Public Assessment Report

UKPAR

Fluoxetine 20mg Capsules
(Fluoxetine hydrochloride)

UK Licence No: PL 44041/0016

Noumed Life Sciences Limited.
LAY SUMMARY

Fluoxetine 20mg Capsules
(Fluoxetine hydrochloride, capsule, hard, 20 mg)

This is a summary of the Public Assessment Report (PAR) for Fluoxetine 20mg Capsules (PL 44041/0016). It explains how Fluoxetine 20mg 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 Fluoxetine 20mg Capsules.

For practical information about using Fluoxetine 20mg Capsules patients should read the package leaflet or contact their doctor or pharmacist.

What are Fluoxetine 20mg Capsules and what are they used for?
Fluoxetine 20mg Capsules are used to treat:
- Depression
- Obsessive-compulsive disorder (also known as OCD)
- The eating disorder bulimia nervosa.

This medicine is the same as Fluoxetine 20mg Capsules/Olena 20 mg Capsules (PL 21880/0009) which is already authorised.

The company (Medreich Plc) that makes Fluoxetine 20mg Capsules/Olena 20 mg Capsules (PL 21880/0009) has agreed that its scientific data can be used as a basis for the grant of an identical licence [informed consent] for Fluoxetine 20mg Capsules (PL 44041/0016).

How do Fluoxetine 20mg Capsules work?
This medicine contains the active ingredient called fluoxetine hydrochloride which belongs to the group of medicines called selective serotonin re-uptake inhibitors (SSRI) antidepressants. Serotonin is a compound that exists naturally in the brain where it acts as a chemical messenger between the nerve cells. When serotonin is released from nerve cells in the brain it improves mood. When it is reabsorbed into the nerve cells, it no longer has an effect on mood. SSRIs work by preventing serotonin from being reabsorbed back into the nerve cells in the brain. This helps to improve mood and relieves depression.

It is not fully understood how fluoxetine works in the treatment of bulimia nervosa and obsessive compulsive disorder in adults.

How are Fluoxetine 20mg Capsules used?
The pharmaceutical form of this medicine is a capsule, hard and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor has told them. They should check with their doctor or pharmacist if they are not sure.

Taking this medicine
The capsules are for adults only and should be swallowed whole with a glass of water.

How much to take
Depression: The usual dose for depression is one capsule (20 mg) per day for at least six months.

Obsessive Compulsive Disorder: The usual dose for OCD is one capsule (20 mg) per day.
Bulimia nervosa: The usual dose for bulimia nervosa is 3 capsules (60 mg) per day.

For all conditions, the patient’s doctor may adjust their dose depending on the patient’s response to treatment.

Dosage in the Elderly
The patient’s doctor may prescribe a lower dose up to a maximum of 60 mg (3 capsules) a day.

Dosage in patients with liver problems
The patient’s doctor may prescribe a lower or less frequent dose e.g. once capsule every other day.

Please refer to section 3 of the package leaflet for information on how to use this medicine.

This medicine can only be obtained with a prescription.

For further information on how Fluoxetine 20mg Capsules are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Fluoxetine 20mg Capsules have been shown in studies?
Fluoxetine 20mg Capsules are considered identical to previously authorised Fluoxetine 20mg Capsules/Olena 20 mg Capsules (PL 21880/0009), with the same benefits and risks. So no new studies have been provided for Fluoxetine 20mg Capsules but reference is made to the studies for Fluoxetine 20mg Capsules/Olena 20 mg Capsules (PL 21880/0009).

What are the possible side effects from Fluoxetine 20mg Capsules?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Fluoxetine 20mg Capsules are considered to be identical to the previously authorised application for Fluoxetine 20mg Capsules/Olena 20 mg Capsules (PL 21880/0009) with the same benefits and risks.

For a full list of all the side effects reported with Fluoxetine 20mg Capsules see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

Why are Fluoxetine 20mg Capsules approved?
The MHRA decided that the benefits of Fluoxetine 20mg Capsules are greater than their risks and recommended that they be approved for use.

What measures are being taken to ensure the safe and effective use of Fluoxetine 20mg Capsules?
A Risk Management Plan has been developed to ensure that Fluoxetine 20mg Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Fluoxetine 20mg 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/healthcare professionals will be monitored/reviewed continuously.

Other information about Fluoxetine 20mg Capsules
A Marketing Authorisation was granted in the UK on 20 January 2017.
The full PAR for Fluoxetine 20mg Capsules follows this summary.

For more information about treatment with Fluoxetine 20mg Capsules read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2017.
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Introduction</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>9</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>9</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>10</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>recommendation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Table of content of the PAR update</td>
<td>13</td>
</tr>
</tbody>
</table>
INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Noumed Life Sciences Limited a Marketing Authorisation for the medicinal product Fluoxetine 20mg Capsules (PL 44041/0016) on 20 January 2017. The product is a Prescription Only Medicine (POM) indicated for:

- Major depressive disorders/episodes.
- Obsessive-compulsive disorder.
- Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

This application was submitted as a simple abridged (informed consent) application according to Article 10c of Directive 2001/83/EC, as amended.

