Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Methocarbamol 1500 mg film-coated Tablets

Methocarbamol

PL 24837/0132

Consilient Health Ltd.,

LAY SUMMARY

Methocarbamol 1500 mg film-coated Tablets
Methocarbamol

This is a summary of the Public Assessment Report (PAR) for Methocarbamol 1500 mg film-coated Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as methocarbamol in this lay summary for ease of reading.

For practical information about using methocarbamol, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is methocarbamol and what is it they used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Ortoton 750mg and 1500mg film-coated tablets.

This medicine contains the active substance methocarbamol. Methocarbamol is used for the symptomatic treatment of painful muscular tension, especially in the lower back (lumbago).

How does methocarbamol work?
Methocarbamol belongs to the group of medicinal products known as muscle relaxants.

How are methocarbamol used?
The pharmaceutical form of this medicine is film-coated tablets and the route of administration is by mouth (oral).

The recommended dose for adults is 1500 mg methocarbamol 3 times a day (corresponding to 1 tablet 3 times daily). At the beginning of the treatment a dose of 1500 mg methocarbamol 4 times a day (corresponding to 1 tablet four times daily) is recommended. In severe cases at dose up to 7500 mg can be taken each day.

Use in elderly patients
Elderly patients may only need half the usual dose to give the same relief from the pain and muscle spasms.

Use in patients with liver problems
Patients with liver disease may need a longer interval between taking the tablets.

Method of administration
Methocarbamol is for oral use. The tablets should be taken with sufficient water.

The duration of treatment depends on the symptoms induced by muscle tension but should not exceed 30 days.

For further information on how methocarbamol is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of methocarbamol have been shown in studies?
Because methocarbamol is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of methocarbamol?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at www.yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because methocarbamol is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was methocarbamol approved?
It was concluded that, methocarbamol has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of methocarbamol?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for methocarbamol The RMP details the important risks of methocarbamol, how these risks can be minimised, any uncertainties about methocarbamol (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of methocarbamol.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of methocarbamol are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about methocarbamol

A Marketing Authorisation for methocarbamol was granted in the United Kingdom (UK) consisting of England, Scotland and Wales, and Northern Ireland (NI) on 8 April 2022.

The full PAR for methocarbamol follows this summary.

This summary was last updated in June 2022.

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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 1500 mg film-coated Tablets (PL 24837/0132) could be approved.

The product is approved for the following indication:
Symptomatic treatment of painful muscular tension, especially in the lower back (lumbago). Methocarbamol is indicated in adults.

Mechanism of action
The active substance methocarbamol is a centrally acting muscle relaxant.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of suitable originator medicinal products, Ortoton 750mg and 1500mg film-coated tablets that has been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence studies were 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.

A Marketing Authorisation for methocarbamol was granted in the United Kingdom (UK) consisting of England, Scotland and Wales, and Northern Ireland (NI) on 8 April 2022.

II QUALITY ASPECTS

II.1 Introduction

The active substance is methocarbamol. Each film-coated tablet contains 1500 mg of methocarbamol. The other ingredients are:

Tablet core: sodium starch, glycolate type A, pregelatinised starch (maize), sodium lauryl sulphate, povidone K29/32, magnesium stearate

Tablet coating: hypromellose, titanium dioxide (E171) lactose monohydrate, macrogol 3000, triacetin.

The finished product is packaged in white opaque PVC/PVDC/Al blisters containing 24, 48 or 96 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 regulations concerning materials in contact with food.

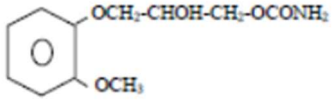
II.2 ACTIVE SUBSTANCE

rINN: Methocarbamol

Chemical Name: (±)1,2-Propanediol, 3-(2-methoxyphenoxy)-, 1-carbamate.

Molecular Formula: $C_{11}H_{15}NO_5$

Chemical Structure:



(±)1,2-Propanediol, 3-(2-methoxyphenoxy)-, 1-carbamate.

Molecular Weight: 241.24

Appearance: White powder

Solubility:

Solvent	Solubility	Temperature
Water	8.33mg/mL	34°C
Chloroform	10 mg/mL	34°C
Alcohol	33 mg/mL	27°C

Methocarbamol is not 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 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 profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national 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 products.

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

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.

Satisfactory batch formulation data have 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 Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. 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 30 months, without special storage conditions, 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.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of methocarbamol are 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 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.1 Introduction

The clinical pharmacology, efficacy and safety of methocarbamol is well-known. With the exception of data from a bioequivalence study, 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 this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study (C15315).

1. Bioequivalence study (C15315).

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study of Methocarbamol Tablets 750 mg versus Ortoton 750 mg Filmtablette, in normal healthy adult human subjects under fasting conditions.

Following a 10 hour fast, subjects received a single dose of test or reference product. Blood samples were collected pre-dose and up to 16.00 hours post dose. The washout period was 7 days.

A summary of the pharmacokinetic results are presented below:

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

The upper bound of the 90% confidence interval for Cmax was marginally above 125.00%. Therefore, the bioequivalence has not been shown. The applicant submitted a second bioequivalence study, (C17169), detailed below.

2. Bioequivalence study (C17169)
An open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study of Methocarbamol Tablets 750 mg with Ortoton 750 mg Filmtablette in normal healthy adult human subjects under fasting conditions.

Following a 10 hour fast, subjects received a single dose of test or reference product with water. Blood samples were collected pre-dose and up to 16.00 hours post dose. The washout period was 8 days.

