Public Assessment Report

Decentralised Procedure

Methocarbamol 750mg Film-coated Tablets

Methacarbamol

UK/H/1876/001/DC

UK licence no: PL 20620/0017

NRIM Limited
LAY SUMMARY

On 1st October 2010, the Concerned Member State (CMS) and the Reference Member State (RMS) agreed to grant Marketing Authorisation to NRIM Limited for the medicinal product Methocarbamol 750mg Film-coated Tablets. The marketing authorisation was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 5th November 2010. This medicine is only available on prescription from your doctor.

Methocarbamol belongs to a group of medicines called ‘muscle relaxants’. They are used for the short term treatment of pain and muscle spasm caused by injuries such as sprains and strains.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Methocarbamol 750mg Film-coated Tablets outweigh the risks, hence a Marketing Authorisation has been granted.
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# Module 1

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<th><strong>Product Name</strong></th>
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<tr>
<td></td>
<td>Marlborough House</td>
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<td>298, Regents Park Road</td>
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<td>Finchley N3 2UA</td>
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Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Methocarbamol 750mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 750mg of methocarbamol.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet
A white capsule shaped film-coated tablet with break line on one side
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
As a short-term adjunct to the symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasms.

4.2 Posology and method of administration
Route of administration
For oral use
Dosage:
Adults: The usual dose is 2 tablets four times daily but therapeutic response has been achieved with doses as low as 1 tablet three times daily.
Elderly: Half the maximum dose or less may be sufficient to produce a therapeutic response.
Children: Not recommended.
Hepatically impaired: In patients with chronic hepatic disease the elimination half-life may be prolonged. Therefore, consideration should be given to increasing the dose interval.
Duration of Treatment: The duration of administration depends on the symptoms induced by increased muscle tone, but should not exceed 30 days.

4.3 Contraindications
Hypersensitivity to methocarbamol or any of the other excipients in methocarbamol tablets. Coma or pre-coma states. Known brain damage or epilepsy. Myasthenia gravis.

4.4 Special warnings and precautions for use
Methocarbamol should be used with caution in patients with renal and hepatic insufficiency. Since methocarbamol may possess a general CNS depressant effect, patients should be cautioned about combined effects with alcohol and other CNS depressants.

4.5 Interaction with other medicinal products and other forms of interaction
This product may potentiate the effects of other central nervous system depressants and stimulants including alcohol, barbiturates, anaesthetics and appetite suppressants. The effects of anticholinergics, e.g. atropine and some psychotrophic drugs may be potentiated by methocarbamol. Methocarbamol may inhibit the effect of pyridostigmine bromide. Therefore methocarbamol should be used with caution in patients with myasthenia gravis receiving anticholinesterase agents. Little is known about the possibility of interactions with other drugs.
Methocarbamol may cause colour interference in certain screening tests for 5-hydroxyindolacetic acid (5-HIAA) using nitrosoaphthol reagent and in screening tests for urinary vanillymandelic acid (VMA) using the Gitlow method.

4.6 Pregnancy and lactation
Animal reproductive studies have not been conducted with methocarbamol. It is also not known whether methocarbamol can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity.
Safe use of methocarbamol has not been established with regard to possible adverse effects upon foetal development. There have been very rare reports of foetal and congenital abnormalities following in utero exposure to methocarbamol. Therefore methocarbamol tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.
Methocarbamol and/or its metabolites are excreted in the milk of dogs; however, it is not known whether methocarbamol or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Methocarbamol tablets are administered to a nursing woman.

4.7 Effects on ability to drive and use machines
Methocarbamol has moderate influence on the ability to drive and use machines as methocarbamol may cause dizziness or drowsiness - especially if other medications capable of causing drowsiness are also being taken. Patients should be cautioned that if dizziness or drowsiness are experienced these activities have to be avoided.

4.8 Undesirable effects
The following undesirable effects have been reported in the context of treatment with methocarbamol and - as far as information on frequency is stated in the literature - are based on the following groups of frequency:

<table>
<thead>
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<th>Frequency</th>
<th>Examples</th>
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<tr>
<td>Very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥1/100 to &lt; 1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥1/1000 to &lt; 1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10 000 to &lt; 1/1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10 000</td>
</tr>
<tr>
<td>Not known</td>
<td>(cannot be estimated from the available data)</td>
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</table>

The most frequent undesirable effect of the drug is headache.

