

# **Public Assessment Report**

## **Scientific discussion**

**Meloxicam “Ozone” 15 mg tablets**  
**Meloxicam “Pharmasolve” 7.5 mg and 15 mg tablets**  
**Meloxicam “Apothecon” 7.5 mg and 15 mg tablets**

## **Meloxicam**

**This module reflects the scientific discussion for the approval of Meloxicam “Ozone”/Meloxicam “Pharmasolve”/Meloxicam “Apothecon”. The procedure was finalised on 29 April 2008. For information on changes after this date please refer to the module ‘Update’.**

## I. INTRODUCTION

This assessment report concerns a generic version of meloxicam 7.5 mg and 15 mg tablets approved through DCP DK/H/1319/001/DC, DK/H/1320-1321/001-002/DC) on 29 April 2008 with Denmark acting as RMS.

Based on the review of the data on quality, safety and efficacy, the applications for Meloxicam 7.5 mg and 15 mg tablets, in the short-term symptomatic treatment of exacerbation of osteoarthritis and in the long-term symptomatic treatment of rheumatoid arthritis or of ankylosing spondylitis, have been accepted by the RMS and all CMS.

These decentralised procedure applications concern generic versions of meloxicam according to Article 10(1) of Directive 2001/83/EC (generic application).

The originator product is Mobic 7.5 and 15 mg tablets from Boehringer Ingelheim International GmbH registered in United Kingdom since 21 February 1996.

With Denmark as the Reference Member State in these Decentralised Procedures,

- Ozone Laboratories BV is applying for the Marketing Authorisation of Meloxicam “Ozone” 15 mg tablets in: BG, CZ, HU, PL, RO and SK.
- Pharmasolve Consultancy Ltd is applying for the Marketing Authorisation of Meloxicam “Pharmasolve 7.5 and 15 mg tablets in: HU, NL, PL.
- Apothecon BV is applying for the Marketing Authorisation of Meloxicam “Apothecon” 7.5 and 15 mg tablets in: NL.

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam-group with anti-inflammatory, analgesic and antipyretic properties.

The anti-inflammatory activity of meloxicam has been demonstrated in classical models of inflammation.

As with other NSAIDs the precise mechanism of action is unknown. However, there is at least one common mode of action of all NSAIDs (including meloxicam): Inhibition of the biosynthesis of prostaglandins, known as inflammation mediators.

The bioavailability of meloxicam following oral administration is 89% on average. At doses of 7.5 mg and 15 mg the plasma concentrations are proportional with the doses: 0.4-1.0 mg/ml for 7.5 mg and 0.8-2 mg/ml for 15 mg on average (C<sub>min</sub> and C<sub>max</sub> at steady-state).

Meloxicam is strongly bound to plasma proteins, mainly albumin (99%). Meloxicam is extensively metabolised mainly by oxidation of the methyl radical bound to the thiazolyl ring. Elimination in unchanged form stands for 3% of the dose. Half of the dose is excreted in urine and the rest in faeces. The mean elimination half-life is about 20 hours. Steady state is reached after 5 days.

## II. QUALITY ASPECTS

### II.1 Introduction

The chemical-pharmaceutical documentation and Expert Report in relation to these generic meloxicam applications are of sufficient quality in view of the present European regulatory requirements.

The finished product is presented as tablets in the strength of 7.5 mg and 15 mg packed in PVC/PVDC/aluminium blisters.

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

### II.2 Drug Substance

The control tests and specifications for the drug substance meloxicam are adequately drawn up and are in compliance with the BP monograph for meloxicam.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 4 years when stored in the proposed packaging is justified.

Notice has been drawn to the monograph on Meloxicam in Pharmeuropa 18.3. The applicant has confirmed that this monograph will be fulfilled when coming into force.

### **II.3 Medicinal Product**

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

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 2 production scale batches (1,000,000 tablets) for the 7.5 mg strength and 3 production scale batches (500,000 tablets) for the 15 mg strength. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 36 months with no special storage conditions is considered acceptable for both strengths applied for.

## **III. NON-CLINICAL ASPECTS**

Pharmacodynamic, pharmacokinetic and toxicological properties of meloxicam are well known. As meloxicam is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

## **IV. CLINICAL ASPECTS**

### **IV.1 Introduction**

No specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended.

A bioequivalence study has been conducted to demonstrate essential similarity between the generic product and the originator product Mobic.