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* ***(96.51-104.74)***	*100.48* ***(96.45-104.68)***	*98.83* ***(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 Cmax is reached*

Overall conclusion of both studies
Bioequivalence was not demonstrated based on the results of study C15315 since the upper bound of the 90% confidence interval for Cmax was 125.61%, just above the 125.00% bioequivalence criterion. Study C17169 had a similar design to study C15315, and no concerns are raised. The number analysed was higher: n=65 compared to n=49. The bioequivalence criteria were met; in this case Cmax was well within the 80.00-125.00% criteria. Considering the data from studies C15315 and C17169, Methocarbamol 750 mg film-coated tablets is considered bioequivalent with Ortoton 750 mg film-coated tablet by Recordati Pharma GmbH.

The biowaiver criteria specified in the current bioequivalence guideline are met, the results and conclusions from the bioequivalence study on the 750 mg product can be extrapolated to the 1500 mg product.

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 Regulation 182 of The Human Medicines Regulation 2012, 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

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

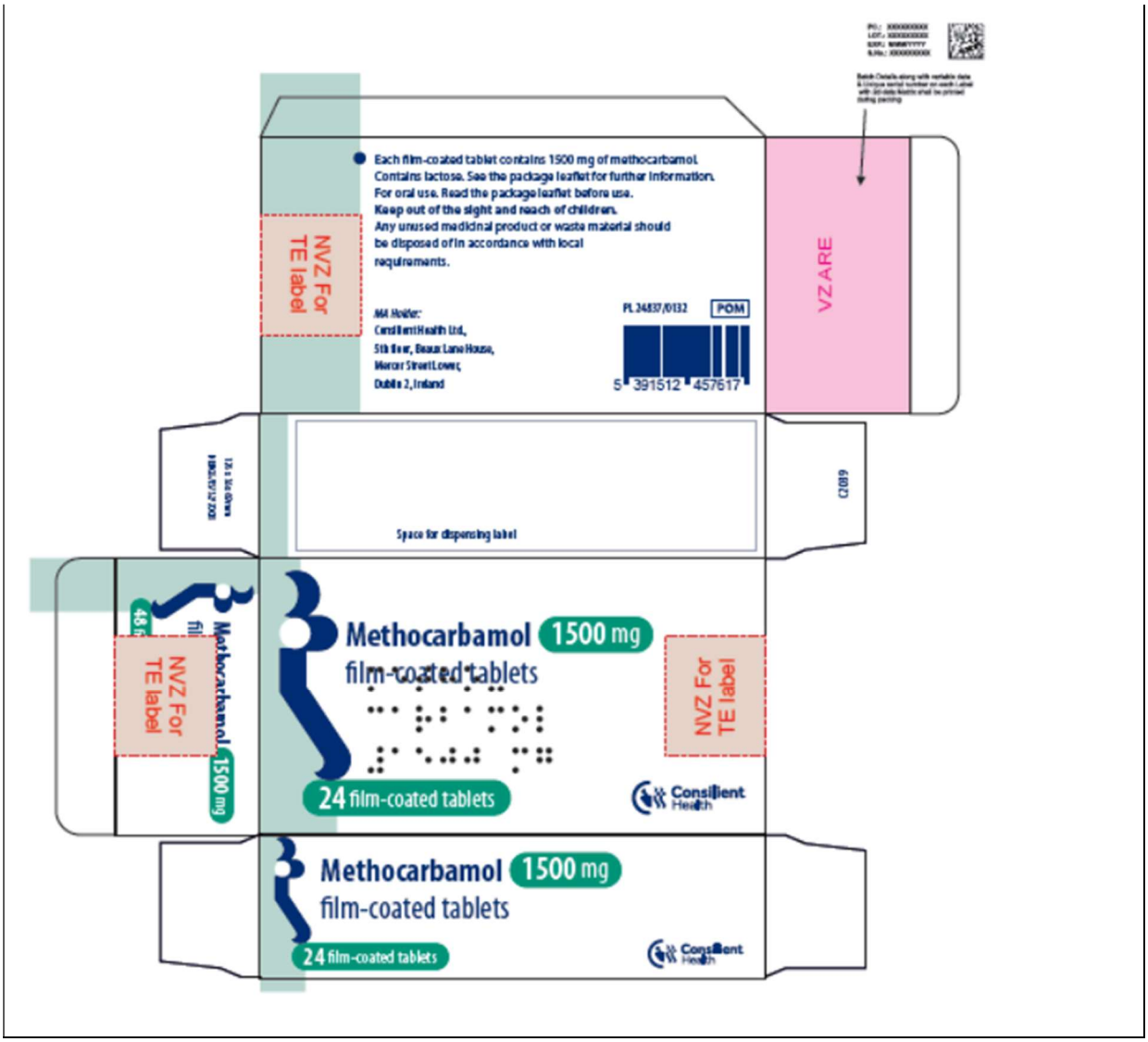
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


Each film-coated tablet contains 1500 mg of methocarbamol.
Contains lactose. See the package leaflet for further information.
For oral use. Read the package leaflet before use.
Keep out of the sight and reach of children.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
MA Holder:
Consilient Health Ltd,
5th floor, Beaux Lane House,
Mercer Street Lower,
Dublin 2, Ireland
PL 24837/0132
POM
5 391512 457617
NVZ For TE label
VZARE
Space for dispensing label
Methocarbamol 1500 mg
film-coated tablets
24 film-coated tablets
Consilient Health
Methocarbamol 1500 mg
film-coated tablets
24 film-coated tablets
Consilient Health
NVZ For TE label
NVZ For TE label

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**