UK Public Assessment Report

Zatim XL 200 mg Prolonged-release Capsules
Zatim XL 300 mg Prolonged-release Capsules

PL 33579/0004-0005

Neopharma Limited
Lay Summary

Zatim XL 200 mg Prolonged-release Capsules
Zatim XL 300 mg Prolonged-release Capsules
(diltiazem hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Zatim XL 200 mg and 300 mg Prolonged-release Capsules (PL 33579/0004-0005). Zatim XL 200 mg and 300 mg Prolonged-release Capsules will be referred to as Zatim XL Prolonged-release Capsules throughout this PAR, for ease of reading. It explains how Zatim XL Prolonged-release Capsules 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 Zatim XL Prolonged-release Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Zatim XL Prolonged-release Capsules and what are they used for?
Zatim XL Prolonged-release Capsules are identical to Diltiazem HCL 200mg and 300mg prolonged-release hard capsules (PL 39560/0002-0003), which are authorised to ADOH BV. The company that makes Diltiazem HCL 200mg and 300mg prolonged-release hard capsules has agreed that its scientific data can be used as a basis for the grant of identical licences for Zatim XL Prolonged-release Capsules.

Zatim XL Prolonged-release Capsules are used to treat high blood pressure and angina (chest pain).

How do Zatim XL Prolonged-release Capsules work?
Zatim XL Prolonged-release Capsules contain the active substance diltiazem, which belongs to a group of medicines called ‘calcium channel blockers’. Diltiazem works by making blood vessels wider, which helps to lower blood pressure. Diltiazem also makes it easier for the heart to pump blood around the body, which prevents the chest pain caused by angina.

How are Zatim XL Prolonged-release Capsules used?
These capsules should be swallowed whole with a drink of water before or during a meal. It is very important that the capsules are not broken, crushed or chewed as this can affect the way that the active substance is released into the body.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

In adults, the usual starting dose is one Zatim XL 200 mg Prolonged-release capsule a day.

If necessary, the prescribing doctor may increase the dose to:
- one Zatim XL 300 mg Prolonged-release capsule a day
- two Zatim XL 200 mg Prolonged-release capsules a day, or
- one Zatim XL 300 mg Prolonged-release capsule and one Zatim XL 200 mg Prolonged-release capsule a day.
These medicines can only be obtained with a prescription.

**How have Zatim XL Prolonged-release Capsules been studied?**
Zatim XL Prolonged-release Capsules are identical to the previously granted marketing authorisations for Diltiazem HCL 200mg and 300mg prolonged-release hard capsules (PL 39560/0002-0003), authorised to ADOH BV. This Marketing Authorisation holder has agreed that scientific data presented for Diltiazem HCL 200mg and 300mg prolonged-release hard capsules can be used for these applications for Zatim XL Prolonged-release Capsules.

**What are the benefits and risks of Zatim XL Prolonged-release Capsules?**
As Zatim XL Prolonged-release Capsules are considered identical to Diltiazem HCL 200mg and 300mg prolonged-release hard capsules their benefits and risks are taken as being the same as those for Diltiazem HCL 200mg and 300mg prolonged-release hard capsules.

**Why are Zatim XL Prolonged-release Capsules approved?**
No new or unexpected safety concerns arose from these applications. It was, therefore, considered that the benefits of Zatim XL Prolonged-release Capsules outweigh their risks, and the grant of these marketing authorisations was recommended.

**What measures are being taken to ensure the safe and effective use of Zatim XL Prolonged-release Capsules?**
A risk management plan has been developed to ensure that Zatim XL Prolonged-release Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Zatim XL Prolonged-release Capsules, 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 and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Zatim XL Prolonged-release Capsules**
The marketing authorisations were granted in the UK on 25 March 2015.

For more information about taking Zatim XL Prolonged-release Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.

