Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Meloxicam 7.5mg Tablets
Meloxicam 15mg Tablets

(meloxicam)

PL 14251/0097-0098

Manx Healthcare Ltd

LAY SUMMARY

Meloxicam 7.5mg Tablets
Meloxicam 15mg Tablets
(meloxicam)

This is a summary of the Public Assessment Report (PAR) for Meloxicam 7.5mg and 15mg Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Meloxicam 7.5mg and 15mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Meloxicam 7.5mg and 15mg Tablets and what are they used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Mobic 7.5 mg and 15 mg tablets.

Meloxicam 7.5mg and 15mg Tablets are used for the:
- short-term treatment of flare ups of osteoarthrosis
- long-term treatment of
  - rheumatoid arthritis
  - ankylosing spondylitis (also known as Bechterew's Disease)

How do Meloxicam 7.5mg and 15mg Tablets work?
The active ingredient in these medicines is called meloxicam and it belongs to a group of drugs called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which are used to reduce inflammation and pain in the joints and muscles.

How are Meloxicam 7.5mg and 15mg Tablets used?
The pharmaceutical form of these medicines is a tablet and the route of administration is oral (via the mouth). The tablets should be swallowed with a glass of water during a meal.

The recommended dose is as follows.
Flare-ups of osteoarthrosis
One 7.5mg tablet a day, which may be increased after consultation with the patient's doctor to 15mg a day (two 7.5mg tablets or one 15mg tablet).

Rheumatoid arthritis
One 15mg tablet per day (or two 7.5mg tablets). This may be reduced to one 7.5mg tablet once a day.

Ankylosing spondylitis
One 15mg tablet per day (or two 7.5mg tablets). This may be reduced to one 7.5mg tablet once a day.

Do **not** exceed the maximum dose of 15mg a day.

Elderly patients and patients with impaired kidney or liver function
For elderly patients, the recommended dose for long-term treatment of rheumatoid arthritis or ankylosing spondylitis is 7.5mg per day.

Also, patients at high risk of side effects should start treatment with 7.5mg a day.
If the patient has severe kidney disease and receives dialysis, the maximum dose of meloxicam should be 7.5mg per day.

Use in children and adolescents
Meloxicam must not be given to children and adolescents under 16 years of age.

For further information on how Meloxicam 7.5mg and 15mg Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines 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 Meloxicam 7.5mg and 15mg Tablets have been shown in studies?
Because Meloxicam 7.5mg and 15mg Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Meloxicam 7.5mg and 15mg Tablets?
Because Meloxicam 7.5mg and 15mg Tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why were Meloxicam 7.5mg and 15mg Tablets approved?
It was concluded that, in accordance with EU requirements, Meloxicam 7.5mg and 15mg Tablets have been shown to be comparable to and to be bioequivalent to the reference medicines. 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 Meloxicam 7.5mg and 15mg Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Meloxicam 7.5mg and 15mg Tablets is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Meloxicam 7.5mg and 15mg Tablets

Marketing Authorisations for Meloxicam 7.5mg and 15mg Tablets were granted in the UK on 11 December 2020.

The full PAR for Meloxicam 7.5mg and 15mg Tablets follows this summary.

This summary was last updated in December 2020.

TABLE OF CONTENTS

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 applications for Meloxicam 7.5mg and 15mg Tablets (PL 14251/0097-0098) could be approved.

The products are approved for the following indications:

- Short-term symptomatic treatment of exacerbations of osteoarthrosis
- Long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis

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

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

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of suitable originator medicinal products, Mobic 7.5 mg and 15 mg tablets that have 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 applications are based on being generic medicinal products of reference products that have been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have 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 these products at all sites responsible for the manufacture, assembly and batch release of these products.

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

Marketing authorisations were granted for these products on 11 December 2020.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 7.5mg or 15mg meloxicam.

In addition to meloxicam, these products also contain the excipients maize starch, pregelatinized maize starch, colloidal silicon dioxide, trisodium citrate, lactose monohydrate, microcrystalline cellulose and magnesium stearate.

