Public Assessment Report

Decentralised Procedure

Olena 20mg Dispersible Tablets

(fluoxetine hydrochloride)

Procedure No: UK/H/5297/001/DC

UK Licence No: PL 12762/0475

Mercury Pharmaceuticals Limited
This is a summary of the Public Assessment Report (PAR) for Olena 20mg Dispersible Tablets (PL 12762/0475; UK/H/5297/001/DC). It explains how Olena 20mg Dispersible 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 Olena 20mg Dispersible Tablets.

For practical information about using Olena 20mg Dispersible Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Olena 20mg Dispersible Tablets and what are they used for?**
Olena 20mg Dispersible Tablets are a medicine that contain the active substance fluoxetine hydrochloride. Olena 20mg Dispersible Tablets belong to a group of medicines called antidepressants that will relieve the symptoms of depression. They may also be used to treat the eating disorder bulimia nervosa and the condition obsessive compulsive disorder.

Olena 20mg Dispersible Tablets are a ‘generic’ medicine. This means that Olena 20mg Dispersible Tablets are similar to a reference medicine already authorised in the European Union (EU) called Prozac 20 mg dispersible tablets (Lilly France S.A., France).

**How are Olena 20mg Dispersible Tablets used?**
Olena 20 mg Dispersible Tablets are taken by mouth. Olena 20 mg Dispersible Tablets can only be obtained on prescription.

**How do Olena 20mg Dispersible Tablets work?**
Olena 20mg Dispersible Tablets contain the active substance fluoxetine hydrochloride, which belongs to a group of medicines called selective serotonin re-uptake inhibitors (SSRIs); fluoxetine hydrochloride influences the central nervous system.

**How have Olena 20mg Dispersible Tablets been studied?**
Because Olena 20mg Dispersible Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are similar to the reference medicine, Prozac 20 mg dispersible tablets (Lilly France S.A., France). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company provided data from the published literature on fluoxetine hydrochloride.

**What are the benefits and risks of Olena 20mg Dispersible Tablets?**
Because Olena 20mg Dispersible Tablets are a generic medicine and are bioequivalent to the reference medicine, their benefits and risks are taken as being the same as the reference medicine.

**Why are Olena 20mg Dispersible Tablets approved?**
It was concluded that, in accordance with EU requirements, Olena 20mg Dispersible Tablets have been shown to have comparable quality and to be bioequivalent to Prozac 20 mg dispersible tablets (Lilly France S.A., France). Therefore, the view was that, as for Prozac 20 mg dispersible tablets (Lilly France S.A., France), the benefit outweighs the identified risk.
What measures are being taken to ensure the safe and effective use of Olena 20mg Dispersible Tablets?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Olena 20mg Dispersible Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Olena 20mg Dispersible Tablets.
A Marketing Authorisation was granted in the UK on 19 September 2013.

The full PAR for Olena 20mg Dispersible Tablets follows this summary.

For more information about treatment with Olena 20mg Dispersible Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2013.
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Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Olena 20mg Dispersible Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<tr>
<td><strong>Active Substance(s)</strong></td>
<td>Fluoxetine hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Dispersible tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>20 mg</td>
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</table>
| **MA Holder** | Mercury Pharmaceuticals Limited  
No 1 Croydon  
12-16 Addiscombe Road  
Croydon  
CR0 0XT |
| **Reference Member State (RMS)** | UK |
| **Concerned Member State (CMS)** | Ireland |
| **Procedure Number** | UK/H/5297/001/DC |
| **Timetable** | Day 210 – 22 August 2013 |
Module 2
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.
Module 3
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.
Module 4
Labelling

The Marketing Authorisation Holder has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING</th>
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<tbody>
<tr>
<td>Carton</td>
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1. **NAME OF THE MEDICINAL PRODUCT**

Olena 20 mg Dispersible Tablets
Fluoxetine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each dispersible tablet contains fluoxetine hydrochloride equivalent to 20mg of fluoxetine.

3. **LIST OF EXCIPIENTS**

Also contains sorbitol (E420) and sulfur dioxide (E220).

4. **PHARMACEUTICAL FORM AND CONTENTS**

Dispersible tablet.
20 mg:
- 1 x 7 dispersible tablets
- 1 x 10 dispersible tablets
- 1 x 14 dispersible tablets
- 1 x 20 dispersible tablets
- 1 x 28 dispersible tablets
- 1 x 30 dispersible tablets
- 1 x 60 dispersible tablets
- 1 x 70 dispersible tablets
- 1 x 100 dispersible tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.
Use as directed by your doctor.
Read the package leaflet carefully before use.