General disorders
Rare: headache, fever, angioneurotic oedema
Gastrointestinal disorders
Very rare: nausea and vomiting
Nervous system disorders
Rare: dizziness
Very rare: blurred vision, drowsiness, tremor, convulsion
Psychiatric disorders
Very rare: restlessness, anxiety, confusion, anorexia
Skin and subcutaneous tissue disorders
Rare: hypersensitive reactions (pruritus, skin rash, urticaria)
Eye disorders
Rare: conjunctivitis with nasal congestion
The following side effects have also been reported.
Blood and Lymphatic system
Leucopenia
Cardiovascular system disorders
flushing, bradycardia, hypotension and syncope.
General disorders
Anaphylactic reaction
Gastrointestinal disorders
dyspepsia, jaundice (including cholestatic jaundice)
Nervous system disorders
Vertigo, mild muscular in coordination, amnesia, diplopia, nystagmus, insomnia, seizures (including grand mal)
Skin, subcutaneous tissue disorders, and special senses
Metallic taste

4.9 Overdose
Limited information is available on the acute toxicity of methocarbamol. Overdose of methocarbamol is frequently in conjunction with alcohol or other CNS depressants and includes the following symptoms: nausea, drowsiness, blurred vision, hypotension, seizures and coma. One adult survived the deliberate ingestion of 22 to 30 grams of methocarbamol without serious toxicity. Another adult survived a dose of 30 to 50 grams. The principal symptom in both cases was extreme drowsiness. Treatment was symptomatic and recovery was uneventful. However, there have been cases of fatal overdose.
Management of overdose includes symptomatic and supportive treatment. Supportive measures include maintenance of an adequate airway, monitoring urinary output and vital signs, and administration of intravenous fluids if necessary. The usefulness of haemodialysis in managing overdose is unknown.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmcotherapeutic group: Muscle relaxant s, centrally acting agents; Carbamic acid esters
ATC Code: M03BA03
Methocarbamol is used as a short-term adjunct to the symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasms. 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.

5.2 Pharmacokinetic properties
After oral administration methocarbamol is absorbed rapidly and completely from the gastro-intestinal tract. The substance can be detected in blood already 10 minutes after intake and produces peak plasma concentrations after about 1-3 hours. Its activity derives from the intact molecule and only a small proportion is converted to guaiphenesin. Plasma half-life in plasma amounts to approximately 2 hours. Methocarbamol and its two main metabolites are bound to glucuronic and to sulfuric acid and are eliminated nearly exclusively via the kidneys. About half of an applied dose is excreted into urine within 4 hours, only a small part of which is eliminated as unchanged methocarbamol.

Renally impaired
The clearance of methocarbamol in renally-impaired patients on maintenance haemodialysis was reduced about 40% compared to a normal population, although the mean elimination half-life in these two groups was similar (1.2 versus 1.1 hours, respectively).

Hepatically impaired
In patients with cirrhosis secondary to alcohol abuse, the mean total clearance of methocarbamol was reduced approximately 70% compared to a normal population (11.9 L/hr), and the mean elimination half-life was extended to approximately 3.4 hours. The fraction of methocarbamol bound to plasma proteins was decreased to approximately 40 to 45% compared to 46 to 50% in an age and weight-matched normal population.

5.3 Preclinical safety data
The acute toxicity of methocarbamol is comparatively low. In animal testing the following signs of intoxication were observed: ataxia, catalepsy, seizures and coma. In-vitro and in-vivo examinations as to the genetic toxicology of methocarbamol did not reveal any mutagenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core Tablet
Propylene Glycol
Maize Starch
Povidone (PVPK-30)
Sodium lauryl sulphate
Sodium starch glycolate Type A (Glycolys)
Talc
Magnesium stearate

Film-coating
Opadry II White 85F18422
Consisting of: -
Polyvinyl Alcohol-Part. Hydrolyzed
Titanium Dioxide (E171)
Macrogol/PEG 3350
Talc (E553b)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years
6.4 Special precautions for storage
No special storage conditions are necessary.