The finished products are packaged in Aluminium-PVC/PVDC blisters in pack sizes of 20 and 30 tablets.

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.

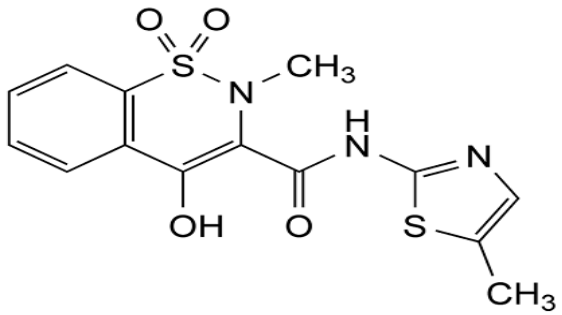
II.2 ACTIVE SUBSTANCE

rINN: Meloxicam

Chemical Name: 4-Hydroxy-2-methyl-N-(5-methylthiazol-2-yl)-2H-1,2-benzothiazine-3- carboxamide 1, 1-dioxide

Molecular Formula: $C_{14}H_{13}N_3O_4S_2$

Chemical Structure:



Molecular Weight: 351.4

Appearance: Pale yellow powder

Solubility: Practically insoluble in water, soluble in dimethyl formamide, very slightly soluble in ethanol (96%).

Meloxicam is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

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/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.

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

This products do not contain or consist of genetically modified organisms (GMO).

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

Satisfactory batch formulae have been provided for the manufacture of the products, 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 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 36 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 products.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of meloxicam 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 these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of meloxicam is well-known. With the exception of data one 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 applications, the applicant submitted the following bioequivalence study:

STUDY

This study was a randomised, open-label, balanced, two treatment, two period, two sequence, single dose, two-way truncated crossover oral bioequivalence comparing the test product Meloxicam 15mg Tablets versus the reference product Mobic 15 mg tablets in subjects under fed conditions.

A single dose of meloxicam 15 mg tablet (test or reference product) was administered in each study period 30 minutes after a standard high-fat, high-calorie (approximately 800 to 1000 kcal), veg/non-veg breakfast that had been preceded by an overnight fast of at least 10 hours.

Standard meals were provided at appropriate time intervals (at around 04.00 (lunch), 08.00 (snacks), 12.00 (dinner), 24.00 (breakfast), 28.00 (lunch), 32.00 (snacks) and 36.00 (dinner) hours post-dose). All meal plans were identical for each period of study. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 8 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Table : Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals

	Geometric mean ratio Test/Reference	90% Confidence Intervals	CV%
C_{max} (ng/mL)	107.15	99.85 - 114.98	13.63
AUC_{0-t} (ng.h/mL)	101.27	96.70 - 106.06	8.9

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test

product and the reference product.

As the additional strength of the product meets the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 15mg product strength can be extrapolated to the other strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study 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 marketing authorisations is recommended for these applications.

V USER CONSULTATION

The Patient Information Leaflet (PIL) 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 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.