The full PAR for Zatim XL Prolonged-release Capsules follows this summary.
TABLE OF CONTENTS

I  Introduction .................................................. Page 5
II  Quality aspects ............................................... Page 6
III Non-clinical aspects .......................................... Page 7
IV  Clinical aspects ............................................... Page 7
V   User consultation ............................................ Page 10
VI  Overall conclusion, benefit/risk assessment and recommendation ................................ Page 10

Annex – Table of content of the PAR update ................ Page 17
I  Introduction

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations to Neopharma Limited for the medicinal products Zatim XL Prolonged-release Capsules (PL 33579/0004-0005) on 25 March 2015. These are prescription-only medicines (legal status POM) and indicated for mild to moderate hypertension and angina pectoris.

These applications were submitted as abridged simple applications according to Article 10c of Directive 2001/83/EC, as amended. The applications cross-refer, and claim to be identical, to Diltiazem HCL 200mg and 300mg prolonged-release hard capsules (PL 39560/0002-0003), which were granted to ADOH BV on 14 August 2012.

These medicinal products contain the active substance diltiazem hydrochloride, which belongs to a group of medicines called calcium channel blockers. Diltiazem restricts calcium entry into the slow calcium channel of vascular smooth muscle and myocardial muscle fibres in a voltage-dependent manner. By this mechanism, diltiazem reduces the concentration of intracellular calcium in contractile protein.

Diltiazem acts to treat angina perctoris by increasing coronary blood flow through a reduction of coronary resistance. Due to its moderate bradycardia-inducing activity and the reduction in systemic arterial resistance, diltiazem reduces cardiac workload. Electrophysiologically, diltiazem causes moderate bradycardia in normal subjects, marginally prolongs intranodal conduction and has no effect on hisian and infrahisian conduction.

At the vascular level, the calcium antagonist effect of diltiazem produces moderate arterial vasodilatation and improves large artery compliance. The vasodilatation leads to a decrease in blood pressure in the hypertensive subject, due to lowered peripheral resistance, without producing reflex tachycardia.

No new data were submitted nor were any data necessary for these simple applications, as the data are identical to those of the previously granted, cross-referred products.
II Quality aspects

II.1 Introduction
These are simple, piggyback (informed consent) applications for Zatim XL 200 mg and 300 mg Prolonged-release Capsules, submitted under Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to Diltiazem HCL 200mg and 300mg prolonged-release hard capsules (PL 39560/0002-0003). The current applications are considered valid.

Zatim XL 200 mg Prolonged-release capsules are formulated as opaque capsules with a white body and cap, containing white to whitish pellets. Each capsule contains 200 mg of the active substance diltiazem hydrochloride. The excipients present in each capsule are povidone, talc, ethylcellulose, stearic acid, and a capsule shell comprising gelatin and titanium dioxide (E171). The quantitative and qualitative composition and description of these capsules are identical to the cross-reference product, Diltiazem HCL 200mg prolonged-release hard capsules.

Zatim XL 300 mg Prolonged-release capsules are formulated as opaque capsules with a white body and green cap, containing white to whitish pellets. Each capsule contains 300 mg of the active substance diltiazem hydrochloride. The excipients present in each capsule are povidone, talc, ethylcellulose, stearic acid, and a capsule shell comprising gelatin and titanium dioxide (E171), indigo carmine (E132) and quinoline yellow (E104). The quantitative and qualitative composition and description of these capsules are identical to the cross-reference product, Diltiazem HCL 300mg prolonged-release hard capsules.

Zatim XL 200 mg and 300 mg Prolonged-release Capsules are each packed in Polyvinyl chloride-polyvinylidene chloride/aluminium (PVC-PVDC/Aluminium) foil blisters containing 7 or 28 capsules. This packaging is identical to the cross-reference products.

II.2 Drug Substance
Diltiazem hydrochloride
The drug substance specification is identical to that of the cross-reference products and is acceptable.

II.3 Medicinal Product
Pharmaceutical development
A quality expert statement was provided by an appropriately qualified person, confirming that the chemical and pharmaceutical data supporting the applications are identical to those of the respective cross-reference products.

