Public Assessment Report

UKPAR

Duloxetine 30 mg gastro-resistant hard capsules
Duloxetine 60 mg gastro-resistant hard capsules

(Duloxetine hydrochloride)

UK Licence No: PL 15764/0119-0120

Strandhaven Limited (t/a Somex Pharma)
LAY SUMMARY

Duloxetine 30 mg gastro-resistant hard capsules
Duloxetine 60 mg gastro-resistant hard capsules

This is a summary of the Public Assessment Report (PAR) for Duloxetine 30 mg gastro-resistant hard capsules (PL 15764/0119) and Duloxetine 60 mg gastro-resistant hard capsules (PL 15764/0120). It explains how Duloxetine 30 mg gastro-resistant hard capsules and Duloxetine 60 mg gastro-resistant hard capsules were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Duloxetine 30 mg gastro-resistant hard capsules and Duloxetine 60 mg gastro-resistant hard capsules.

The product will be referred to as Duloxetine gastro-resistant capsules throughout the remainder of this public assessment report.

For practical information about using Duloxetine gastro-resistant capsules patients should read the package leaflet or contact their doctor or pharmacist.

What are Duloxetine gastro-resistant capsules and what are they used for?
Duloxetine gastro-resistant capsules are ‘generic medicines’. This means that Duloxetine gastro-resistant capsules are similar to ‘reference medicines’ already authorised in the European Union (EU) called Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands) first authorised in the EU on 17 December 2004.

Duloxetine gastro-resistant capsules are used in adults to treat:

- depression
- generalised anxiety disorder (chronic feeling of anxiety or nervousness)
- diabetic neuropathic pain (often described as burning, stabbing, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain).

This medicine starts to work in most patients with depression or anxiety within two weeks of starting treatment, but it may take 2-4 weeks before the patient begins to feel better.

How do Duloxetine gastro-resistant capsules work?
This medicine contains the active substance duloxetine (as duloxetine hydrochloride). Duloxetine increases the levels of serotonin and noradrenaline in the nervous system.

How are Duloxetine gastro-resistant capsules used?
The pharmaceutical form of this medicine is a gastro-resistant hard capsule, and the route of administration is by mouth (oral). The tablet should be swallowed whole with a glass of water.

The patient should always use this medicine exactly as advised by their doctor or pharmacist. If unsure, the patient should ask their doctor or pharmacist.

The recommended dose of this medicine for:

Depression and diabetic neuropathic pain:
The usual dose of Duloxetine is 60 mg once a day, but the patient’s doctor will prescribe the dose that is right for the individual.

For generalised anxiety disorder:
The usual starting dose of Duloxetine is 30 mg once a day after which most patients will receive 60 mg once a day, but their doctor will prescribe the dose that is right for them. The dose may be adjusted up to 120 mg a day based on the patient’s response to this medicine.

The patient may find it easier to take this medicine at the same times every day.

The patient should talk to their doctor about how long to take this medicine. It should not be stopped, or dose changed without consulting the prescriber.

This medicine can only be obtained with a prescription.

For further information on how to use Duloxetine gastro-resistant capsules see section 3 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Duloxetine gastro-resistant capsules have been shown in studies?
Because Duloxetine gastro-resistant capsules are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects from Duloxetine gastro-resistant capsules?
Because Duloxetine gastro-resistant capsules are generic medicines and are bioequivalent to the reference medicines Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands), their benefits and possible side effects are taken as being the same as the reference medicines.

For a full list of all the side effects reported with Duloxetine gastro-resistant capsules see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why are Duloxetine gastro-resistant capsules approved?
It was concluded that, in accordance with EU requirements, Duloxetine gastro-resistant capsules have been shown to be bioequivalent to the reference medicines Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands). Therefore, the MHRA decided that, as for Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands), the benefits are greater than its risk and recommended that Duloxetine gastro-resistant capsules can be approved for use.

What measures are being taken to ensure the safe and effective use of Duloxetine gastro-resistant capsules?
A Risk Management Plan has been developed to ensure that Duloxetine gastro-resistant capsules are used as safely as possible. Based on this plan, safety information, including the appropriate precautions to be followed by healthcare professionals and patients, has been included in the Summaries of Product Characteristics and the package leaflet for Duloxetine gastro-resistant capsules.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Duloxetine gastro-resistant capsules
A Marketing Authorisation was granted in the UK on 21 June 2018.

The full PAR for Duloxetine gastro-resistant capsules follows this summary.