Based on the submitted bioequivalence study this generic meloxicam product is considered bioequivalent with Mobic 7.5 mg and 15 mg tablets with respect to rate and extent of absorption of meloxicam.

### **IV.2 Pharmacokinetics**

In order to demonstrate essential similarity with the brand leader the applicant has submitted one single dose bioequivalence study carried out under fed conditions. The 15 mg tablet strength was used and biowaiver for the 7.5 mg strength has been justified according to the guideline. It is considered acceptable that the study was performed under fed conditions, since it is recommended in the SPC to take the drug product with a meal.

The study included 26 subjects; 24 subjects completed both periods and were included in the pharmacokinetic and statistical analysis. Two subjects were withdrawn due to adverse events, which were considered not related to the study medication. A total of 19 plasma samples were withdrawn during 120 hours in each of the two periods.

Bioequivalence between the test product and the reference product, Mobic tablets by Boehringer Ingelheim has been demonstrated since the 90% confidence interval for the ln-transformed primary variables AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, C<sub>max</sub> and C<sub>max</sub> /AUC<sub>0-inf</sub> was well within the acceptance range of 80-125%.

The absolute bioavailability of meloxicam is 89% following a single oral dose of 30 mg compared with 30 mg IV bolus injection. After multiple oral doses the pharmacokinetics of meloxicam capsules are dose-proportional over the range of 7.5 to 15 mg. Mean  $C_{max}$  is achieved within 4 to 5 hours after a 7.5 mg tablet is taken under fasting conditions. The rate and extent of absorption is not affected by multiple dose administration suggesting linear pharmacokinetics. With multiple dosing, steady state is reached by day 5. A second meloxicam concentration peak occurs about 12 to 14 hours post-dose suggesting gastrointestinal recirculation.

After a single oral dose of 7.5 mg or 15 mg the time to reach  $C_{max}$  ( $t_{max}$ ) is 5 to 6 hours and the peak concentrations are 0.57-1.03  $\mu\text{g/ml}$  and 0.93-1.51  $\mu\text{g/ml}$ , respectively.

Administration of meloxicam capsules with a high fat breakfast results in mean peak levels increased approximately 22%, while the extent of absorption (AUC) is unchanged.

Meloxicam is 99.4% bound to human plasma proteins.

Meloxicam is almost completely metabolized to four pharmacologically inactive metabolites. The major metabolite, 5'-carboxy meloxicam (60% of dose), from P-450 mediated metabolism is formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam, which is also excreted to a lesser extent (9% of dose). The cytochrome P-450 2C9 plays an important role in this metabolic pathway with a minor contribution of the CYP 3A4 isozyme. Peroxidase activity is probably responsible for the other two metabolites.

Meloxicam is predominantly excreted as metabolites, and occurs to equal extents in the urine and faeces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and faeces (1.6%).

The mean elimination half-life ( $t_{1/2}$ ) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism within the therapeutic dose range.

### **Clinical study reports**

To support the application, the applicant has submitted as report 1 bioequivalence study.

### **Biowaiver**

The application concerns 2 dosage strengths (7.5 mg and 15 mg). The bioequivalence study was carried out with the 15 mg strength. A biowaiver for the 7.5 mg strength has been justified, since the 2 strengths are manufactured by the same manufacturer and process, the pharmacokinetic is linear over the therapeutic dosage range, the ratio between the amount of active substance and excipients is the same and the dissolution profiles are comparable under identical conditions, i.e. the conditions in section 5.4 of the guideline on bioavailability & bioequivalence are fulfilled.

### **Pharmacokinetic studies**

#### Study design

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 14 days between the two administrations. 15 mg was administered in each period.

The subjects were required to fasting for 10 hours before dosing and for at least 4 hours post-dose. At 2 hours post-dose, the subjects received 200 ml of water and additional fluid was provided with the meals. Standardised meals were provided 10.5 hours before dosing and 5, 9, 12 and 15 hours after dosing. From 4 hours after dosing the subjects were free to drink additional water or rose-hip tea.

The subjects were confined at the clinic until collection of the 24-hour blood sample and returned for the 36, 48, 72, 96 and 120-hour blood draws.

Blood samples were collected pre-dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours post administration of a single-dose 15 mg tablet with 200 ml of water for the analyses of meloxicam.

### *Test and reference products*

Meloxicam 15 mg tablets (manufactured by Unichem Lab. Ltd. Goa India, batch No. PTD/1048E/20, batch size 200,000 tablets, mfg. date 05/2001, exp. date 04/2002) has been compared to Mobic 15 mg tablets by Boehringer Ingelheim (Batch No: 009621, from the UK market, exp. date 12/2005).