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

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Not applicable
8. EXPIRY DATE

EXP (MM/YYYY)

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Limited
No. 1 Croydon
12-16 Addiscombe Road,
Croydon, CRO XOT, UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 12762/0475

13. BATCH NUMBER

N°......

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

olena 20mg dispersible tablets
Olena 20mg Dispersible Tablets

| Blister |

<table>
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<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<td>Olena 20 mg Dispersible Tablets</td>
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<tr>
<td>Fluoxetine</td>
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<th>4. BATCH NUMBER</th>
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<th>5. OTHER</th>
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<tr>
<td>Not applicable.</td>
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Module 5
Scientific discussion during initial procedure

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the application for Olena 20mg Dispersible Tablets (PL 12762/0475; UK/H/5297/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for the treatment of:

Adults for:
- Major depressive episodes
- Obsessive-compulsive disorder
- Bulimia nervosa: Olena Tablets are indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

and

Children and adolescents aged 8 years and above for:
- Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Prozac 20 mg dispersible tablets (Lilly France SA, France) which was authorised in France on 01 January 1988.

The active ingredient fluoxetine hydrochloride is a selective inhibitor of serotonin reuptake, and this accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors, such as $\alpha_1$, $\alpha_2$, and $\beta$-adrenergic; serotonergic; dopaminergic; histaminergic; muscarinic and GABA receptors.

A single-dose bioequivalence study was submitted to support this application, comparing the applicant’s test product Fluoxetine hydrochloride 20 mg dispersible tablets versus the reference product Prozac 20 mg dispersible tablets (Lilly France S.A., France). The bioequivalence study is stated to have been conducted in compliance with the Declaration of Helsinki and in compliance with the International Conference on Harmonisation Good Clinical Practice (GCP) guidelines (1996), and European Guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical efficacy studies were performed for this application, 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 RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. 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.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 22 August 2013. After a subsequent national phase, a licence was granted in the UK on 19 September 2013.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Olena 20mg Dispersible Tablets</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Fluoxetine hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Selective serotonin reuptake inhibitors (ATC code: N06A B03)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength</td>
<td>Dispersible tablets; 20 mg</td>
</tr>
<tr>
<td>Reference number(s) for the Decentralised Procedure</td>
<td>UK/H/5297/001/DC</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member State (CMS)</td>
<td>Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number</td>
<td>PL 12762/0475</td>
</tr>
</tbody>
</table>
| Name and address of the authorisation holder      | Mercury Pharmaceuticals Limited  
No 1 Croydon  
12-16 Addiscombe Road  
Croydon  
CR0 0XT |

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Fluoxetine hydrochloride
Chemical name(s): (3RS)-N-Methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine hydrochloride

Structure:

![Fluoxetine Hydrochloride Structure](image)

Molecular formula: C_{17}H_{19}ClF_{3}NO
Molecular mass: 345.8
Appearance: A white to almost white crystalline powder.
Solubility: Sparingly soluble in water, freely soluble in methanol and sparingly soluble in methylene chloride.

Fluoxetine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients mannitol (E421), croscarmellose sodium, magnesium stearate, saccharin sodium, peppermint flavour (contains sorbitol [E420] and sulfur dioxide [E220]). Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of peppermint flavour (E220), which is controlled to a suitable in-house specification. Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specification.

None of the excipients contain materials of animal or human origin.
No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, stable dispersible tablet that could be considered a generic medicinal product of the reference product Prozac 20 mg dispersible tablets (Lilly France S.A., France).

Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution profiles have been provided for this product and the reference product.

**Manufacturing Process**

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 with full-scale production-scale batches and has shown satisfactory results.

**Control of Finished Product**

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided, which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

The tablets are packaged in polyvinyl chloride/polyethylene/polyvinylidene chloride/aluminium (PVC/PE/PVDC/aluminium) blisters packed with the Patient Information Leaflet in cartons, in pack sizes of 7, 10, 14, 20, 28, 30, 60, 70 and 100 dispersible tablets.

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 current European regulations concerning materials in contact with foodstuff.

**Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months, with the storage conditions ‘Do not store above 30°C. Store in the original package in order to protect from moisture.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

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

The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective. Final text versions of the labelling and PIL have been provided. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant competent authorities for approval before marketing any pack size.

User-testing of the PIL has been accepted based on the bridging report provided by the applicant making reference to the successful user-testing of the PIL for Paroxetine 20mg and 30mg tablets (Wintrop
Pharmaceuticals Ltd) as the ‘parent PIL’. As the products belong to the same class of medication, no further user testing of the leaflet for Olena 20mg Dispersible Tablets is considered necessary.