For more information about treatment with Duloxetine gastro-resistant capsules read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in August 2018.
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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Strandhaven Limited Marketing Authorisations for the medicinal products Duloxetine 30 mg gastro-resistant hard capsules (PL 15764/0119) and Duloxetine 60 mg gastro-resistant hard capsules (PL 15764/0120) on 21 June 2018. The products are prescription only medicine (POM), indicated for the treatment of:

- major depressive disorder
- diabetic peripheral neuropathic pain
- generalised anxiety disorder.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the European reference product, Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands) authorised in the EU, via the centralised procedure (EU/1/04/296/001-002) on 17 December 2004.

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor (SNRI). The SNRIs are efficacious in treating a variety of anxiety disorders. In contrast to selective serotonin reuptake inhibitors (SSRIs), which are generally ineffective in treating chronic pain, all SNRIs are helpful in relieving chronic pain associated with and independent of depression.

Five bioequivalence studies (fasting and fed studies in healthy volunteers) were submitted to support these applications, of which one study was discontinued. The discontinued study (an open label, balanced, randomised, two treatment, two sequence, two period, single dose, crossover oral bioequivalence study of two formulations of Duloxetine 60 mg gastro-resistant capsules in healthy, adult, human subjects under fasting conditions) was repeated with co-medication to counteract side effects experienced by the volunteers in this study. Therefore, this study will not be discussed in further detail. The applicant has stated that these bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out-letters’ or exchange of information’ issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

A Marketing Authorisation was granted in the UK on 21 June 2018.
II QUALITY ASPECTS

II.1 Introduction
The finished product is formulated as a gastro-resistant hard capsule. Each capsule contains 30 mg or 60 mg of duloxetine equivalent to 33.650 mg and 67.30 mg of duloxetine hydrochloride respectively. Other ingredients consist of the pharmaceutical excipients:

Capsule content:
Hypromellose, hypromellose phthalate, sucrose, sugar spheres, talc and triethyl citrate.

Capsule shell:
Gelatin, sodium lauryl sulphate, indigo carmine (E132), titanium dioxide (E171) and edible green printing ink.

30 mg edible green printing ink contains (TekPrint SB-4020 Green Ink):
Titanium dioxide (E171), iron oxide yellow (E172), indigo carmine aluminium Lake E132, propylene glycol and shellac.

60 mg edible green printing ink contains (TekPrint SW-0012 White Ink):
Titanium dioxide (E172), propylene glycol and shellac.

The finished product is packaged into cartons containing aluminium/aluminium (Alu/Alu) blisters packs and or clear polyvinyl chloride/ polychlorotrifluoroethylene (PVC/Aclar) blister packs containing 7, 14, 28, 30, 50, 56, 84, 98 and 100 capsules in carton. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance
INN: Duloxetine hydrochloride
Chemical name: (3S)-N-Methyl-3-(naphthanlen-1-ylloxy)-3-(thiophen-2-yl)propan-1-amine hydrochloride
(+)-(S)-N-Methyl-γ-(1-naphthyloxy)-2-thiophene propanamine hydrochloride
(S)-N-Methyl-γ-(1-naphthalenylloxy)-2-thiophene propanamine hydrochloride
(+)-N-Methyl-γ-(1-naphthalenylloxy)-3-(2-thienyl)-propanamine hydrochloride

Structure:

Molecular formula: C₁₈H₁₉NOS.HCl
Molecular weight: 333.9 g/mol
Appearance: White to almost white powder
Solubility: sparingly soluble in water, freely soluble in methanol, practically insoluble in hexane.

Duloxetine hydrochloride is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, duloxetine hydrochloride, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, gastro-resistant hard capsules containing duloxetine hydrochloride equivalent to 30 mg and 60 mg of duloxetine per capsule that are, generic versions of the reference products Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands). 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 their respective European Pharmacopeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

With the exception of gelatin, none of the excipients used contain material of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

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

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification

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

Stability of the product

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

The data from these studies support a shelf-life of 36 months with the storage conditions ‘store in the original package in order to protect from moisture. Do not store above 30° C.’ Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of duloxetine hydrochloride 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.

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

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Duloxetine gastro-resistant capsules are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical point of view therefore grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of Duloxetine hydrochloride is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of duloxetine hydrochloride.

Based on the data provided, Duloxetine gastro-resistant capsules can be considered bioequivalent to Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands).

IV.2 Pharmacokinetics
In support of these applications, four bioequivalence studies were conducted (two supportive pivotal studies and two bioequivalence studies) as detailed below:

Study 1 (fasting conditions)
An open label, balanced, randomised, two treatment, two sequence, two periods, single dose, crossover, oral bioequivalence study of the test product; Duloxetine 60 mg gastro-resistant capsules (Strandhaven Limited) versus the reference product Cymbalta 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands) in healthy, adult, human subjects under fasting conditions.
Following an overnight fast of at least 8 hours, a single dose of 60 mg of the test or reference formulation was administered orally in each period with 240ml water as per randomisation scheme. Blood samples were collected for plasma levels before dosing and up to and including 72 hours after the drug administration. The washout period between treatment phases was 7 days.