Manufacture of the product
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.
The proposed compositions are identical to those of the respective cross-reference products and are acceptable.

The proposed manufacturing process is identical to that of the cross-reference products and is acceptable.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of the gelatin have provided certificates of suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Finished Product Specification**

The proposed finished product specifications are identical to those of the cross-reference products and are acceptable.

**Stability of the product**

The proposed shelf-life for Zatim XL 200 mg and 300 mg Prolonged-release Capsules is 2 years. The shelf-life for each strength product is identical to that of each respective cross-reference product.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

The data submitted with these applications are acceptable. The grant of marketing authorisations is recommended.

**III Non-clinical aspects**

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data has been supplied and none are required.

Since Zatim XL Prolonged-release Capsules are intended for generic substitution, they will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

The grant of marketing authorisations is recommended.

**IV Clinical aspects**

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The grant of marketing authorisations is recommended.
Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Zatim XL 200 mg and 300 mg Prolonged-release Capsules.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td>Bradycardia, heart failure and heart block</td>
<td>Intestinal obstruction in pre-disposed patients</td>
<td>Paediatric use</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td>Use during pregnancy and breastfeeding</td>
<td></td>
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<tr>
<td></td>
<td>Mood changes or depression especially in pre-disposed patients</td>
<td>Ergotism when used with ergot derivatives (ergotamines)</td>
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<tr>
<td></td>
<td>Drug interactions leading to ventricular fibrillation or torsades de pointe</td>
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<td></td>
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<tr>
<td></td>
<td>Increase in circulating levels of statins, corticosteroids and benzodiazepines through inhibition of CYP3A4</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Increase in circulating levels of nifedipine, lithium, carbamazepine, theophylline and immunosuppressants</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Planned risk minimisation activities

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Summary of Routine Risk Minimisation Activities</th>
<th>Summary of Additional Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia, heart failure and heart block.</td>
<td>Routine risk minimisation measures are sufficient for this safety concern as bradycardia, heart failure and heart block is covered in Sections 4.3 and 4.4 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Routine risk minimisation measures are sufficient for this safety concern as hypersensitivity is covered in Sections 4.3 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Mood changes or depression especially in pre-disposed patients.</td>
<td>Routine risk minimisation measures are sufficient for this safety concern as mood changes or depression especially in pre-disposed patients is covered in Sections 4.4 and 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug interactions leading to ventricular fibrillation or torsades de pointe.</td>
<td>Routine risk minimisation measures are sufficient for this safety concern as drug interactions leading to ventricular fibrillation or torsades de pointe is covered in Section 4.5 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Increase in circulating levels of statins, corticosteroids and benzodiazepines through inhibition of CYP3A4.</td>
<td>Routine risk minimisation measures are sufficient for this safety concern as Increase in circulating levels of statins, corticosteroids and benzodiazepines through inhibition of CYP3A4 is covered in Section 4.5 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Increase in circulating levels of nifedipine, lithium, carbamazepine, theophylline and immunosuppressants.</td>
<td>Routine risk minimisation measures are sufficient for this safety concern as Increase in circulating levels of nifedipine, lithium, carbamazepine, theophylline and immunosuppressants is covered in Section 4.5 of the SmPC</td>
<td>N/A</td>
</tr>
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</table>

Important potential risks

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Summary of Routine Risk Minimisation Activities</th>
<th>Summary of Additional Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal obstruction in pre-disposed patients</td>
<td>Place on monitoring list as part of signal management activities</td>
<td>N/A</td>
</tr>
<tr>
<td>Use during pregnancy and breastfeeding</td>
<td>Place on monitoring list as part of signal management activities</td>
<td>N/A</td>
</tr>
<tr>
<td>Ergotism when used with ergot derivatives (ergotamines)</td>
<td>Place on monitoring list as part of signal management activities</td>
<td>N/A</td>
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</table>

Missing Information

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<tr>
<th>Safety Concern</th>
<th>Summary of Routine Risk Minimisation Activities</th>
<th>Summary of Additional Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric use</td>
<td>1) Information is included in Section 4.2 of the SmPC 2) Place on monitoring list as part of signal management activities</td>
<td>N/A</td>
</tr>
</tbody>
</table>
V  User consultation
A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the cross-reference products Diltiazem HCL 200mg and 300mg prolonged-release hard capsules. The bridging report submitted by the applicant is acceptable.

