Menisor XL 60 mg Prolonged-Release Tablets

(Isosorbide mononitrate)

PL 17521/0086

UKPAR

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MENISOR XL 60 MG PROLONGED-RELEASE TABLETS

PL 17521/0086

LAY SUMMARY

This is a summary of the public assessment report (PAR) for Menisor XL 60 mg Prolonged-Release Tablets (PL 17521/0086). It explains how Menisor XL 60 mg Prolonged-Release Tablets 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 Menisor XL 60 mg Prolonged-Release Tablets.

For practical information about using Menisor XL 60 mg Prolonged-Release Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Menisor XL 60 mg Prolonged-Release Tablets and what are they used for?
Menisor XL 60 mg Prolonged-Release Tablets is a ‘generic medicine’. This means that Menisor XL 60 mg Prolonged-Release Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Imdur® Tablets 60mg.

Menisor XL 60 mg Prolonged-Release Tablets are used to prevent angina (chest pain). The tablets contain the active ingredient isosorbide mononitrate, which belongs to a group of medicines called the nitrates, and have been made so that they release the isosorbide mononitrate slowly over a number of hours.

How do Menisor XL 60 mg Prolonged-Release Tablets work?
The tablets work by relaxing and widening the blood vessels of the heart, making it easier for the heart to pump blood around the body.

How are Menisor XL 60 mg Prolonged-Release Tablets used?
Menisor XL 60 mg Prolonged-Release Tablets should be swallowed whole (or broken in half if this is easier to swallow) with half a glass of water. The tablets should not be crushed or chewed.

The usual dose is one tablet a day, taken in the morning. This may be increased to two tablets a day on the advice of a doctor; if so, both tablets should be taken in the morning. To reduce the possibility of getting headaches, patients may start on a dose of half a tablet once a day for the first 2-4 days. To help patients keep track of their treatment the blister strips are marked with the days of the week.

The medicine can be obtained from a pharmacy without a prescription.
What benefits of Menisor XL 60 mg Prolonged-Release Tablets have been shown in studies?
Because Menisor XL 60 mg Prolonged-Release Tablets is a generic medicine, studies in patients have been limited to tests to determine that this medicine is bioequivalent to the reference medicine, Imdur® Tablets 60mg. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Menisor XL 60 mg Prolonged-Release Tablets?
Because Menisor XL 60 mg Prolonged-Release Tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as those of the reference medicine.

Why are Menisor XL 60 mg Prolonged-Release Tablets approved?
It was concluded that, in accordance with EU requirements, Menisor XL 60 mg Prolonged-Release Tablets have been shown to have comparable quality and to be bioequivalent to Imdur® Tablets 60mg. Therefore, the MHRA decided that, as for Imdur® Tablets 60mg, the benefits this medicine are greater than its risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Menisor XL 60 mg Prolonged-Release Tablets?
Suitable safety information has been included in the Summary of Product Characteristics and package leaflet for Menisor XL 60 mg Prolonged-Release Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Menisor XL 60 mg Prolonged-Release Tablets
The Marketing Authorisation for Menisor XL 60 mg Prolonged-Release Tablets was granted in the UK on 17 July 2014.

This summary was last updated in September 2014.

The full PAR for Menisor XL 60 mg Prolonged-Release Tablets follows this summary.
MENISOR XL 60 MG PROLONGED-RELEASE TABLETS

PL 17521/0086

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for the medicinal product Menisor XL 60 mg Prolonged-Release Tablets (PL 17521/0086) to Metwest Pharmaceuticals Limited on 17 July 2014. This pharmacy medicine (P) is used in adults for the prophylactic treatment of angina pectoris.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal product of the reference product Imdur ® Tablets 60mg (PL 17901/0129). Imdur ® Tablets 60mg were first authorised to Astra Pharmaceuticals Ltd on 21 July 1987 (PL 00017/0226) and, following a change of ownership on 14 May 2002, are now authorised to AstraZeneca UK Ltd.