The main pharmacokinetic results for the Test (T) versus Reference (R) are presented below:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Duloxetine (In-transformed)</th>
<th>Least Square Means</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>Ratio (T/R)%</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>4.0120</td>
<td>3.9582</td>
<td>105.53%</td>
</tr>
<tr>
<td>$AUC_{\text{Cmax}}$ (ng.hr/mL)</td>
<td>6.8230</td>
<td>6.8081</td>
<td>101.50%</td>
</tr>
</tbody>
</table>

**Conclusion (study 1 fasting conditions)**
The 90% confidence intervals of the test/reference ratio for AUC and $C_{\text{max}}$ values for duloxetine lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands).

**Study 2 (fed conditions)**
An open label, balanced, randomised, two treatment, two sequence, two periods, single dose, crossover, oral bioequivalence study of the test product; Duloxetine 60 mg gastro-resistant capsules (Strandhaven Limited) versus the reference product Cymbalta 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands) in healthy, adult, human subjects under fed conditions.

Following an overnight fast of at least 8 hours, subjects were given a high fat, high calorific breakfast 30 minutes prior to dosing. Following which, a single dose of 60 mg of the test or reference formulation was administered orally in each period with 240ml water as per randomisation scheme. Blood samples were collected for plasma levels before dosing and up to and including 72 hours after the drug administration. The washout period between treatment phases was 7 days.

The main pharmacokinetic results for the Test (T) versus Reference (R) are presented below:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Duloxetine (In-transformed)</th>
<th>Least Square Means</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>Ratio (T/R)%</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>3.9501</td>
<td>4.0323</td>
<td>92.11%</td>
</tr>
<tr>
<td>$AUC_{\text{Cmax}}$ (ng.hr/mL)</td>
<td>6.9450</td>
<td>6.8927</td>
<td>106.42%</td>
</tr>
</tbody>
</table>

**Conclusion (study 2 fed conditions)**
The 90% confidence intervals of the test/reference ratio for AUC and $C_{\text{max}}$ values for duloxetine lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands).
Study 3 (fasting conditions)
An open label, balanced, randomised, two treatment, two sequence, two periods, single dose, crossover, oral bioequivalence study of two formulations of the test product; Duloxetine 60 mg gastro-resistant capsules (Strandhaven Limited) versus the reference product Cymbalta 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands) in healthy, adult, human subjects under fed conditions.

Following an overnight fast of at least 10 hours a single dose of 60 mg of the test or reference formulation was administered orally in each period ((period I and period II)) with 240ml water as per randomisation scheme. Subjects received the product they did not receive in period I during period II dosing. Blood samples were collected for plasma levels before dosing and up to and including 72 hours after the drug administration. The washout period between treatment phases was 7 days.

The main pharmacokinetic results for the Test (T) versus Reference (R) are presented below:

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>C_{max}(ng/mL)</th>
<th>AUC_{0-t}(ng.hr/mL)</th>
<th>AUC_{0-} (ng.hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (T)</td>
<td>38.1957</td>
<td>710.2044</td>
<td>764.3400</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>37.6521</td>
<td>696.5454</td>
<td>746.3058</td>
</tr>
<tr>
<td>N</td>
<td>52</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Geometric Least square mean</td>
<td>38.0379</td>
<td>705.6779</td>
<td>760.5474</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>37.6954</td>
<td>696.6546</td>
<td>746.7495</td>
</tr>
<tr>
<td>Ratio (T/R)</td>
<td>100.91</td>
<td>101.30</td>
<td>101.85</td>
</tr>
<tr>
<td>90% C.I. (T Vs R)</td>
<td>LCL 96.03</td>
<td>96.33</td>
<td>97.40</td>
</tr>
<tr>
<td></td>
<td>UCL 106.04</td>
<td>106.51</td>
<td>106.50</td>
</tr>
<tr>
<td>p-values</td>
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<td>Sequence</td>
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<td>Intra Subject CV%</td>
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<tr>
<td>Power %</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: Statistical analysis was done on the log transformed values; the antilog of the mean is reported.

Conclusion (study 3 fasting conditions)
Both the Test and Reference products were well tolerated upon single-dose administration in each period. The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for duloxetine lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands).

Study 4 (fed conditions)
An open label, balanced, randomised, two treatment, two sequence, two periods, single dose, crossover, oral bioequivalence study of two formulations of the test product; Duloxetine 60 mg gastro-resistant capsules (Strandhaven Limited) versus the reference product Cymbalta 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands) in healthy, adult, human subjects under fed conditions.

