marketed 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 manufacturing process is a two-step synthesis. The route of synthesis is adequately described and a thorough discussion on (potentially genotoxic) impurities, solvents, reagents and catalyst resulting from or used in the manufacture is provided.

Quality control of drug substance
The specifications on identification are identical to the requirements of the draft Ph. Eur. mono-graph, and are herewith acceptable. The microbial requirements are in accordance with Ph. Eur., the in-house requirements on residual solvents are equal or tighter than corresponding ICH limits, and the remaining in-house requirements are based on custom requirements. All quantitative methods are satisfactorily validated, and satisfactory cross-validations have been performed for the in-house HPLC methods for assay and related substances. Batch analysis results were satisfactory. Sufficient data on the reference- and working standards, and on the impurity reference standards, have been provided.

Stability of drug substance
Three batches have been put on stability for 3 years at 25°C and 6 months at 40°C/75% RH. All stability results are in accordance with the set requirements. Based on the provided stability data the claimed re-test period of 3 years was granted, without specific storage temperature if stored in the original packaging in order to protect from moisture.

** 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
Rizatriptan Aurobindo 5 mg are pale pink coloured, circular, flat, beveled edge uncoated tablets debossed with 'X' on one side and '13' on other side. The tablets may be mottled.
Rizatriptan Aurobindo 10 mg are pale pink coloured, circular, flat, beveled edge uncoated tablets debossed with 'X' on one side and '14' on other side. The tablets may be mottled.

The tablets are packed in Polyamide/Aluminium/PVC - Aluminium foil blister packs.

The excipients are: cellulose microcrystalline [E460], lactose monohydrate, maize starch, iron oxide red [E172], pregelatinized starch and magnesium stearate.

The two strengths are dose proportional.

Pharmaceutical development

An adequate description of the pharmaceutical development has been provided. The proposed excipients are well-known and partially based on the innovator's composition. A bioequivalence study was carried by comparing the test product Rizatriptan Aurobindo 10 mg tablets with the reference product Maxalt 10 mg tablets. The dissolution profiles of the 10 mg test bio-batch and the 10 mg reference test product are highly similar in four different test media, and in all media > 85% of the drug is released within 15 min. Also the 5 & 10 mg strengths of the proposed product have been compared in the 4 dissolution media. All profiles were found similar and in all media > 85% of the drug is released within 15 min. Based on this data and other data the MAH justified a bio-waiver for the proposed 5 mg strength. The description of the development of the dissolution method is accepted. The manufacturing development and up-scaling activities of the proposed manufacturing process have been adequately described.

Manufacturing process

Rizatriptan tablets are manufactured using a wet granulation process. It involves use of standard procedures well known for manufacture of tablets, namely sifting, mixing, granulation, drying, size reduction, blending, lubrication and compression. A list of equipment applicable for all three scale blend sizes, a flow diagram and detailed descriptions of the manufacturing steps are provided.
Three batches of the common blend have been validated, as well as the resulting 5 & 10 mg tablets. The validation results on the preparation of the common blend and the compression quality parameters were satisfactory. Validation schemes are provided for validation of batches for both the blend and resulting 5 & 10 mg tablets. The limited validation data confirms so far that the manufacturing process is fully under control.

Control of excipients

All excipients, excluding the colourant ferric oxide, are in accordance with the requirements of the corresponding Ph.Eur. monographs. Ferric oxide is in accordance with the monograph in USP/NF. Additional tests are applied for microcrystalline cellulose, pregelatinized starch and ferric oxide, and are acceptable.

Quality control of drug product

Drug product specifications are applied for description, identification by HPLV and TLC, average weight, thickness, KF water content, HPLC assay, uniformity of dosage units (content uniformity), dissolution, HPLC related substances and microbiological purity.
In general all proposed release and shelf life specifications are considered acceptable. The release and shelf life specifications – with minor differences for KF water content and HPLC related substances – are considered adequate. Batch analysis results have been provided for three submission batches per strength. All results are in accordance with the set drug product release specification.

Stability of drug product

The MAH claims a shelf life of 2 years if stored in triple laminated cold form Alu-Alu blister pack without specific storage condition. For 3 batches of each strength 12 months normal stability data and 6 months accelerated stability data are available. Test parameters are description, HPLC assay, HPLC related substances, dissolution, microbial contamination, KF water content, disintegration and friability, the latter two for information only. No significant changes regarding the test parameters have been observed for both the accelerated as well as the long term stability studies. The drug product was shown to be photostable. Based on the satisfactory stability data the claimed shelf-life of 2 years in the proposed blister packaging without specific storage condition can be accepted. The hold time of bulk tablets in double LDPE bags of NMT 12 months has been adequately demonstrated.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For magnesium stearate it has been stated that the stearic acid used is from vegetable origin (natural palm oil). Lactose is manufactured using milk and using no other ruminant material except calf rennet. The milk used in the process is sourced from healthy animals in the same conditions as milk collected for human consumption. The calf rennet used in the manufacture of lactose is produced in accordance with the applicable EU requirements.

