

**PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands**

**Frovatriptan DOC Generici 2.5 mg, film-coated tablets  
DOC Generici Srl, Italy**

**frovatriptan (as succinate monohydrate)**

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/2758/001/DC  
Registration number in the Netherlands: RVG 112365**

**28 October 2013**

Pharmacotherapeutic group:	selective 5-HT <sub>1</sub> receptor agonists
ATC code:	N02CC07
Route of administration:	oral
Therapeutic indication:	acute treatment of the headache phase of migraine attacks with or without aura.
Prescription status:	prescription only
Date of authorisation in NL:	15 August 2013
Concerned Member States:	Decentralised procedure with IT
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 Frovatriptan DOC Generici 2.5 mg, film-coated tablets from DOC Generici Srl. The date of authorisation was on 15 August 2013 in the Netherlands.

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

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

Frovatriptan is a selective agonist for 5-HT receptors, which shows high affinity for 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> binding sites in radioligand assays and exhibits potent agonist effects at 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors in functional bioassays.

It exhibits marked selectivity for 5-HT<sub>1B/1D</sub> receptors and has no significant affinity for 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>6</sub>,  $\alpha$ -adrenoreceptors, or histamine receptors.

Frovatriptan has no significant affinity for benzodiazepine binding sites.

Frovatriptan is believed to act selectively on extracerebral, intracranial arteries to inhibit the excessive dilatation of these vessels in migraine. At similar concentrations to those obtained in humans, frovatriptan produced constriction of human isolated cerebral arteries with little or no effect on isolated human coronary arteries.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Migard 2.5 mg film-coated tablets (NL License RVG 27211) which has been registered in the Netherlands by Menarini International Operations Luxembourg S.A. since 19 April 2002 (original product). The registration was part of MRP FR/H/0195/001. In addition, reference is made to Migard authorisations in the individual member states, in France named Tigreat 2.5 film-coated tablets (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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Tigreat 2.5 film-coated tablets, registered in France. 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 frovatriptan succinate monohydrate, an established active substance described in the European, British or United States Pharmacopoeia (Ph.Eur.\*). The drug substance is a white to off-white powder, which is soluble in water and very slightly soluble in methanol. Frovatriptan succinate monohydrate is known to exhibit isomerism. The crystalline form manufactured is the R-isomer.

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 synthesis has been sufficiently described. Adequate specifications are applied for starting materials and intermediates. Adequate in-process controls and controls on the intermediates are applied. Potential (geno-)toxic impurities are discussed and adequate controls are applied.

#### Quality control of drug substance

The drug substance specification of the MAH is identical to that of the active substance manufacturer with an additional specification on particle. The specifications are acceptable. Batch analysis results have been provided for 3 batches of drug substance.

#### Stability of drug substance

Three batches have been stored for 36 months at 25°C/60% RH and for 6 months at 40°C/75% RH. All stability results meet the set drug substance requirements and there are no clear trends to be observed. In view of the available stability results the claimed re-test period of 3 years was granted.

*\* Ph.Eur., BP and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, UK or USA, respectively..*

### **Medicinal Product**

#### Composition

Frovatriptan DOC Generici 2.5 mg is a white to off-white round film-coated tablet, plain on both sides.

The tablets are packed in blister strips formed from PVC/PE/PCTFE white opaque copolymer: Al lidding foil blisters.

The excipients are:

*Tablet core* - silicified microcrystalline cellulose, lactose anhydrous, silicon dioxide, sodium starch glycolate type A, magnesium stearate

*Film coat* - hypromellose (E464), lactose monohydrate, macrogol 3350 (E1521), triacetin, titanium dioxide (E171).

#### Pharmaceutical development

In general the pharmaceutical development has been adequately described. Formulation development has been largely based on the known qualitative composition of the innovator product. Subsequently the final formulation has been developed and optimized by seven trial formulation steps. Particle size has been discussed. A bioequivalence study has been performed between the test bio-batch and the French reference bio-batch. Based on comparative batch analysis results the test and reference products are considered essentially similar.

Comparative dissolution studies have been performed between the test and reference bio-batches used in the bioequivalence study in 3 different media. In all media the dissolution profiles of the test and reference bio-batches are considered similar. The development of the dissolution method has been adequately described. For all other pharmaceutical development sections sufficient data has been provided.

#### Manufacturing process

The manufacturing process of both manufacturers consists of the usual steps of weighing, blending, compression, film-coating, and packing. The validation results for pilot-scale batches at the first manufacturing site are acceptable. No critical issues have been observed.

The proposed manufacturing process for one manufacturer is considered a non-standard process. However, for the other manufacturing site the manufacturing process for Frovatriptan DOC Generici 2.5 mg film-coated tablets is considered a standard process. The guideline on process validation ensures that the manufacturing process will be validated for three production batches at a larger scale before batches will be released to the market.

The MAH provided additional data on the manufacture at the first site. Process validation reports on 2 batches were submitted. The validation results of the two validation batches meet the set validation acceptance criteria. The MAH committed to finalize the process validation of the Frovatriptan DOC Generici 2.5 mg film-coated tablets on a third batch.