The principal pharmacological action of isosorbide mononitrate, an active metabolite of isosorbide dinitrate, is relaxation of vascular smooth muscle, producing vasodilation of both arteries and veins with the latter effect predominating. The effect of the treatment is dependent on the dose. Low plasma concentrations lead to venous dilatation, resulting in peripheral pooling of blood, decreased venous return and reduction in left ventricular end-diastolic pressure (preload). High plasma concentrations also dilate the arteries reducing systemic vascular resistance and arterial pressure leading to a reduction in cardiac afterload. Isosorbide mononitrate may also have a direct dilatory effect on the coronary arteries. By reducing the end diastolic pressure and volume, the preparation lowers the intramural pressure, thereby leading to an improvement in the subendocardial blood flow. The net effect when administering isosorbide mononitrate is, therefore, a reduced workload of the heart and an improved oxygen supply/demand balance in the myocardium.

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

With the exception of the bioequivalence/bioavailability studies no clinical studies were conducted, which is acceptable given that the application was based on the product being a generic medicinal product of the reference product, which has been licensed for over 10 years.

Bioequivalence/bioavailability studies were performed which compared the pharmacokinetics of Menisor XL 60 mg Prolonged-Release Tablets with those of Imdur ® Tablets 60mg and investigated the effects of fasting and a high fat meal on the bioavailability of Menisor XL 60 mg Prolonged-Release Tablets. The studies were carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.
DRUG SUBSTANCE: ISOSORBIDE MONONITRATE

INN: Isosorbide-5-mononitrate
Chemical name: 3,6-dianhydro-D-glucitol 5-nitrate
CAS: 16051-77-7
Molecular formula: C6H9NO6
Molecular weight: 191.1

General properties: White, crystalline powder, freely soluble in water, in acetone, in alcohol and in methylene chloride

Synthesis of the drug substance from the designated starting materials 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.

Appropriate specifications are provided for the drug substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Satisfactory specifications have been provided for all packaging used for storing the drug substance. The primary packaging has been shown to comply with current legislation concerning materials in contact with foodstuff.

Appropriate stability data have been generated showing the drug substance to be physically and chemically stable. A suitable retest period has been set based on stability data submitted for the drug substance stored in the proposed packaging.

MEDICINAL PRODUCT: MENISOR XL 60 MG PROLONGED-RELEASE TABLETS

Description and composition
The white, capsule-shaped tablets are imprinted with MP86 on one side and reverse scored. Each tablet contains 60 mg isosorbide mononitrate and the excipients lactose monohydrate, hydroxypropylmethylcellulose (Methocel K4M), glyceryl palmitostearate, maize starch and magnesium stearate.
All excipients comply with their European Pharmacopoeia monographs with the exception of glyceryl palmitostearate, which is controlled in line with the German monograph. In the absence of a European Pharmacopoeia monograph for this excipient this is acceptable.

A statement of BSE/TSE safety has been presented, certifying that the milk used for the manufacture of lactose is appropriately sourced.

**Pharmaceutical Development**

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the reference product, Imdur® Tablets 60mg. A satisfactory account of the pharmaceutical development has been provided.

**Manufacture**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on pilot scale batches of the finished product and the results are satisfactory.

**Control of medicinal product**

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

**Container Closure System**

The finished product is packaged in PVC film 250 μm/aluminium foil 25 μm blister packs of 28 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 foodstuffs.

**Stability**

Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**

The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Isosorbide Mononitrate 20 mg and 40 mg Tablets (PL 16363/0001-0002). The bridging report submitted by the applicant has been found acceptable.

**Marketing Authorisation Application (MAA) form**

The MAA form is satisfactory from a pharmaceutical perspective.
Quality Overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of isosorbide mononitrate are well-known, no non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
In support of these applications, the Marketing Authorisation Holder has submitted two bioequivalence studies.

The first study was a single dose bioequivalence study comparing Menisor XL 60 mg Prolonged-Release Tablets to Imdur® 60mg durules (Astra Pharmaceuticals Ltd).

The pharmacokinetic and statistical parameters for isosorbide mononitrate at Days 1 and 8 are summarised in the tables below.