Following an overnight fast of at least 10 hours, subjects were given a high fat, high calorific breakfast 30 minutes prior to dosing. Following which, a single dose of 60 mg of the test or reference formulation was administered orally in each period (period I and period II) with 240ml water as per randomisation scheme. Subjects received the product they did not receive in period I during period II dosing. Blood samples were collected for plasma levels before dosing and up to and including 72 hours after the drug administration. The washout period between treatment phases was 7 days.

The main pharmacokinetic results for the Test (T) versus Reference (R) are presented below:

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.hr/mL)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean</td>
<td>T: 53.6304</td>
<td>1062.9552</td>
<td>1119.7649</td>
</tr>
<tr>
<td></td>
<td>R: 51.2931</td>
<td>927.5306</td>
<td>983.6672</td>
</tr>
<tr>
<td>N</td>
<td>T: 46</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>R: 46</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Geometric Least square mean</td>
<td>T: 53.5968</td>
<td>1061.4430</td>
<td>1117.9778</td>
</tr>
<tr>
<td></td>
<td>R: 51.3738</td>
<td>928.1773</td>
<td>984.1849</td>
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<tr>
<td>Ratio (T/R)</td>
<td>104.33</td>
<td>114.36</td>
<td>113.59</td>
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<tr>
<td>90% C.I. (T Vs R)</td>
<td>LCL: 99.55</td>
<td>108.83</td>
<td>108.34</td>
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<tr>
<td></td>
<td>UCL: 109.33</td>
<td>120.17</td>
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<td>p-values</td>
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<td></td>
<td>Period: 0.0765</td>
<td>0.1052</td>
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<td></td>
<td>Form: 0.1357</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intra Subject CV%</td>
<td>13.42</td>
<td>14.20</td>
<td>13.56</td>
</tr>
<tr>
<td>Power %</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: Statistical analysis was done on the log transformed values; the antilog of the mean is reported.

**Conclusion (study 4 fed conditions)**

Both the Test and Reference product were well tolerated upon single-dose administration in each period. The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for duloxetine lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Cymbalta 30 mg and 60 mg hard gastro-resistant capsules (Eli Lilly Nederland B.V., the Netherlands).
Biowaiver
The justification for biowaiver for the 30 mg strength can be accepted as per EMA guideline on the investigation of bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev.1/Corr**; 20 January 2010) states if bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in vivo bioequivalence studies for the other strength(s) can be waived. As the 30 mg strength test product meets the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 60 mg strength can be extrapolated to the 30 mg strength capsules.

Overall Conclusion
Clinical studies have demonstrated bioequivalence of Duloxetine 60 gastro-resistant capsules (Strandhaven Limited) to the corresponding reference products. Since biowaiver criteria are fulfilled, the conclusions from the bioequivalence studies can also be applied to the 30mg strength.

IV.3 Pharmacodynamics
No new pharmacodynamics data are required for these applications and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for these applications and none have been submitted.

IV.5 Clinical safety
Apart from the data from the studies stated above, no new clinical safety data are required for these applications and none have been submitted. No new or unexpected safety issues were identified in these clinical studies.

IV.6 Risk Management Plan (RMP)
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the national competent authority
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report (PSUR) and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects
The grant of Marketing Authorisation is recommended.

V User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Duloxetine Alembic 20 mg gastro-resistant capsules, hard; Duloxetine Alembic 40 mg gastro-resistant capsules. The bridging report submitted by the applicant has been found acceptable.

The results show that the package leaflet 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.

IV OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with duloxetine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the reference product and its benefit/risk balance is, therefore, considered to be similar and positive.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

The SmPC and PIL are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling for this medicine is presented below:
DULOXETINE 30 mg gastro-resistant hard capsules

Duloxetine hydrochloride

Each capsule contains 30 mg of duloxetine (as hydrochloride). Also contains lactose.

28 Capsules

Oral use. Read the package leaflet before use. Keep out of the sight and reach of children.

Duloxetine #30 mg hard capsules
Duloxetine 30 mg and 60 mg gastro-resistant hard capsules

PL 15764/0119-0120

MA Holder: Somex Pharma
Ilford, Essex IG3 0BS, UK

Store in the original package in order to protect from moisture. Do not store above 30°C.

Duloxetine hydrochloride
Each capsule contains 60 mg of duloxetine (as hydrochloride). Also contains sucrose.

28 Capsules

Oral use. Read the package leaflet before use. Keep out of the sight and reach of children.

Duloxetine 60 mg gastro-resistant hard capsules

Coping Area
Unvarnished Area

Unvarnished Area (21.75 x 63 mm)
Space for 2D Barcode online printing
Sample 2D Barcode as shown

CIN:
Exp:
B. No.:
Sr. No.: 
Annex 1

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)

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