**Marketing Authorisation Application (MAA) Form**
The MAA form is satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**
The quality overall summary has been 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.

### III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of fluoxetine hydrochloride are well-known, no new non-clinical data have been submitted and none are required.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The Marketing Authorisation Holder (MAH) has provided adequate justification for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.

### III.3 CLINICAL ASPECTS

#### Clinical Pharmacology
The clinical pharmacology of fluoxetine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

**A randomised, two-period, two-treatment, two sequence, single dose, cross over study comparing the applicant’s Fluoxetine 20mg dispersible tablets (Mercury Pharmaceuticals Limited, UK) with the reference product Prozac 20mg dispersible tablets (Lilly France S.A., France) in healthy male and female adult subjects, under fasting conditions.**

The subjects were administered a single dose (2 x 20 mg tablets) of either the test or the reference product with 150 ml of water, after an overnight fast. Blood sampling was performed pre-dose and up to 648 hours post-dose in each treatment period and analysed for the parent drug and main active metabolite (norfluoxetine). The washout period between the two treatment arms was 56 days. The pharmacokinetic results are presented below.
Pharmacokinetic parameters (geometric least square means, ratios and confidence intervals [CI] for fluoxetine)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GEOMETRIC LS MEANS *</th>
<th>RATIO (%)</th>
<th>90% CONFIDENCE LIMITS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEST</td>
<td>REFERENCE</td>
<td>LOWER</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>26.422</td>
<td>25.178</td>
<td>104.94</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt;</td>
<td>1125.191</td>
<td>1072.760</td>
<td>104.89</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt;</td>
<td>1194.712</td>
<td>1135.364</td>
<td>105.23</td>
</tr>
</tbody>
</table>

* units are ng/mL for C<sub>max</sub> and ng·h/mL for AUC<sub>T</sub> and AUC<sub>∞</sub>

- C<sub>max</sub>     maximum plasma concentration
- AUC<sub>T</sub>     area under the plasma concentration-time curve from time zero to t hours
- AUC<sub>∞</sub>     area under the plasma concentration-time curve from time zero to infinity

Ratios and 90% CI calculated from ln-transformed data

Pharmacokinetic parameters (geometric least square means, ratios and confidence intervals [CI] for norfluoxetine)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GEOMETRIC LS MEANS *</th>
<th>RATIO (%)</th>
<th>90% CONFIDENCE LIMITS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEST</td>
<td>REFERENCE</td>
<td>LOWER</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>18.602</td>
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<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt;</td>
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<td>4865.007</td>
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<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt;</td>
<td>5079.114</td>
<td>5193.689</td>
<td>97.79</td>
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</table>

* units are ng/mL for C<sub>max</sub> and ng·h/mL for AUC<sub>T</sub> and AUC<sub>∞</sub>

- C<sub>max</sub>     maximum plasma concentration
- AUC<sub>T</sub>     area under the plasma concentration-time curve from time zero to t hours
- AUC<sub>∞</sub>     area under the plasma concentration-time curve from time zero to infinity

Ratios and 90% CI calculated from ln-transformed data

Bioequivalence Conclusion
The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the 90% confidence limits as 80.00% to 125.00% for C<sub>max</sub> and AUC values. The 90% confidence intervals of the test/reference ratio for AUC<sub>T</sub>, AUC<sub>∞</sub> and C<sub>max</sub> lie within the acceptable limits for both fluoxetine and norfluoxetine. Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Prozac 20mg dispersible tablets (Lilly France S.A., France) under fasting conditions.

Efficacy
The efficacy of fluoxetine hydrochloride is well-known. No new efficacy data have been submitted and none are required for this type of application.

Safety
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.

Pharmacovigilance System and Risk Management Plan
The RMS considers that the Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
Suitable justification has been provided for non-submission of a Risk Management Plan (RMP) for this application which was received prior to 21 July 2012, the date from which the pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product. No safety concerns leading to special risk minimization activities have been identified by the innovator. There is no need for a detailed European Risk Management Plan and the routine pharmacovigilance activities are sufficient.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the originator product. The PIL is consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with the current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Olena 20mg Dispersible 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. As the pharmacokinetics, pharmacodynamics and toxicology of fluoxetine hydrochloride are well-known, no additional data were required.

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

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s test product and the reference product Prozac 20mg dispersible tablets (Lilly France S.A., France).

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of fluoxetine hydrochloride is well known, no additional safety data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling text are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.
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 fluoxetine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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