6.5 Nature and contents of container
150 cc HDPE white opaque tablet container with 38mm child resistant cap. Each bottle contains 100 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20620/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/11/2010

10 DATE OF REVISION OF THE TEXT
05/11/2010
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
METHOCARBAMOL 750MG FILM-COATED TABLETS

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING THIS MEDICINE.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Methocarbamol is and what it is used for.
2. Before you take Methocarbamol
3. How to take Methocarbamol
4. Possible side effects
5. How to store Methocarbamol
6. Further Information

1. WHAT METHOCARBAMOL IS AND WHAT IT IS USED FOR?

Methocarbamol belongs to a group of medicines called ‘muscle relaxants’. They are used for the short term treatment of pain and muscle spasm caused by injuries such as sprains and strains.

2. BEFORE YOU TAKE METHOCARBAMOL

Do not take this medicine and tell your doctor if you:
- are allergic (hypersensitive) to methocarbamol or have had any problems in the past with methocarbamol
- are allergic to any of the other ingredients of methocarbamol (listed in Section 6 below)
- have ever suffered any brain damage or coma
- suffer from epilepsy or convulsions
- suffer from muscle weakness (a disease called myasthenia gravis)

Take special care with methocarbamol if you:
- are pregnant or thinking of becoming pregnant
- are breastfeeding
- have, or have had, any kidney or liver problems
- are having any medical investigations or tests as methocarbamol could interfere with the results. Tell your doctor that you are taking methocarbamol before you have the test.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking methocarbamol.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Methocarbamol affects the way some other medicines work. Also some medicines can affect the way methocarbamol works.

If you are taking any of the following medicines, you should tell your doctor or pharmacist as methocarbamol may interact with them:

- Barbiturates which can be taken for epilepsy or to help you sleep.
- Appetite suppressants to help you lose weight.
- Medicines for stomach upsets or sea-sickness (anti-cholinergics).
- Psychotropic drugs for the treatment of anxiety, depression or other mental illnesses.
- If you are due to have anaesthetic for any reason, tell your doctor or dentist that you are taking methocarbamol.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking methocarbamol.

Taking methocarbamol with food or drink
Methocarbamol should be taken with a drink that does not contain alcohol. Do not drink alcohol while you are taking methocarbamol.

Pregnancy or breast-feeding
Do not take this medicine if you are pregnant or might become pregnant unless your doctor tells you to. Contact your doctor if you think you may be pregnant, or are intending to become pregnant.

Do not take this medicine if you are breast-feeding or planning to breast-feed.

Driving and using machines:
Methocarbamol may make you feel sleepy and may affect your ability to drive, operate machinery and carry out other hazardous activities. These activities should therefore be avoided altogether until you are sure you are not affected

3. HOW TO TAKE METHOCARBAMOL

Always take methocarbamol exactly as your doctor has told you. You should check with your doctor if you are not sure.

Adults: Take TWO tablets with a little water, FOUR times a day. Sometimes a lower dose may be sufficient. You should spread the doses as evenly as possible over a 24-hour period.

Elderly: older patients may only need half the usual dose to give the same relief from the pain and muscle spasms.

Children: These tablets should not be given to children

Liver impairment: you may need a longer interval between taking the tablets if you have liver disease. You should always follow your doctor's instructions carefully.

These tablets are for short-term treatment. Take them for as long as your doctor has recommended, or until you no longer need them to ease the pain. Return any unused tablets to your pharmacist.
If you take more methocarbamol than you should
It is important to stick to your prescribed dose. If you or someone else takes too much medicine, contact your doctor or nearest hospital emergency department immediately. Always take any medicine left over with you and also the bottle, as this will allow easier identification of the medicine.

If you forget to take methocarbamol
If you forget to take a dose, simply take the next dose when it is due. Do not take a double dose of tablets to make up for a missed dose.

If you stop taking methocarbamol
Keep taking methocarbamol until your doctor tells you to stop.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, methocarbamol can cause side effects although not everybody gets them.

STOP taking this medicine and tell your doctor immediately if you experience any of the following rare symptoms:
- confusion, convulsions, fits, and rash or swelling of the face or neck and shortness of breath which may be a sign of an allergy.