VI  Overall conclusion, benefit/risk assessment and recommendation

Quality
The quality data for these applications is identical to those previously assessed for the marketing authorisations to Diltiazem HCL 200mg and 300mg prolonged release hard capsules (PL 39560/0002-0003; ADOH BV).

Non-clinical
No new clinical data were submitted with these applications and none are required.

Clinical pharmacology/Efficacy
No new clinical data were submitted with these applications and none are required.

Safety
No new or unexpected safety concerns arose from these applications.

Product literature
The SmPCs, package leaflet and labels are identical to those approved for Diltiazem HCL 200mg and 300mg prolonged release hard capsules (PL 39560/0002-0003; ADOH BV).

Benefit/risk assessment
The quality of these products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products Diltiazem HCL 200mg and 300mg prolonged release hard capsules (PL 39560/0002-0003; ADOH BV) The benefit-risk assessment is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), package leaflets and labelling are satisfactory, in line with current guidelines and consistent with the cross-reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and package leaflet for these products are available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labelling is listed below:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton box

1. NAME OF THE MEDICINAL PRODUCT
Zatim XL 200 mg Prolonged-release Capsules
Diltiazem hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each capsule contains 200 mg diltiazem hydrochloride.

3. LIST OF EXCIPIENTS
Also contains povidone, talc, ethylcellulose, stearic acid, gelatin, titanium dioxide (E171).

4. PHARMACEUTICAL FORM AND CONTENTS
7 Capsules
28 Capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use.
Swallow whole. Do not chew or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Neopharma Limited  
57 High Street  
Odham  
Hampshire  
RG29 1LF

12. MARKETING AUTHORISATION NUMBER(S)

PL 33579/0004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zatim XL 200 mg Prolonged-release Capsules  
diltiazem
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Blister

1. NAME OF THE MEDICINAL PRODUCT
Zatim XL 200 mg Prolonged-release Capsules
Diltiazem hydrochloride

2. NAME OF THE MARKETING AUTHORITY HOLDER
Neopharma Limited

3. EXPIRY DATE
EXP

4. BATCH NUMBER
Lot

5. OTHER
UKPAR Zatim 200 mg and 300 mg Prolonged-release Capsules

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Zatim XL 300 mg Prolonged-release Capsules
Diltiazem hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 300 mg diltiazem hydrochloride.

3. LIST OF EXCIPIENTS

Also contains povidone, talc, ethylcellulose, stearic acid, gelatin, titanium dioxide (E171), indigo carmine (E132), quinoline yellow (E104)

4. PHARMACEUTICAL FORM AND CONTENTS

7 Capsules
28 Capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Swallow whole. Do not chew or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. **NAME AND ADDRESS OF THE MARKETING AUTHORIZATIION HOLDER**

Neopharma Limited  
57 High Street  
Odham  
Hampshire  
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12. **MARKETING AUTHORIZATION NUMBER(S)**

PL 33579/0005

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Zatim XL 300 mg Prolonged-release Capsules  
diltiazem
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<tbody>
<tr>
<td>Blister</td>
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</table>

1. **NAME OF THE MEDICINAL PRODUCT**
   - Zatim XL 300 mg Prolonged-release Capsules
   - Diltiazem hydrochloride

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   - Neopharma Limited

3. **EXPIRY DATE**
   - EXP

4. **BATCH NUMBER**
   - Lot

5. **OTHER**
Annex – Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
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