The application cross-refers to the reference product Fluoxetine 20mg Capsules/Olena 20 mg Capsules, which was first authorised to the marketing authorisation holder (MAH) Karib Kemi Pharm Limited (PL 18224/0059) on 01 October 2007 and underwent a change of ownership procedure to the current MAH Medreich Plc (PL 21880/0009) on 03 December 2008.

Fluoxetine is a potent and highly selective serotonin (5-hydroxytryptamine, 5HT) reuptake inhibitor. The antidepressant, antiobsessive-compulsive, and antibulimic actions of fluoxetine are presumed to be linked to this inhibition of neuronal uptake of serotonin in the central nervous system. Fluoxetine is chemically unrelated to tricyclic and tetracyclic antidepressant agents. Fluoxetine is a 50:50 mixture of two isomers which have equivalent pharmacological activity in animals. Individuals with reduced P45011D6 isoenzyme activity (3-10% of the normal human population - 'poor metabolisers') have been compared to normal metabolisers. The total sum at steady state of the two isomers and their active norfluoxetine metabolites was reported to be similar. Thus, net pharmacodynamic activities were essentially the same.

No new data were submitted nor were necessary to be submitted for this application, as the data are identical to the data for the previously granted cross-referenced product.
II QUALITY ASPECTS

II.1 Introduction
This is an abridged application for Fluoxetine 20mg Capsules (PL 44041/0016) submitted under Article 10c of Directive 2001/83/EC, as amended.

II.2 Drug Substance
Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3 Medicinal Product
Name
The proposed product name for this application is Fluoxetine 20mg Capsules. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes
Each capsule contains 22.5mg fluoxetine hydrochloride equivalent to 20mg fluoxetine. The finished product is packed into blister packs containing polyvinyl chloride (PVC) film with a backing of aluminium foil (coated with heat seal lacquer) and is available in pack sizes of 10, 14, 20, 30, 50, 70 or 100 capsules. Not all pack sizes may be marketed.

The proposed shelf life is 36 months with the storage condition, ‘Store in the original package. Do not store above 30°C.’

The proposed packaging, shelf-life and storage conditions are consistent with the details registered for the cross-reference product.

Legal status
Prescription only medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Noumed Life Sciences Limited, McGraw Hill House, Shoppenhangers Road, Maidenhead, Berkshire SL6 2QL, United Kingdom.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process
The proposed manufacturing processes are consistent with the details registered for the cross-reference product and the maximum batch size is stated.
Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

TSE Compliance
With the exception of gelatin, none of the excipients contain materials 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).

Bioequivalence
No bioequivalence data are required to support this simple abridged application because the proposed product is manufactured to the same formula utilising the same processes as the cross-reference product, Fluoxetine 20mg Capsules/Olena 20 mg Capsules (PL 21880/0009).

Expert Reports
The applicant cross-refers to the data for Fluoxetine 20mg Capsules/Olena 20 mg Capsules (PL 21880/0009) to which this application is claimed to be identical. This is acceptable.

Product Name and Appearance
See Section II.3 ‘Medicinal Product; Name’ for details of the proposed product name. The appearance of the product is identical to that of the cross-reference product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.
III  NON-CLINICAL ASPECTS

Introduction
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is an identical 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.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV  CLINICAL ASPECTS

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

Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (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 Fluoxetine 20mg Capsules.

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

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important Identified Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Withdrawal symptoms</td>
</tr>
<tr>
<td>Concomitant use with monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension (PPHN) in the newborn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important Potential Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Mania</td>
</tr>
<tr>
<td>Suicide/ suicidal thoughts or clinical worsening of disease</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td>Use in children and adolescents under the age of 18 years</td>
</tr>
<tr>
<td>Concomitant use with St John’s Wort</td>
</tr>
<tr>
<td>Use in patients with diabetes</td>
</tr>
<tr>
<td>Akathisia/ psychomotor restlessness</td>
</tr>
<tr>
<td>Haemorrhage</td>
</tr>
<tr>
<td>Mydriasis</td>
</tr>
<tr>
<td>Use in patients receiving electroconvulsive therapy</td>
</tr>
<tr>
<td>Use in pregnancy</td>
</tr>
<tr>
<td>Cardiovascular defects in infants</td>
</tr>
</tbody>
</table>

| Missing Information                                            |
| Effect on fertility                                           |

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.
Discussion on the clinical aspects
The grant of a 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 the PIL for Fluoxetine 20mg Capsules/Olena 20 mg Capsules (PL 21880/0009). The bridging report submitted by the applicant is acceptable.

VI 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. The applicant’s product is identical to the cross-reference product. 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.
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 product.

In accordance with Directive 2010/84/EU the SmPCs and PILs for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
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)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>