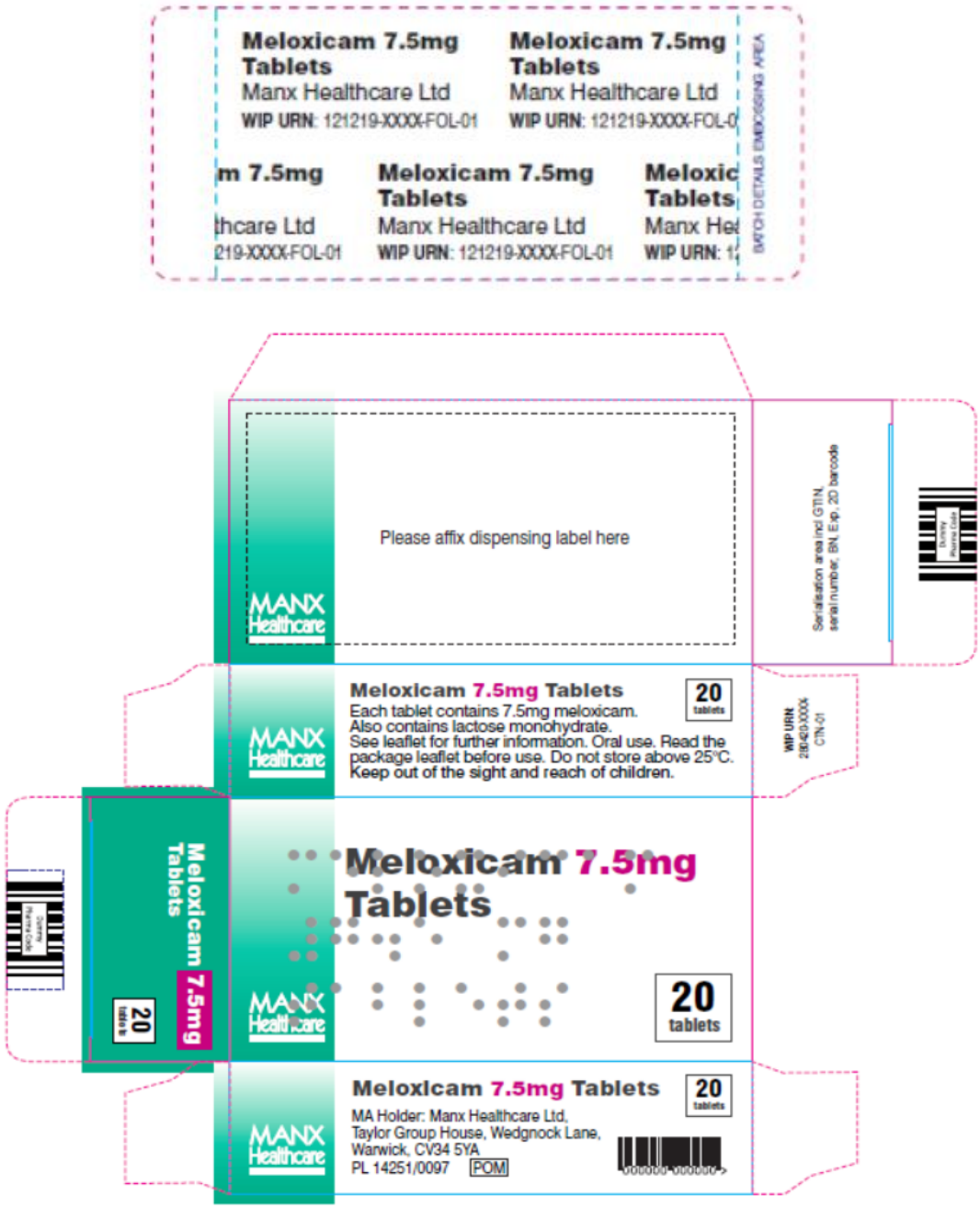
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

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

In accordance with Directive 2012/84/EU, 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 UK licensing are provided below.

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nx Healthcare Ltd
URN: 121219-XXXX-FOL-01
Meloxicam 15mg
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Manx Healthcare Ltd
WIP URN: 121219-XXXX-FOL-01
Meloxicam 15mg
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Manx Healthcare Ltd
WIP URN: 121219-XXXX-FOL-0
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Meloxicam 15mg
Tablets
Meloxicam 15mg
Tablets


Please affix dispensing label here
Serialisation area incl GTIN, serial number, BN, Exp, 2D barcode
Pharma Code
MANX Healthcare
Meloxicam 15mg Tablets
Each tablet contains 15mg meloxicam. Also contains lactose monohydrate. See leaflet for further information.
Oral use. Read the package leaflet before use.
Do not store above 25°C
20 tablets
WIP URN:
Meloxicam 15mg Tablets
20 tablets
Meloxicam 15mg Tablets
Keep out of the sight and reach of children.
MA Holder: Manx Healthcare Ltd, Taylor Group House, Wedgnock Lane, Warwick, CV34 5YA
PL 14251/0098 POM
20 tablets

TABLE OF CONTENT OF THE PAR UPDATE

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**