CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Meloxicam Aurobindo 7.5 mg and 15 mg, tablets
Aurobindo Pharma B.V., the Netherlands

meloxicam

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 107063, 107068

10 January 2013

Pharmacotherapeutic group:	anti-inflammatory and antirheumatic products, non-steroids - oxicams
ATC code:	M01AC06
Route of administration:	oral
Therapeutic indication:	short-term symptomatic treatment of exacerbations of osteoarthritis; long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis
Prescription status:	prescription only
Date of authorisation in NL:	20 September 2011
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 Meloxicam Aurobindo 7.5 mg and 15 mg, tablets from Aurobindo Pharma B.V. The date of authorisation was on 20 September 2011 in the Netherlands.

The product is indicated for:
- short-term symptomatic treatment of exacerbations of osteoarthritis
- long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

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

The anti-inflammatory activity of meloxicam has been proven in classical models of inflammation. As with other NSAIDs, its precise mechanism of action remains unknown. However, there is at least one common mode of action shared by all NSAIDs (including meloxicam): inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

This national procedure concerns a generic application claiming essential similarity with the innovator products Movicox 7.5 mg and 15 mg, tablets (NL License RVG 19375-19376) which have been registered in the Netherlands by Boehringer Ingelheim B.V. since 9 January 1996.

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 products is compared with the pharmacokinetic profile of the reference products Mobic 7.5 and 15 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 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 meloxicam, an established active substance described in the European and British Pharmacopoeia (Ph.Eur., BP*). It is a pale yellow powder, which is soluble in N,N-dimethylformamide, very slightly soluble in ethanol and practically insoluble in water. Crystalline polymorph form I is used.

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. monograph for meloxicam and the additional CEP requirements. The specification is acceptable in view of the CEP and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for six production-scale batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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

Medicinal Product

Composition
Meloxicam Aurobindo 7.5 and 15 mg tablets are light yellow, round, uncoated tablets with a score line between ‘F’ and ‘1’ or ‘2’ respectively debossed on one side and plain on the other side. The 15 mg tablet can be divided into equal halves.

The tablets are packed in white opaque PVC-PVdC/Aluminum blister packs.

The excipients are: lactose monohydrate, microcrystalline cellulose, sodium citrate, crospovidone, povidone, colloidal anhydrous silica and magnesium stearate.

The tablets are not dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of the excipients is justified and their functions explained. Optimum amounts of the pharmaceutically active excipients have been established. The score lines of both tablets comply with the requirements of the Ph. Eur. However, the SPC states that only the 15 mg tablet can be divided into equal halves. Breakability tests with the 7.5 mg and the 15 mg tablets demonstrated that the tablets comply with the Ph. Eur. requirement for uniformity of mass of subdivided tablets. The use of the UK reference products in the bioequivalence studies has been justified. Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products. The test products are acceptable.

Manufacturing process

The manufacturing process for meloxicam 7.5 and 15 mg tablets consists of the following steps: sifting, dry mixing, preparation of the binder solution, granulation, drying, sifting and milling, sifting, blending and lubrication and compression and packing. Adequate in-process controls have been set.
The manufacturing process has been adequately validated according to the relevant European guidelines. Process validation data on the products have been presented for two small scale batches of both strengths. Full scale validation will be conducted post-approval. The product is manufactured using standard, conventional manufacturing techniques. In view of that, this approach is acceptable.

Control of excipients

The excipients comply with the specifications and analytical procedures of the corresponding monographs in the Ph.Eur. and USP. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identity (by TLC and HPLC), average weight, dissolution, assay, related substances, uniformity of dosage units and microbial contamination. The release and shelf-life requirements are identical and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from two small scale batches for both strengths have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for two small-scale production batches, stored at 25°C/60% RH (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 the proposed blister packaging. No significant changes in the drug product were observed after 6 months of accelerated and 24 months of long-term stability study for meloxicam 7.5 mg and 15 mg tablets. It demonstrated that the tablets are not sensitive to light. Based on the data provided, a shelf life of 2 years was granted. No additional storage conditions are required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Only lactose is of animal origin. The lactose used comes from milk for human consumption and does not present any risk of TSE contamination. A declaration on its TSE safety was provided.

