CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Clobazam TioFarma 10 mg and 20 mg, tablets
TioFarma b.v., the Netherlands

clobazam

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 105491-105492

6 December 2012

Pharmacotherapeutic group:	anxiolytics; benzodiazepine derivatives
ATC code:	N05BA09
Route of administration:	oral
Therapeutic indication:	pathological anxiety; adjunctive therapy in patients with epilepsy who are not adequately stabilized with their anticonvulsant therapy.
Prescription status:	prescription only
Date of authorisation in NL:	2 September 2010
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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Clobazam TioFarma 10 mg and 20 mg, tablets from TioFarma b.v. The date of authorisation was on 2 September 2010 in the Netherlands.

The product is indicated for:

- Pathological anxiety. Benzodiazepines should only be used when the condition is severe, disabling, or subjecting the individual to extreme distress.
- Adjunctive therapy in patients with epilepsy who are not adequately stabilized with their anticonvulsant therapy.

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

Clobazam is a long-acting 1,5-benzodiazepine and a 'defined daily dose of 20mg. It potentiates the inhibitory action of the neurotransmitter, gamma-aminobutyric acid (GABA). Regular dose in anxiety treatment is 20 -30 mg/day. In epilepsy, a starting dose of 5-15 mg/day is recommended, to be titrated to maximal 80 mg/day. Clobazam is well absorbed from the gastrointestinal tract and peak plasma concentrations are reached 1 to 4 hours after oral administration. It is about 85% bound to plasma proteins.
Clobazam is highly lipophilic and rapidly crosses the blood-brain barrier. It is metabolised in the liver by dimethylation and hydroxylation but unlike the 1,4-benzodiazepines such as diazepam, clobazam, a 1,5-benzodiazepine, is hydroxylated at the 4-position rather than the 3-position. Clobazam is excreted unchanged and as metabolites mainly in the urine. Mean half lives of 18 hours and 42 hours have been reported for clobazam and its main active metabolite N-desmethylclobazam, respectively

This national procedure concerns a generic application claiming essential similarity with the innovator products Frisium 10 mg and 20 mg tablets (NL License RVG 09600-09601) which have been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 9 February 1982 (original 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 Frisium 10 mg tablets, registered in the UK. 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 an 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 clobazam, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white to almost white crystalline powder, which is slightly soluble in water, sparingly soluble in alcohol and freely soluble in methylene chloride.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP. The specification is acceptable in view of the various European guidelines. Batch analytical data on three full scaled batches have been provided demonstrating compliance with the specification.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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
Clobazam TioFarma 10 mg is a white to off-white circular (7 mm) tablet, one-side scored, the other marked ‘CB10’. The tablet can be divided into equal halves.
Clobazam TioFarma 20 mg is a white to off-white circular (9 mm) tablet, one-side marked ‘CB20’.

The tablets are packed in PVC/Alu blisters.

The excipients are: lactose monohydrate, microcrystalline cellulose (E460), sodium starch glycolate, talc (E553b) and magnesium stearate (E470b).

The 10 mg and 20 mg tablets are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.

The manufacturing process is a standard direct compression process. The English and Dutch marketed reference products Frisium® are comparable. Therefore the bioequivalence study performed with the UK reference product is acceptable. Comparative dissolution profiles in the three media of the 10 mg clobazam tablets and the marketed product, Frisium® have been provided. No difference in the dissolution profiles was observed. Breakability of the 10 mg tablet has been demonstrated.

Manufacturing process
The manufacturing process consists of a straightforward standard direct compression process. The process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches of 10 mg and three full-scale batches of 20 mg tablets. It has been adequately demonstrated that the manufacturing process is capable of producing the drug product in compliance with the finished product specification.

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 appearance, identification by IR and HPLC, average mass, uniformity of dosage units, dissolution rate, assay, related substances, microbiological purity, hardness and friability. The release and shelf-life specifications are identical with the exception of assay and related substances. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three full-scale batches of 20 mg tablets, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided three full-scale batches of 10 mg and four full-scale batches of 20 mg stored at 25°C/60% RH (10 mg: 12 months; 20 mg up to 24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/Aluminium blister strips.
No trends or out-of-specification results are observed under either long term or accelerated conditions. A photostability study was performed in line with the ICH Q1B guidance. It has been adequately demonstrated that the clobazam tablets are not photosensitive
Given the available data the claimed shelf-life of 24 months without special storage conditions can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The lactose monohydrate is sourced from healthy animals in the same condition as milk collected for human consumption and prepared without the use of other ruminant materials than calf rennet. Magnesium stearate is derived from vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Frisium, which is available on the Dutch 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 Board 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 clobazam 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

Clobazam 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 Board 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 Clobazam TioFarma 10 mg (TioFarma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Frisium 10 mg tablets (Sanofi Aventis, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The English and Dutch marketed reference products Frisium® are comparable.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 18-32 years. Each subject received a single dose (10 mg) of one of the 2 clobazam formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose at 0.5, 1, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 4.0, 6.0, 8.0, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours after administration of the products.

The study design is considered adequate taken into account the pharmacokinetics of clobazam.

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
Two subjects dropped out. One was tested positive for benzodiazepines in period 2 and one subject did not report in for period 2. Twenty-four subjects were analyzed.

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

Treatment N=24	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6.17 ± 1.93	7.15 ± 3.44	0.194 ± 0.053	2.3 (1.3 – 16)	41 ± 30
Reference	5.97 ± 1.58	7.01 ± 3.82	0.223 ± 0.039	2.0 (0.5 – 3.66)	42 ± 45
***Ratio (90% CI)**	1.02 (0.97 – 1.07)	1.02 (0.94 – 1.10)	0.86 (0.80 – 0.92)	--	--
CV (%)	10.4	15.5	13.5	--	--

$AUC_{0-\infty}$ 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 clobazam under fasted conditions, it can be concluded that Clobazam TioFarma 10 mg and Frisium 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.

Clobazam may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of clobazam. 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.

Biowaiver
In accordance with the CPMP guideline "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98), the bioequivalence study investigating only one tablet strength is acceptable, as all of the following conditions are 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 should be similar under identical conditions for the additional strengths and the strength of the biobatch

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
Clobazam was first approved in 1982, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of clobazam 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 national procedure is in accordance with that accepted for the reference product Frisium.

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 report demonstrates that during the first test round with 10 participants 99.3 % of the requested information in the package leaflet was found and understood. During the second test round, with again 10 participants, 98.6 % of the requested information was found and understood. This means that more than 90% of the participants were able to find the requested information, and of those, more than 90% were able to understand the information that was found and would act appropriately.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Clobazam TioFarma 10 mg and 20 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Frisium 10 mg and 20 mg tablets. Frisium 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. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Clobazam TioFarma 10 mg and 20 mg, tablets were authorised in the Netherlands on 2 September 2010.

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
Addition of a new specification parameter to the specification with its corresponding test method for the final product.	--	IA/G	12-11-2010	11-1-2011	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product.	--	IA/G	20-4-2011	19-6-2011	Approval	N