If you notice any of these symptoms, you should contact your doctor:
- yellowing of the skin and/or whites of the eyes.

The levels of your white blood cells may also be reduced which can lead to recurrent:
- infections
- mouth ulcers.

If any of the following side effects are troublesome, you should tell your doctor:
- drowsiness, difficulty in sleeping,
- restlessness, anxiety or worry,
- eating disorders
- dizziness
- memory loss
- blurred or double vision, rapid or unusual eye movements,
- reddening of the eyes together with nasal stuffiness,
- feeling sick or vomiting,
- heartburn,
- taste disturbance,
- tremor or shakiness, mild muscle incoordination,
- headache.
- fever,
- itching,
- a slow heartbeat,
- flushing
- fainting or feeling faint,
- low blood pressure.

If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE METHOCARBAMOL
- Keep out of the reach and sight of children.
- Do not use methocarbamol after the expiry date, which is stated on the bottle label. The expiry date refers to the last day of the month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What methocarbamol contains?
The active substance in your tablet is methocarbamol. Each film-coated tablet contains 750mg of methocarbamol. The other ingredients are maize starch, povidone (PVPK-30), sodium lauryl sulphate, sodium starch glycolate Type A (Glycolys), talc, magnesium stearate and opadry II white which consists of polyvinyl alcohol part hydrolyzed, titanium dioxide (E171), Macrogol/PEG 3350, Tale (E553b).

What methocarbamol looks like and contents of the pack
Methocarbamol 750mg Tablets are white capsule shaped film-coated tablets with break line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Methocarbamol tablets are packed in a white HDPE tablet container with a child resistant cap. Each bottle contains 100 tablets.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation holder and manufacturer of this medicine is NRIM Limited Marlborough House, 298 Regents Park Road, Finchley, London, N3 2UA, United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:
UK: Methocarbamol 750mg Film-coated Tablets
DE: Methocarbamol NRIM 750mg Filmtabletten

This leaflet was approved in 07/2010
Module 4
Labelling

For oral use.
Use as directed by your physician.
Each film-coated tablet contains 750mg of Methocarbamol.

WARNING: May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drinks.

Keep out of the reach and sight of children.
Read the attached leaflet

PL 20620/0017
PL Holder: NRIM Limited, Marlborough House,
298 Regents Park Road, Finchley,
London N3 2UA, UK

100 Film-coated Tablets POM
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) consider that the application for Methocarbamol 750mg Film-coated Tablets in the treatment of acute musculoskeletal disorders associated with painful muscle spasms, could be approved.

This application was submitted under Article 10.1, claiming to be generic medicinal product of Robaxin 750mg Tablets (PL 08081/0035), which was first licensed to Shire Pharmaceuticals Ltd, UK, on 26th August 2003.

With the UK as the RMS in this Decentralised Procedure (UK/H/1876/01/DC), NRIM Limited applied for the Marketing Authorisation for Methocarbamol 750mg Film-coated Tablets in Germany.

Methocarbamol is an oral, centrally acting skeletal muscle-relaxing agent with sedative properties. It is used as an adjunct to rest, physical therapy, analgesics and other measures in the treatment of acute musculoskeletal pain. The mechanism of action of methocarbamol in humans has not been established, but it may be due to general central nervous system (CNS) depression. Clinically, pain relief, a reduction in muscle spasm and enhanced mobility of the affected muscle occurs. Pain relief is postulated to be due to alterations in the perception of pain. Unlike neuromuscular blockers, methocarbamol does not have an effect on neuronal conduction, neuromuscular transmission or muscle excitability. A common property of virtually all drugs which have been classified as centrally acting skeletal muscle relaxants is their ability to abolish polysynaptic reflex contractions at dose levels which have no effect on monosynaptic contractions. It has been suggested that the locus of action of the centrally acting muscle relaxants is the spinal interneurone.