#### Control of excipients

All excipients are in compliance with their corresponding Ph. Eur. or USP monographs. These specifications are acceptable.

#### Quality control of drug product

In general adequate drug product specifications are applied. These include tests on identification, uniformity of dosage units, moisture, disintegration time, dissolution, related substances, assay and microbiological quality. The dissolution specification NLT 80% (Q) at 30 min is considered acceptable and being in line with the dissolution result of the test bio-batch. The applicant committed to review the total impurity limit on the finished product once additional data is generated, and ensures that the proposed specification (for release and shelf-life) on total impurities will reasonably be based on the batch and stability results observed.

Batch analysis data has been presented on 3 batches from one manufacturer and on 2 batches from the other. The results meet the requirements.

#### Stability of drug product

Stability data have been provided on the drug product from both manufacturers. The following conditions were used:

25°C ± 2°C, RH=60% ± 5% (18 months data provided)

30°C ± 2°C/65% RH ± 5% (9 months data available)

40°C ± 2°C, RH=75% ± 5% (6 months data provided)

At all conditions no specific or significant changes are noted. The available stability results meet the shelf life specifications. Photostability studies showed that the product does not need to be protected from light. Based on the results, the proposed shelf-life of 30 months, if stored not above 30°C, can be accepted. The storage statement "Do not store above 30°C" is in line with the brand leader storage statement

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies  
Magnesium stearate is of vegetable origin. For lactose anhydrous an adequate TSE statement has been presented.

## II.2 Non-clinical aspects

This product is a generic formulation of Migard which is 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 frovatriptan 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

Frovatriptan 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.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Frovatriptan DOC Generici 2.5 mg (DOC Generici Srl, Italy) is compared with the pharmacokinetic profile of the reference product Tigreat 2.5 film-coated tablets (Menarini, France).

### *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*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy subjects (20 males and 12 females), aged 18-45 years. Each subject received a single dose (2.5 mg) of one of the 2 frovatriptan formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48 and 72 hours after administration of the products.

The procedures followed for a fasting condition and a wash-out period of 7 days (*i.e.* at least 5 terminal half-lives to exclude carry-over effects) are in accordance with the Guideline on bioequivalence and hence agreed. The study is considered to be appropriate.

### *Analytical/statistical methods*

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

### *Results*

One male subject and one female subject were withdrawn from the study before treatment period 2 due to common cold and influenza, respectively. Hence 30 subjects (19 males and 11 females) completed the study and were included in the analysis.

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

Treatment N=30	AUC <sub>0-72h</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	22.1 $\pm$ 7.3	23.3 $\pm$ 9.1	2.6 $\pm$ 0.8	2.6 (1.5– 5)	--
<b>Reference</b>	22.1 $\pm$ 9.1	23.1 $\pm$ 7.2	2.7 $\pm$ 0.6	2.5 (2 – 5)	--
<b>*Ratio (90% CI)</b>	0.97 (0.90 – 1.05)	0.98 (0.91 – 1.06)	0.94 (0.88 – 1.02)	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> 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 frovatriptan under fasted conditions, it can be concluded that Frovatriptan DOC Generici 2.5 mg and Tigreat 2.5 film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

#### Safety

A total of 23 adverse events (AEs) were reported by 14 of the 32 subjects, 2 (hypertension) of which are considered related to the test product. These AEs are in accordance to the known safety profile of frovatriptan in the literature. All AEs were assessed as mild or moderate and the most common AEs are headache and fatigue. There were no clinically significant and/or consistent drug-related changes in vital signs with an exception of one subject who presented with hypertension after ingestion of both products.

Frovatriptan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of frovatriptan. Therefore, a food interaction study is not deemed necessary. 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.

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

Frovatriptan has been on the market for more than 10 years. The safety profile of the active substance 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 Migard 2.5 mg.

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 a pilot test with 2 participants, followed by two rounds with 10 participants each. As a result of the pilot testing no changes to either the leaflet or the questionnaire were deemed necessary. This is also the case after the first round of testing. After two rounds of user testing, 100% of the subjects were able to locate the requested information and gave the correct answer. As a result, no changes were deemed necessary to the patient information leaflet of Frovatriptan DOC Generici 2.5 mg film-coated tablets.

Overall, it can be concluded that the readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Frovatriptan DOC Generici 2.5 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Migard 2.5 mg film-coated tablets. Migard 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.

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 Frovatriptan DOC Generici 2.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 July 2013. Frovatriptan DOC Generici 2.5 mg, film-coated tablets was authorised in the Netherlands on 15 August 2013.

The date for the first renewal will be: 2 July 2018.

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

#### Quality - medicinal product

- The MAH committed to finalize the process validation for a third batch of the second manufacturing site.
- The MAH committed to review the total impurity limit on the finished product once additional data is generated, and ensures that the proposed specification (for release and shelf-life) on total impurities will reasonably based on the batch and stability results observed.



## 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 <sub>max</sub>	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 <sub>1/2</sub>	Half-life
t <sub>max</sub>	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