CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Trazodon HCl Sandoz 100 mg, tablets
Sandoz B.V., the Netherlands

trazodone 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/2506/001/DC
Registration number in the Netherlands: RVG 111061

6 May 2014

Pharmacotherapeutic group:	other antidepressants
ATC code:	NO6AX05
Route of administration:	oral
Therapeutic indication:	major depressive episode
Prescription status:	prescription only
Date of authorisation in NL:	24 March 2014
Concerned Member States:	Decentralised procedure with BE, ES, LU, PT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Trazodon HCl Sandoz 100 mg, tablets from Sandoz B.V. The date of authorisation was on 24 March 2014 in the Netherlands. In addition, an application in accordance with article 10(3) was made for Trazodon HCl Sandoz 150 mg. This application was withdrawn during the procedure.

The product is indicated for treatment of major depressive episode.

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

Trazodone is a sedative antidepressant with dual-serotonergic mechanism of action. Trazodone pre-synaptically inhibits serotonin re-uptake and post-synaptically blocks $5HT_{2A}$-receptors. The sedative component of action is presumably based on the relatively highly pronounced antagonistic affinity for central α_1 receptors and a relatively poorly antagonistic affinity for H_1 receptors.
Besides the antidepressant and anxiolytic effect, trazodone has pro-sexual properties (promoting libido and erectile potency). The mechanism of this action, however, is not yet known. Anti-α_1, anti-α_2 adrenergic and anti-serotonergic mechanisms in periphery and central nervous system are discussed.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Molixapan 100 mg capsules which has been registered in the UK by Sanofi Avantis since 1980. In the Netherlands, the innovator product Trazolan 100 mg tablets (NL License RVG 09145) has been registered since 1983.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In support of the application for the 150 mg strength a biowaiver was requested as a bioequivalence study was already performed with the lower 100 mg strength. This is however not considered to be in line with the current NfG on Investigation of Bioequivalence. The applicant therefore decided to withdraw the application for the 150 mg strength. For further details, refer to section II.3 ‘Clinical aspects’.

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 Molipaxan 100 mg capsules, 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 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 trazodone hydrochloride, an established active substance however not yet described in the European Pharmacopoeia (Ph.Eur.*). The British Pharmacopoeia (BP) contains a monograph on trazodone hydrochloride, as well as the pharmacopoeia of the United States (USP), which includes a monograph on trazodone hydrochloride tablets. The drug substance is a white or almost white crystalline powder, which is soluble in water and methanol, sparingly soluble in ethanol 96% and chloroform, practically insoluble in ether and acetone. No polymorphism of trazodone hydrochloride is described in the literature; stereochemistry is not applicable either.

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
Trazodone hydrochloride is prepared in one reaction step. Sufficient information is submitted on the synthesis of the final drug substance out of the starting materials.

Quality control of drug substance
In general the drug substance specification is in line with the monograph for trazodone hydrochloride of the BP, with additional requirements for residual solvents and particle size. The proposed specifications are acceptable. Batch analytical data demonstrating compliance with this specification have been provided for eight commercial-scale batches.

Stability of drug substance
Stability data have been obtained during storage at 25°C/60% RH (up to 60 months) and 40°C/75% RH (up to 6 months) for trazodone hydrochloride. The drug substance was adequately stored. Based on the results, the proposed re-test period of 60 months without special storage conditions is acceptable.

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

Medicinal Product

Composition
Trazodon HCl Sandoz 100 mg contains as active substance 100 mg trazodone hydrochloride and is a capsule shaped white tablet, with a triple scoreline. The tablet is about 18.5 mm long and about 6.7 mm wide.
The tablet can be divided into equal halves if broken in the middle, into a threequarter and a quarter tablet, if broken at an end scoreline, or into four equal quarters if broken at all three scorelines.

The tablets are packed in opalescent PVC/Al blister and clear PVC/Al blisters.

The excipients are: maize starch, lactose monohydrate, polyvidone K30 (E 1201), calcium hydrogen phosphate (E 341), microcrystalline cellulose 102 (E 460i), sodium starch glycollate type A (E 468), magnesium stearate (E 470b).

Pharmaceutical development
Development was performed based on the innovator product. Some amendments were made, resulting in the final composition. Subsequently, bioequivalence studies were performed against the UK innovator product with the 100 mg strength. *In vitro* dissolution studies were performed against innovator products from various EU-countries, including the Netherlands. The submitted dissolution profiles show that the *in-vitro* dissolution characteristics of the different product strengths are comparable. The breakability of the 100 mg tablets has been tested in conformity with the current Ph.Eur. and shows compliance with the requirements. The pharmaceutical development has been described in sufficient detail.

Manufacturing process
The manufacturing of the process consists of two critical steps, i.e. blending of the active substance and excipients for tabletting, and the tabletting process itself. The process is sufficiently validated.

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

Quality control of drug product
The product specification for the tablets includes general description, identification, average weight, uniformity of weight, tablet breakability, disintegration, hardness, assay, content uniformity, related substances, dissolution and microbiological purity. The specifications set are acceptable, also in view of BP and ICH-Guidelines. The MAH has submitted batch analysis data of three batches. All batches comply with the proposed specifications.

Stability of drug product
The stability of the drug product was tested at 25°C/60% RH (up to 36 months), 30°C/65% RH and 40°C/75% RH. The tablets were stored in their commercial packaging. The MAH has shown that the active substance is not sensitive to light.
Based on the results, a shelf-life of 36 months when packed in clear and opalescent PVC-Aluminium blisters is considered to be acceptable, when stored below 25ºC and protected from moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Of all the excipients, only for lactose monohydrate and magnesium stearate a risk of TSE agents exists.
Magnesium stearate is of vegetable origin, and therefore there is no risk of TSE transmission for this material either. Lactose monohydrate is produced from milk obtained from healthy animals in the same conditions as those used to collect milk for human consumption.