II.2 Non-clinical aspects

This product is a generic formulation of Movicox, 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 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 meloxicam 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

Meloxicam 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 two bioequivalence studies in which the pharmacokinetic profile of the test products Meloxicam Aurobindo 7.5 mg and 15 mg tablets (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference products Mobic 7.5 mg and 15 mg tablets (Boehringer Ingelheim, UK).

The choice of the reference products
The choice of the reference products in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – 7.5 mg tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 19-36 years. Each subject received a single dose (7.5 mg) of one of the 2 meloxicam formulations. The tablet was orally administered after an overnight fast of 10 hours with 240 ml water 30 minutes after a high caloric, high fat meal (985 kCal). There were 2 dosing periods, separated by a washout period of 11 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 120.0 hours after administration of the products. The overall study design is considered acceptable considering the absorption rate and half-life.
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 did not show up in the second period. The dropout was not included in the statistical analysis.

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

Treatment N=27	**AUC_{0-t}** ug.h/ml	**$AUC_{0-\infty}$** ug.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	29.52 ± 13.48	32.35 ± 15.60	1.05 ± 0.25	4.5 1.0 – 7.0	24 ± 9
Reference	31.37 ± 14.33	33.84 ± 16.12	1.05 ± 0.27	4.5 3.0 – 6.5	25 ± 9
***Ratio (90% CI)**	0.95 (0.91 – 0.98)	0.96 (0.93 – 0.99)	1.00 (0.95 – 1.06)	--	--
CV (%)	8	8	13	--	--

$AUC_{0-\infty}$ 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 meloxicam under fasted conditions, it can be concluded that Meloxicam Aurobindo 7.5 mg and Mobic 7.5 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.

Safety
The formulations were well tolerated, only three adverse events were reported.

Bioequivalence study II – 15 mg tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 26 healthy male subjects, aged 18-41 years. Each subject received a single dose (15 mg) of one of the 2 meloxicam formulations. The tablet was orally administered after an overnight fast of 10 hours with 240 ml water during a high caloric, high fat meal (985 kCal). There were 2 dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 120.0 hours after administration of the products. The overall study design is considered acceptable considering the absorption rate and half-life.

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 did not show up in the second period, and one subject vomited after the first dose. Both subjects were withdrawn from the study. The dropouts were not included in the statistical analysis.

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

Treatment N=27	**AUC_{0-t}** ug.h/ml	**$AUC_{0-\infty}$** ug.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	37.54 ± 15.48	40.72 ± 19.12	1.16 ± 0.21	4.5 1.5 – 16.0	25 ± 10
Reference	37.67 ± 15.00	41.48 ± 19.06	1.05 ± 0.18	6.5 4.5 – 12.0	26 ± 11
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	0.99 (0.94 – 1.04)	1.10 (1.05 – 1.15)	--	--
CV (%)	10	9.9	9	--	--

$AUC_{0-\infty}$ 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 meloxicam under fasted conditions, it can be concluded that Meloxicam Aurobindo 15 mg and Mobic 15 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.

Safety
The formulations were well tolerated. Three adverse events were reported during the entire duration of the study, all adverse events were post study lab abnormalities.

As meloxicam should be taken with food, as described in the SPC, a study under fed conditions with a high fat, high caloric meal is justified according the new guideline on Bioequivalence.
The MEB has been assured that the bioequivalence studies have 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
Meloxicam was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of meloxicam 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 national procedure is in accordance with that accepted for the reference product Movicox tablets.

Readability test
The package leaflet has not been evaluated via a user consultation study. Instead, a bridging report was provided. Reference is made to the successfully user tested PIL for another meloxicam 7.5 mg/15 mg product. Both PILs contain the same information for the sections ‘indications’, ‘contra-indications’, ‘warnings’, ‘other safety information’ and ‘side-effects’. Layout and design of the two PILs are also the same (in-house style). The bridging report was accepted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Meloxicam Aurobindo 7.5 mg and 15 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Movicox 7.5 mg and 15 mg tablets. Movicox is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence of both tablet formulations 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, package leaflet and labelling are in the agreed templates and are in agreement with other meloxicam containing products.

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. Meloxicam Aurobindo 7.5 mg and 15 mg, tablets were authorised in the Netherlands on 20 September 2011.

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
Transfer of the marketing authorisation.	--	MA transfer	17-10-2011	15-11-2011	Approval	N