Satisfactory certificates of analysis of the test and reference product are presented (assay test product: 99.4%/ assay reference product: 98.5%).

Detailed information on the formulations is found in module 3.

### *Population(s) studied*

26 healthy subjects (13 male and 13 female, 19-44 years) participated in the study. 24 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Drop-outs: Subject no. 22 was withdrawn during the wash-out period due to adverse event (thorax contusion), which required concurrent medication (paracetamol and codeine) and subject no. 23 was withdrawn during period 2 due to vomiting. The adverse events were considered not to be related to the study medication.

### *Analytical methods*

The plasma samples were stored at -20°C until analysed.

The samples were analyzed by HPLC/UV method for detection of meloxicam.

The analytical method was validated in the range 0.030 µg/ml (=LOQ) to 3.00 µg/ml.

The method has been validated with respect to linearity, intra-assay precision and accuracy, inter-assay precision and accuracy, recovery, selectivity, repeatability and stability (of working solutions and of plasma solution (short term, long term, freeze-thaw and on machine)).

Date of start and finish of the bio-analytical phase: The analyses of the samples were carried out between 12 and 27 November 2001 giving a maximum storage time from the first blood draw to the last sample analysis of about 1.5 month. Long term stability at -20°C has been demonstrated for this duration of time.

Reanalysis of samples: A total of 9 out of 956 samples were re-analysed. One of the samples was reanalysed because the original concentration was above the calibration curve range. The reanalysis was performed after diluting the sample and value obtained after re-assay was reported. The other 8 samples were re-assayed since the slope or shape of the pharmacokinetic curve deviated from what was expected. The re-assay confirmed the original values; therefore the original values were reported.

### *Pharmacokinetic Variables*

The pharmacokinetic parameters were calculated using SAS in-house adjusted software.

Choice of primary variables and secondary PK variables:

The parameters calculated were  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $(AUC_{0-t}/AUC_{0-inf})$ ,  $C_{max}$ ,  $t_{max}$ ,  $K_{el}$  and  $t_{1/2\ el}$ .

Primary variables:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$  and  $C_{max}/AUC_{0-inf}$ .

### *Statistical methods*

The pharmacokinetic parameters were subjected to ANOVA using SAS version 8.2 software (General linear models procedure).

ANOVA was performed on the ln-transformed  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $AUC_{0-t}/AUC_{0-inf}$ .

The ANOVA model included sequence, subject nested within sequence, period and treatment.

Nonparametric test (Wilcoxon) and median test was carried out on  $t_{max}$ ,  $t_{1/2}$  and  $K_{el}$ .

### *Criteria for conclusion of bioequivalence:*

The 90% confidence interval for the LSM ratio of the test vs. reference should be within 80-125% for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$  and  $C_{max}/AUC_{0-inf}$ .

Results

**Summary of the Results on Meloxicam  
Log Normal Distribution  
(24 subjects)**

Parameter		Means		LSM			
		Ref. (R)	Test (T)	Ref. (R)	Test (T)	Ratio T/R (%)	90 % - Confid. Interval (%)
AUC <sub>(0-t)</sub> ( $\mu\text{g}\cdot\text{h}\cdot\text{mL}^{-1}$ )	GMEAN	36.91	35.86	36.97	35.94	97.20	93.75 – 100.78
	GSD	0.3121	0.2802	0.0863	0.0863		
	%CV <sub>res</sub>	7.30					
AUC <sub>(0-inf)</sub> ( $\mu\text{g}\cdot\text{h}\cdot\text{mL}^{-1}$ )	GMEAN	38.90	37.59	39.00	37.70	96.66	93.06 – 100.41
	GSD	0.3376	0.2979	0.2538	0.2538		
	%CV <sub>res</sub>	7.68					
C <sub>max</sub> ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	GMEAN	1.407	1.381	1.404	1.386	98.75	93.86 – 103.89
	GSD	0.2048	0.1810	0.2139	0.2139		
	%CV <sub>res</sub>	10.26					
C <sub>max</sub> /AUC <sub>(0-inf)</sub> (h <sup>-1</sup> )	GMEAN	0.0362	0.0367	0.0360	0.0368	102.16	97.66 – 106.86
	GSD	0.2631	0.2901	0.0730	0.0726		
	%CV <sub>res</sub>	9.10					