II.2 Non-clinical aspects

This product is a generic formulation of Molixapan 100 mg, 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 trazodone 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

Trazodone 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 Trazodon HCl Sandoz 100 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Molipaxan 100 mg capsules (Sanofi Aventis, 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
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 18-45 years. Each subject received a single dose (100 mg) of one of the 2 trazodone formulations, administered 10-15 minutes after a light breakfast (200 ml skimmed milk (1.5% fat), 2 slices of bread spread with jam). The tablets were administered in solid form with 200 ml low carbonated. Six hours after dosing a standard lunch was served. For each subject there were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 96 hours after administration of the products.

The bioequivalence study has been performed under fed conditions, which is acceptable as the product is recommended to be taken after meals. However, the study products were administered after light breakfast while the current NfG on Investigation of Bioequivalence recommends high-fat and high-calorie meal. Tradozone however is recommended to be taken with food for the reduction of side effect and not due to the bioavailability reasons. Meals reduce GI related AE due to decrease in C_{max}. Therefore, it is not expected that high-fat meal would affect the bioequivalence outcome. In addition, although the current guideline recommends high-fat meal, the bioequivalence study under discussion was performed in 2005) at the time when the available previous NfG on Investigation of Bioavailability and Bioequivalence did not contain any specific recommendations regarding a composition of meals.

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 subject was withdrawn from the study because he took counteractive medication for a foot lesion, and another withdrew for personal reasons. The remaining 34 subjects completed the study entirely and were included in the analysis

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

Treatment N=34	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	10.25 ± 4.58	10.81 ± 4.96	1.32 ± 0.46	2.41 ± 1.10	7.8 ± 2.9
Reference	10.72 ± 4.91	11.24 ± 5.08	1.39 ± 0.55	2.08 ± 1.07	7.7 ± 3.4
***Ratio (90%**	0.96 (0.91 - 1.01)	0.96 (0.91 - 1.01)	0.95 (0.85 - 1.06)	--	--

CI)					
CV (%)	11.9	11.4	26.7	--	--

$AUC_{0-\infty}$ 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 trazodone under fed conditions, it can be concluded that Trazodon HCl Sandoz 100 mg, tablets and Molipaxan 100 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

In the submitted bioequivalence study, a capsule was used as the reference product. Trazodone hydrochloride containing products are marketed in various pharmaceutical forms by different MAHs in the member states, in the Netherlands for instance as tablets. Although the use of the innovator product from the UK is considered appropriate from a regulatory point of view since the European Reference Product is used, there are different manufacturing processes for a capsule and a tablet and differences in qualitative and quantitative composition between the innovator capsule and tablet (which is crucial for trazodone as a low solubility drug). The discussion of the MAH on these issues is satisfactory. The use of trazodone capsules is sufficiently justified.

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).

Extrapolation to the 150 mg tablet

To support the applications, one bioequivalence study was submitted, comparing the 100 mg strength to the UK reference product. As indicated in the introduction, the original applications consisted of 2 strengths: 100 mg and 150 mg. The choice of the lower 100 mg strength used in the study, in support of the applications for the 150 mg strength, was however not considered to be in line with the current NfG on Investigation of Bioequivalence.

For a product with linear kinetics but with limited solubility, a bioequivalence study should be carried out with the highest strength applied for since it is the most sensitive strength to detect differences between the test and reference formulation. A lower strength may be only acceptable in this case based on the safety grounds of healthy volunteers which in view of the member states is not applicable in this case. Most reported adverse events (AE) are from multiple dose exposure, mostly with higher doses. The most common AEs after single dosing are gastrointestinal AEs and orthostatic hypotension. These can be very well managed in clinical investigation setting with adequate precautions. Furthermore, it is noticed that there is a marked difference between the formulations involved in the application (100 mg and 150 mg), which supports the view that the most sensitive should be used to detect differences in formulation. In addition, the solubility of trazodone was observed to be lowest at pH 6.8. The product is advised to be administered with food and it is known that food intake increases the pH in stomach to about 6-7. Therefore solubility will be low across the whole gastrointestinal tract, as the pH after passing the stomach is close to the pKa of trazodone. This gave an additional support for the necessity of a bioequivalence trial with the higher strength applied for. In this regards it should also be noted that 50 mg strength capsules of the innovator product are also licensed in the UK: a comparison of 150 mg doses would therefore have been possible. This was considered to be a major objection against approval of the 150 mg strength.

In view of the above discussion, the MAH decided to withdraw the applications for the 150 mg strength. In this situation the application for the 100 mg strength is considered to be adequately supported by the bioequivalence study provided.

Risk management plan

Trazodone was first approved in 1980, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of trazodone 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 Molixapan.

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. Overall, each and every question meets criterion of 81% correct answers. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Trazodon HCl Sandoz 100 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Molixapan 100 mg capsules/tablets. Molixapan 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 for the 100 mg strength. For the 150 mg tablet applied for, a biowaiver could however not be granted. A bioequivalence study should have been conducted with this strength as well. The applicant decided to withdraw the application for the 150 mg strength.

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.

In the Board meeting of 31 January 2013, bioequivalence was discussed. The Board concluded that a biowaiver was not acceptable for the 150 mg strength based on the applicable guidelines.

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 Trazodon HCl Sandoz 100 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 February 2013. Trazodon HCl Sandoz 100 mg, tablets was authorised in the Netherlands on 24 March 2014.

The date for the first renewal will be: 10 February 2018.

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

List of abbreviations

AE	Adverse Event
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