II.2 Non-clinical aspects

This product is a generic formulation of Maxalt 5 mg and 10 mg tablets, which are available on the European market. 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.

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 rizatriptan 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Rizatriptan Aurobindo 10 mg (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Maxalt 10 mg tablets (Merck Sharp & Dohme Limited, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
An open label, randomized, two treatment, two sequence, two period, crossover, single-dose comparative oral bioavailability study was carried out under fasted conditions in 36 healthy male subjects, with a mean age of 28.3 years and a mean BMI of 21.3. Each subject received a single dose (10 mg) of one of the 2 rizatriptan formulations. The tablet was orally administered with 240 ml water after an approximately 10 hours fast. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20 and 24 hours after administration of the products.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The long-term storage stability sufficiently covered the storage period (56 days) of the samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Thirty-five (35) subjects completed the study and were included in the statistical analysis: 1 subject was withdrawn during period II due to vomiting.

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

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	117 ± 37	118± 37	30.2 ± 8.9	0.8 (0.5 – 3.5)	2.3 ± 0.6
Reference	117± 34	117± 34	29.4 ± 7.7	1.0 (0.5 – 3.5)	2.2 ± 0.5
***Ratio (90% CI)**	1.00 (0.96 – 1.05)	1.00 (0.96 – 1.05)	1.02 (0.95 – 1.10)	-	-
CV (%)	11	11	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. Based on the pharmacokinetic parameters of rizatriptan under fasted conditions, it can be concluded that Rizatriptan Aurobindo 10 mg tablets and Maxalt 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Rizatriptan may be taken without reference to food intake. The absorption of rizatriptan is delayed by approximately 1 hour when administered together with food. Therefore, onset of effect may be delayed when rizatriptan is administered in the fed state. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Safety
Two of the thirty-six subjects experienced a total of 2 adverse events during the entire duration of the study. These adverse events were mild and none of these events were considered to be serious.

Extrapolation to 5 mg strength
A biowaiver has been granted for the 5 mg tablet, as the following conditions have been fulfilled:
- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the qualitative composition of the different strengths is the same
- the ratio between amounts of active substance and excipients is the same
- the dissolution profile is similar under identical conditions for the additional strengths and the strength of the bioequivalence batch.

The MEB has been assured that the bioequivalence study has 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

Rizatriptan was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of rizatriptan 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.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Maxalt 5 and 10 mg tablets marketed by Merck Sharp and Dohme B.V.

Readability test
Readability testing was performed on the package leaflet. A bridging report has been provided which stated that, following Directive 2001/83/EC as amended by Directive 2004/27/EC, the readability of the patient information leaflet of the medicinal product Sumatriptan Aurobindo 50 mg & 100 mg tablets (Parent PIL) has been assessed and approved during a DC Procedure (SE/H/686/001-002/DC) to ensure potential users could locate, understand and appropriately act upon the information contained in the leaflet. The MAH proposed to bridge the results of the user test for the PIL of Sumatriptan Aurobindo 50 mg & 100 mg tablets to that of Rizatriptan Aurobindo 5 mg & 10 mg tablets (Daughter PIL).
This is justified on the following grounds:

- Both products are prescription-only medicines.
- Both products belong to the class of 'Selective serotonin (5HT1) agonists'
- Both products are oral preparations.
- The precautions before using the products are similar.
- The expected side effect profiles of both products are similar.

The RMS considers the Bridging Report acceptable and therefore the User Readability is considered appropriate. Furthermore, it is noted that the PIL is in line with the PIL of the innovator Maxalt, which is already tested and considered approvable on readability of the PIL.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rizatriptan Aurobindo 5 mg and 10 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Maxalt 5 mg and 10 mg tablets. Maxalt 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 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 and are in agreement with other rizatriptan containing products.

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 Rizatriptan Aurobindo 5 mg and 10 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 9 August 2012. Rizatriptan Aurobindo 5 mg and 10 mg tablets were authorised in the Netherlands on 18 December 2012.

The date for the first renewal will be: 9 August 2017.

There were no post-approval commitments made during the procedure.

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