**Power of ANOVA Using Multiplicative Model  
(Log Normal Distribution)**

Table 21

Parameter	%CV <sub>res</sub>	Power % (N = 24, $\alpha$ = 5%)
AUC <sub>(0-t)</sub>	7.30	> 99.99
AUC <sub>(0-inf)</sub>	7.68	> 99.99
C <sub>max</sub>	10.26	> 99.99
C <sub>max</sub> /AUC <sub>(0-inf)</sub>	9.10	> 99.99

**Summary of the Results on Meloxicam  
Normal Distribution**

Table 18

Parameter		Means		LSM			
		Ref. (R)	Test (T)	Ref. (R)	Test (T)	Ratio T/R (%)	90 % - Confid. Interval (%)
AUC <sub>(0-t)</sub> ( $\mu\text{g}\cdot\text{h}\cdot\text{mL}^{-1}$ )	MEAN	38.82	37.32	38.93	37.44	96.17	92.08 – 100.26
	SD	13.72	11.51	3.67	3.67		
	%CV	35.35	30.85	9.43	9.80		
AUC <sub>(0-inf)</sub> ( $\mu\text{g}\cdot\text{h}\cdot\text{mL}^{-1}$ )	MEAN	41.35	39.38	41.53	39.56	95.25	90.82 – 99.68
	SD	16.59	13.53	4.37	4.37		
	%CV	40.11	34.35	10.52	11.04		
C <sub>max</sub> ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	MEAN	1.437	1.403	1.434	1.408	98.14	92.72 – 103.56
	SD	0.323	0.254	0.078	0.078		
	%CV	22.45	18.09	5.46	5.56		
t <sub>max</sub> (h)	MEAN	4.67	4.75	4.65	4.76	102.42	97.60 – 107.24
	MAX	5.00	5.00	5.00	5.00		
	MIN	4.00	4.00	4.00	4.00		
	MEDIAN	5.00	5.00	5.00	5.00		
t <sub>1/2e</sub> (h)	MEAN	22.14	21.67	22.26	21.83	98.04	91.07 – 105.01
	SD	9.39	7.53	2.39	2.39		
	%CV	42.41	34.75	10.72	10.93		
k <sub>el</sub> (h <sup>-1</sup> )	MEAN	0.03508	0.03491	0.03504	0.03480	99.32	93.41 – 105.23
	SD	0.00993	0.00935	0.00271	0.00271		
	%CV	28.30	26.77	7.73	7.78		

MEAN = arithmetic mean or LSM  
SD = standard deviation  
%CV = SD/MEAN \* 100

The extrapolated AUC is below 20% for all subjects and treatments.

No subjects had measurable pre-dose plasma concentrations in any of the treatment periods and no subjects reached  $C_{max}$  at the first sampling time point ( $t_{max} = 4$  or 5 hours for all subjects) indicating that the wash out period of 2 weeks are long enough to avoid any carry-over effect and that  $C_{max}$  has been adequately characterised.

ANOVA detected no statistical significant period or treatment effects for  $AUC_{0-t}$  or  $AUC_{0-inf}$ , whereas a significant period effect was detected for  $C_{max}$ . A significant period effect could be an indication of an equal carryover effect. However, since there was no sequence effect for  $C_{max}$ , there is no indication of a carryover effect. Even in the presence of an equal carryover effect, the treatment comparison would not be invalidated, since both treatments would be affected in the same way. Therefore, this finding does not affect the conclusion of the study.

#### **Safety evaluation**

No serious adverse events or unexpected adverse drug reactions occurred. A total of 6 adverse events occurred of which 1 occurred after administration of the test product and 5 after administration of the reference product. The adverse event occurring following the test product was thorax contusion and the adverse events following the reference product were headache (2), nausea (2) and vomiting (1). Only one of the cases of headache was classified as related to the study medication.

The 90% confidence interval for the log transformed primary parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  are within the acceptance range of 80-125%.

#### **Pharmacokinetic conclusion**

Based on the submitted bioequivalence study Meloxicam tablets 7.5 mg and 15 mg are considered bioequivalent with Mobic tablets 7.5 mg and 15 mg tablets, Boehringer Ingelheim.

## **V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that these generic products and the innovators are interchangeable. The benefit risk is, therefore, considered to be positive.

The following commitments have been made:

The applicant has committed to continue the stability studies for each strength and test according to the stability protocol as presented in section P.8.1.

The applicant has committed to implement the E.P. monograph for Meloxicam when it comes into force.