IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Methocarbamol 750 mg film-coated tablets
Methocarbamol
PA2238/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6778/001 with the UK as RMS. The responsibility of RMS was transferred to Ireland on 31/10/2019 under procedure number IE/H/1079/001/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA2238/001/001
Marketing Authorisation Holder: HBS Healthcare UK

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Methocarbamol 750mg film-coated tablets (PL 44404/0013) could be approved.

The product is indicated in adults as a short-term adjunct to the symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasms.

The Reference Member State (RMS) for this procedure was the UK and the Concerned Member State (CMS) was the Republic of Ireland.

The mechanism of action of methocarbamol in humans has not been established, but may be due to general central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fibre.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine. The reference medicinal product is Ortoton 750 mg film-coated tablets, which was first granted in the EU to Recordati Pharma GmbH on 02 September 2005.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 15 and 16 March 2018 owing to questions raised on pharmaceutical aspects and bioequivalence not being demonstrated in the first clinical study. The applicant addressed these issues by conducting a new bioequivalence study and providing additional data.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 03 March 2019. After a subsequent national phase, a licence was granted in the UK on 28 March 2019.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

This product consists of white to off-white slightly curved oblong film coated tablets with double-sided scoring. The dimensions of the tablets are: length 19mm, width 8mm and thickness 6.60±0.4mm.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

In addition to methocarbamol, this product also contains the excipients sodium starch glycolate Type A, starch, pregelatinized, sodium lauryl sulphate, povidone and magnesium stearate making up the tablet core. The tablet coating is composed of hypromellose, titanium dioxide, lactose monohydrate, macrogol and triacetin.

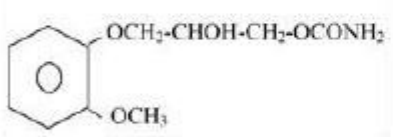
The finished product is packaged in polyvinylchloride (PVC)/polyvinylidenechloride (PVdC) blisters containing 20, 30, 50 or 100 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Methocarbamol
Chemical Name: (±)1,2-Propanediol, 3-(2-methoxyphenoxy)-,1-carbamate
Molecular Formula: $C_{11}H_{15}NO_5$
Chemical Structure:



Molecular Weight: 241.24 g/mol
Appearance: White powder, odourless or having a slight characteristic odour.
Solubility: Soluble in alcohol only with heating; sparingly soluble in water and in chloroform; insoluble in benzene and in n-hexane.

Methocarbamol is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant

specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European monographs or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final product.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions Do not store above 25°C, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of methocarbamol is well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this/these application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of methocarbamol are well-known. With the exception of data from two bioequivalence studies, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of these studies is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence studies.

Study 1
This study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study of Methocarbamol 750 mg film-coated tablets with Ortoton 750 mg Filmtablette (Recordati pharma GmbH, Germany) in normal healthy adult human subjects under fasting conditions.

Subjects were administered a single dose of test or reference product with 240 mL of water. Blood samples were taken pre-dose and up to 16 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) (n=49)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	40623.301 ± 14106.7407	41151.953 ± 14305.9324	13270.528 ± 3795.1945	1.00 (0.33-4.00)
Reference	39782.433 ± 16237.9248	40319.779 ± 16444.3111	11976.076 ± 4363.0630	1.33 (0.33-4.00)
*Ratio (90% CI)	105.11 **(98.13 – 112.58)**	104.99 **(98.05 - 112.42)**	113.80 **(103.11 - 125.61)**	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t} in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

T_{max} was not observed at the first sampling time-point for any subject. There were no pre-dose levels. The maximum observed plasma concentration was within the validated range of the analytical method. The extent of extrapolation of the AUC was <20% for each subject in each period. No safety concerns are raised.

The Test/Reference ratios and their 90% confidence intervals were not within the specified limits to show bioequivalence between the test product and the reference product.

Bioequivalence was not demonstrated based on the results of study 1, since the upper bound of the 90% confidence interval for C_{max} was 125.61%, just above the 125.00% bioequivalence criterion.

The applicant provided the following additional bioequivalence study (Study 2). The design was similar to study 1. The number of subjects analysed was higher: n=65 compared to n=49.

Study 2

This study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study of Methocarbamol 750 mg film-coated tablets with Ortoton 750 mg Filmtablette (Recordati pharma GmbH, Germany) in normal healthy adult human subjects under fasting conditions.

Subjects were administered a single dose of test or reference product with 240 mL of water. Blood samples were taken pre-dose and up to 16 hours post dose, with a washout period of 8 days between the treatment periods.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) (n=65)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	41822.018 ± 12214.4871	42300.826 ± 12329.6228	13744.791 ± 4037.9461	1.33 (0.33-3.50)
Reference	41767.221 ± 12941.3941	42271.494 ± 13068.3734	13987.634 ± 4537.6411	1.00 (0.50-3.00)
*Ratio (90% CI)	100.54	100.48	98.83	

	(96.51-104.74)	(96.45-104.68)	(92.64-105.43)	
AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t.			
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time			
C_{max}	Maximum plasma concentration			
t_{max}	Time until C_{max} is reached			

**ln-transformed values*

T_{max} was not observed at the first sampling time-point for any subject. There were no pre-dose levels. The maximum observed plasma concentration was within the validated range of the analytical method. The extent of extrapolation of the AUC was <20% for each subject in each period. No safety concerns are raised.

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**)'. Thus, these data support the claim that the applicant's test product Methocarbamol 750 mg film-coated tablets is bioequivalent to the reference product Ortoton 750 mg Filmtablette under fasting conditions.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence studies, no new safety data were submitted with this application.

The safety data from the bioequivalence studies showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

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 results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSIONS

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with methocarbamol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/6778/001 to IE/H/1079/001/DC			