**Table 1: First Dose: Day 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (mean)</th>
<th>Imdur Astra (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>545.81 ±97.8</td>
<td>549.84 ±96.48</td>
</tr>
<tr>
<td>$C_{12h}$ (ng/ml)</td>
<td>219.07 ±82.58</td>
<td>219.66 ±82.98</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng*hr/ml)</td>
<td>4327.73 ±962.17</td>
<td>4368.21 ±973.93</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>3.25 ± 0.88</td>
<td>3.29 ± 0.85</td>
</tr>
</tbody>
</table>

**Table 2: Steady State: Day 8**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (mean)</th>
<th>Imdur Astra (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>652.15 ±123.62</td>
<td>653.06 ±112.15</td>
</tr>
<tr>
<td>$C_{12h}$ (ng/ml)</td>
<td>232.4 ±107.78</td>
<td>235.89 ±104.15</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng*hr/ml)</td>
<td>8321.61 ±2186.1</td>
<td>8289.3 ±2199.1</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>3.27 ± 0.88</td>
<td>3.23 ± 0.87</td>
</tr>
</tbody>
</table>

In this 8-day, steady state investigation samples were obtained on the first day and eighth day, up to 12 hours after dosing. $C_{12}$ therefore refers to the plasma concentration 12 hours after dosing.

The 90% confidence intervals for AUC and $C_{\text{max}}$ were also calculated and found to be within the acceptance range of 80.00 to 125.00 %. Bioequivalence between the test product and reference product has been adequately demonstrated.

A two-way, cross-over, controlled, block randomised single dose study of relative bioavailability of the proposed product with and without a high fat meal was also conducted.

The pharmacokinetic and statistical parameters for isosorbide mononitrate are summarised in the table below.
Table 3: Post High Fat Meal Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fed (A)</th>
<th>Fasted (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>788.22 ± 231.23</td>
<td>724.77 ± 232.63</td>
</tr>
<tr>
<td>AUC $0-\infty$ (ng*hr/ml)</td>
<td>8887.18 ± 3865.0</td>
<td>8604.35 ± 2411.12</td>
</tr>
<tr>
<td>AUC $0-\text{inf}$ (ng*hr/ml)</td>
<td>9739.28 ± 4164.67</td>
<td>9497.75 ± 2579.63</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>4.92 ± 1.69</td>
<td>4.64 ± 1.49</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for AUC and $C_{\text{max}}$ were also calculated and found to be within the acceptance range of 80.00 to 125.00 %. Bioequivalence between the test product and reference product has been adequately demonstrated.

EFFICACY
No new data on efficacy have been submitted and none are required for this type of application.

SAFETY
With the exception of the data submitted during the bioequivalence/bioavailability studies, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the studies.

EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
This is consistent with the SmPC for the reference product and is satisfactory.

PATIENT INFORMATION LEAFLETS (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
This is satisfactory

MARKETING AUTHORISATION APPLICATION (MAA) FORM
The MAA form is satisfactory from a clinical perspective.

CONCLUSION
The grant of a marketing authorisation is recommended for this application.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Menisor XL 60 mg Prolonged-Release 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for this type of application.

CLINICAL
The results of the bioequivalence studies are satisfactory.

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with isosorbide mononitrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
MENISOR XL 60 MG PROLONGED-RELEASE TABLETS

PL 17521/0086

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 28 March 2003.

2 Following standard checks the MHRA requested further information relating to the dossier on 17 November 2004. Upon receipt of the applicant’s response the MHRA considered the application valid on 10 March 2010.

3 Following assessment of the application the MHRA requested further information relating to the dossier on 13 May 2011, 31 August 2011, 18 January 2012 and 8 January 2013.

4 The applicant responded to the MHRA’s requests, providing further information on 12 August 2011, 29 November 2011, 21 December 2012, 5 April 2013 and 17 February 2014.

5 The application was granted on 17 July 2014.
STEP TAKEN AFTER INITIAL AUTHORISATION – SUMMARY

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

Blister:

- Menisor XL 60 mg prolonged-release tablets
- Isosorbide Mononitrate

PL 17521/0086 Metwest Pharmaceuticals Ltd., Harrow, HA1 3NY