CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Tramadol HCl Aurobindo 50 mg, capsules, hard
Aurobindo Pharma B.V., the Netherlands

tramadol 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/2480/001/DC
Registration number in the Netherlands: RVG 110742

22 April 2013

Pharmacotherapeutic group:	analgesics, other opioids
ATC code:	N02AX02
Route of administration:	oral
Therapeutic indication:	moderate to severe pain
Prescription status:	prescription only
Date of authorisation in NL:	13 November 2012
Concerned Member States:	Decentralised procedure with DK, ES, FR, MT, PL, SE, UK
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 Tramadol HCl Aurobindo 50 mg, capsules, hard from Aurobindo Pharma B.V. The date of authorisation was on 13 November 2012 in the Netherlands.

The product is indicated for treatment of moderate to severe pain.
A comprehensive description of the indications and posology is given in the SPC.

Tramadol is a centrally acting opioid analgesic. It is a non selective pure agonist at μ-, δ- and κ-opioid receptors with a higher affinity for the μ-receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Tramal® 50 mg capsules, hard (NL License RVG 15511) which has been registered in the Netherlands by Grünenthal B.V. since 21 December 1992. The product is also marketed under the brand names Contramal® (in France), Adolonta® (in Spain) and Zydol® (in the United Kingdom).

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 Zydol® 50 mg capsules, 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 tramadol hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white, crystalline powder, which is freely soluble in water. Tramadol hydrochloride is manufactured as a racemate.

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. with additional requirements for residual solvents, microbiological quality, particle size and bulk density. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60%RH (18 months) and 40°C/75% RH (6 months). No significant changes were seen at both storage conditions. The proposed retest period of 24 months without any special storage requirements is justified.

** 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
Tramadol HCl Aurobindo 50 mg is a green/yellow, size ‘4’ hard gelatin capsule filled with white to off-white powder and imprinted with ‘T’ on green cap and ‘02’ on yellow body with black ink.

The hard capsules are packed in PVC/PVDC/Aluminium foil blister and HDPE bottle packs with polypropylene closure.

The excipients are: microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycolate (Type A) magnesium stearate, gelatin, sodium lauryl sulphate, indigo carmine, iron oxide yellow (E172), titanium dioxide (E171), shellac, black iron oxide (E172).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the originator product, optimization of the excipient concentrations and the performance of comparative dissolution studies between the batches used in the bioequivalence study. The choices of the packaging materials and the manufacturing process are justified. The batch used in the biostudy was manufactured according to the finalized formulation and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are dry mixing of the excipients and filling into capsules. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scaled batches. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur. or in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, average fill mass, related substances, assay, dissolution, water, uniformity of dosage units, lock length and microbial contamination. Except for water content the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches stored at 25°C/60% RH (12 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline or harsher for the intermediate condition. The batches were stored in PVC/PVdC-Al blisters or in HDPE containers. At all storage conditions and in both packaging materials an increase in water content was observed. A decrease in dissolution was observed at accelerated conditions (40°C/75% RH) for the batches packed in PVC/PVdC-Al blisters. No trends or changes were seen at the other parameters tested. Photostability studies showed that the product is not sensitive to light. The proposed shelf-life of 2 years and storage condition 'Store below 30°C' are justified.
Stability data has been provided demonstrating that the product remains stable for 6 months after following first opening of the container, when stored at 25°C/60% RH.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for the gelatine of the capsule shells, there are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product. Certificates of suitability issued by the EDQM have been provided for the different sources of gelatine. So a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Tramal, 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 tramadol 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

Tramadol 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 Tramadol HCl Aurobindo 50 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Zydol® 50 mg Capsules (Grünenthal GmbH, from the UK market).

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 28 healthy male subjects, aged 18-37 years. Each subject received a single dose (50 mg) of one of the 2 tramadol formulations. The tablet was orally administered with 240 ml water after an overnight fast of approximately 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00, 30.00, and 36.00 hours after administration of the products.

The study design is acceptable, and the washout period is considered adequate (t1/2, 5-6 hours).

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. The plasma concentrations of O-desmethyl tramadol (an active metabolite) were also analysed, and only considered to be supportive data for the conclusion.

Results
In total, 28 subjects completed both Period I and Period II. No adverse events were reported during the entire duration of the study. A total of 28 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

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

Treatment N=28	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1629.5 ± 464.6	1689.4 ± 500.7	197.7 ± 40.4	2.25 (1.25 – 4.00)	7.03 ± 1.36

Reference	1475.7 ± 356.5	1527.1 ± 377.2	184.9 ± 37.6	2.25 (1.25 – 3.50)	7.05 ± 1.41
***Ratio (90% CI)**	1.10 (1.03 – 1.17)	1.10 (1.04 – 1.17)	1.07 (1.03 – 1.12)	-	-
CV (%)	13.7	13.5	9.46		

$AUC_{0-\infty}$ 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*

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

Treatment N=28	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	536.8 ± 147.2	560.1 ± 151.9	42.3 ± 13.9	2.38 (1.50 – 5.00)	7.13 ± 1.6
Reference	516.3 ± 131.0	535.6 ± 133.7	41.0 ± 13.2	2.5 (1.25 – 5.00)	6.78 ± 1.2
***Ratio (90% CI)**	1.04	1.04	1.03	-	-
CV (%)	-	-	-	-	-

$AUC_{0-\infty}$ 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 tramadol, supported by data on O-desmethyl tramadol, under fasted conditions, it can be concluded that Tramadol HCl Aurobindo 50 mg and Zydol® 50 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.

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

Tramadol was first approved in 1973, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of tramadol 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 Tramal.

Readability test
The package leaflet has not been evaluated via a user consultation study. Reference is made to the successfully user tested PIL for another tramadol product. The Aurobindo house style has been assessed and found acceptable in other procedures. The bridging report is acceptable. Separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Tramadol HCl Aurobindo 50 mg, capsules, hard has a proven chemical-pharmaceutical quality and is a generic form of Tramal® 50 mg capsules, hard. Tramal 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 Tramadol HCl Aurobindo 50 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 October 2012. Tramadol HCl Aurobindo 50 mg, capsules, hard was authorised in the Netherlands on 13 November 2012.

The date for the first renewal will be: 10 October 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