No new preclinical and clinical studies were conducted, which is acceptable given that the application was based on being generic medicinal product of an originator product that has been licensed for over 10 years. A bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant respective licence for the above product at the end of procedure (Day 210 – 1st October 2010). After a subsequent national phase, the UK granted a licence for this product on 5th November 2010 (PL 20620/0017).
## II. ABOUT THE PRODUCT

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<th>Methocarbamol 750mg Film-coated Tablets</th>
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<td>Marketing Authorisation Number(s)</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>NRIM Limited</td>
</tr>
<tr>
<td></td>
<td>Marlborough House, 298, Regents Park Road, Finchley, London N32UA, UK</td>
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</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Methocarbamol
Chemical Name: 2-hydroxy-3-(2-methoxyphenoxy)propyl carbamate
Structure:

\[ \text{Structure Image} \]

Molecular Formula: C_{11}H_{15}NO_{5}
Molecular Weight: 241.24
Appearance: White powder, odourless or having a slight characteristic odour
Solubility: Sparingly soluble in water and in CHCl₃, soluble in alcohol only with heating, insoluble in benzene and in \( n \)-hexane

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

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

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients propylene glycol, maize starch, povidone (PVPK-30), sodium lauryl sulphate, sodium starch glycolate Type A (glycolys), talc, magnesium stearate, Opadry II White 85F18422 (polyvinyl alcohol-part. hydrolyzed, titanium dioxide (E171), macrogl/PEG 3350 and talc (E553b)).

All excipients comply with their respective European Pharmacopoeia monographs except Opadry II White 85F18422, which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.
**Pharmaceutical Development**
The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Robaxin 750mg Tablets, which was first granted in the UK to Shire Pharmaceuticals Ltd, on 26th August 2003.

Comparative impurity and dissolution profiles have been presented for test and reference products.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished Product Specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
The finished product is packed in HDPE white opaque tablet container with child resistant cap. Each bottle contains 100 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set for this product, with no special storage condition.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.
Marketing Authorisation Application (MAA) Forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
The pharmacological, pharmacokinetic and toxicological properties of methocarbamol are well-known.

No new preclinical data have been supplied with this application and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of this product from a preclinical point of view.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

Study 1
This is a randomised open label single dose, two treatment, two period, two sequence two-way cross over comparative bioavailability study of Methocarbamol 750mg tablets (NRIM Limited, U.K) and Robaxin 750 mg tablets (Shire, UK) in healthy, male adult subjects under fasting conditions.

The study consisted of two periods with a washout period of at least 7 days. The pre-dose blood sample of 5 mL (0.0 hr) was collected within one hour prior to the dosing. The post dose blood samples of 5 mL each were drawn at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00 and 16.00 hours post dose.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀-₁ ng/ml/h</th>
<th>AUC₀-∞ ng/ml/h</th>
<th>Cₘₐₓ ng/ml</th>
<th>tₘₐₓ h</th>
<th>T₁/₂ h</th>
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<tbody>
<tr>
<td>Test</td>
<td>25895.47 +/- 8188.73</td>
<td>26716.29 +/- 8153.31</td>
<td>11238.64 +/- 4029.75</td>
<td>1.5</td>
<td>1.12 +/- 0.18</td>
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<td>Reference</td>
<td>26814.72 +/- 11986.12</td>
<td>27662.91 +/- 11938.71</td>
<td>10459.77 +/- 3515.89</td>
<td>1.5</td>
<td>1.10 +/- 0.22</td>
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<td>*Ratio (90% CI)</td>
<td>91.37-106.38</td>
<td>91.38-106.25</td>
<td>96.68-116.02</td>
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<td>Intrasubject CV (%)</td>
<td>16.1</td>
<td>16.0</td>
<td>19.4</td>
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The 90% confidence intervals for $C_{\text{max}}$ and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (methocarbamol 750mg tablets) and the reference formulation (Robaxin 750mg tablets).

**Pharmacodynamics**
No new data have been submitted and none are required for this generic application.

**Clinical Efficacy**
No new data have been submitted and none are required.

**Clinical Safety**
No new data have been submitted and none are required.

**Expert Report**
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

**Clinical Expert Report**
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Marketing Authorisation Application (MAA) Forms**
The MAA form is medically satisfactory.

**Clinical Conclusion**
There are no objections to the approval of this product from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Methocarbamol 750mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Bioequivalence have been demonstrated between the applicant’s Methocarbamol 750mg Film-coated Tablets and the reference product, Robaxin 750mg Tablets.

No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with methocarbamol is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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