Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Sertraline 50 mg Film-coated Tablets
Sertraline 100 mg Film-coated Tablets
(Sertraline hydrochloride)

PL 08553/0243-0246

Dr Reddy's Laboratory (UK) Ltd

Medicines and Healthcare Products Regulatory Agency

Lay Summary
Sertraline 50 mg Film-coated Tablets
Sertraline 100 mg Film-coated Tablets
(Sertraline hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Sertraline 50 mg Film-coated Tablets and Sertraline 100 mg Film-coated Tablets (PL 08553/0243-0246). It explains how Sertraline 50 mg and 100 mg Film-coated 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 these products.

For practical information about using Sertraline 50 mg and 100 mg Film-coated Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

These medicinal products will be referred to as Sertraline Tablets in this summary, for ease of reading.

What are Sertraline Tablets and what are they used for?
Sertraline Tablets are 'generic medicines'. This means that Sertraline Tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Lustral 50 mg and 100 mg Tablets.

Sertraline Tablets are used to treat:
- depression and prevention of recurrence of depression (in adults)
- social anxiety disorder (in adults)
- post-traumatic stress disorder (PTSD) (in adults)
- panic disorder (in adults)
- obsessive compulsive disorder (OCD) (in adults and children and adolescents aged 6-17 years old)

How do Sertraline Tablets work?
These medicines contain the active ingredient sertraline. Sertraline is one of a group of medicines called selective serotonin re-uptake inhibitors (SSRIs). SSRIs are thought to work by increasing serotonin levels in the brain.

How are Sertraline Tablets used?
These medicines can only be obtained with a prescription.

Sertraline Tablets may be taken with or without food. The tablets should not be chewed or crushed; they should always be swallowed whole, with a drink of water.

Patients should take this medicine once daily either in the morning or evening. A doctor will advise how long the medication should be taken for. This will depend on the nature of the illness and how well the patient is responding to treatment. It may take several weeks before symptoms begin to improve. Treatment of depression should usually continue for 6 months after improvement.

The recommended dose for depression and OCD in adults is 50 mg/day. The daily dose may be increased in 50 mg increments and at intervals of at least one week over a period of weeks. The maximum recommended dose is 200 mg/day.

The recommended dose for PTSD, Panic Disorder and Social Anxiety Disorder is 25 mg daily increasing to 50 mg a day after a week. The daily dose then may be increased in 50 mg increments over a period of weeks. The maximum recommended dose is 200 mg/day.

These medicines must only be used to treat children and adolescents suffering from OCD aged 6-17 years old. For OCD in children aged 6 to 12 years, the recommended starting dose is 25 mg daily. After one week, the doctor may increase this to 50 mg daily. The maximum dose is 200 mg daily. For OCD in adolescents aged 13 to 17, the recommended starting dose is 50 mg daily. The maximum dose is 200 mg daily.

What benefits of Sertraline Tablets have been shown in studies?
Because Sertraline Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Lustral 50 mg and 100 mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Sertraline Tablets?
Because Sertraline Tablets are a generic medicine, their possible side effects are taken as being the same as those of the reference medicines, Lustral 50 mg and 100 mg Tablets.

For the full list of all side effects reported with Sertraline Tablets, see section 4 of the package leaflet.

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

Why were Sertraline Tablets approved?
It was concluded that, in accordance with EU requirements, Sertraline Tablets have been shown to have comparable quality and to be bioequivalent to Lustral 50 mg and 100 mg Tablets. Therefore, the MHRA decided that, as for Lustral 50 mg and 100 mg Tablets, the benefits outweigh the identified risks and recommended that Sertraline Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Sertraline Tablets?
Safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Sertraline Tablets, 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 and reviewed continuously.

Other information about Sertraline Tablets
Marketing Authorisations were granted in the UK on 21 November 2008.

The Marketing Authorisations for Sertraline 50 mg and 100 mg Film-coated Tablets (PL 08553/0245 and 0246) were cancelled on 27 December 2012 and 24 January 2011, respectively.

The full PAR for Sertraline Tablets follows this summary. For more information about treatment with Sertraline Tablets read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in April 2018.

Table of Contents

I Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Dr Reddy's Laboratory (UK) Limited Marketing Authorisations for the medicinal products Sertraline 50 and 100 mg Film-coated Tablets (PL 08553/0243-0246) on 21 November 2008. These were duplicate national abridged applications for both strengths.

These products are prescription only medicines (legal classification POM).

These applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Lustral 50 mg and 100 mg tablets (PL 00057/0308-09; Pfizer Limited), which were originally granted Marketing Authorisations in the UK on 19 November 1990.

Sertraline 50 and 100 mg Film-coated Tablets are indicated for the treatment of:

- Major depressive episodes. Prevention of recurrence of major depressive episodes.
- Panic disorder, with or without agoraphobia.
- Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years.
- Social anxiety disorder.
- Post-traumatic stress disorder (PTSD).

These products contain the active substance sertraline hydrochloride, which is a selective serotonin reuptake inhibitor (SSRI). Sertraline hydrochloride is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake *in vitro*, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of brain norepinephrine receptors as observed with other clinically effective antidepressants and anti-obsessional drugs.

With the exception of the bioequivalence study, no new clinical studies or non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

A bioequivalence study was performed, which compared the pharmacokinetics of the test product, Sertraline 100 mg Film-coated Tablets to those of the reference product, Lustral 100 mg tablets (Pfizer Limited, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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

The Marketing Authorisations for Sertraline 50 mg and 100 mg Film-coated Tablets (PL 08553/0245 and 0246) were cancelled on 27 December 2012 and 24 January 2011, respectively.

II Quality aspects

II.1 Introduction

Sertraline 50 mg film-coated Tablets are white to off-white, capsule shaped, biconvex, film coated tablets embossed with “50” on one side and “SET” on the other side with a bisect line separating “S” from “ET”. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each film-coated tablet contains 50 mg of sertraline, as sertraline hydrochloride.

Sertraline 100 mg film-coated Tablets are white to off-white, capsule shaped, biconvex, film coated tablets embossed with “100” on one side and “SET” on the other side with a bisect line separating “S” from “ET”. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each film-coated tablet contains 100 mg of sertraline, as sertraline hydrochloride.

Other ingredients consist of the pharmaceutical excipients:

Tablet core:
Cellulose, microcrystalline (E460)
Calcium hydrogen phosphate dihydrate
Silica, colloidal anhydrous
Sodium starch glycolate (Type-A)
Hydroxypropyl cellulose (E463)
Magnesium stearate (E470b)

Tablet Coating:
Titanium dioxide (E171)
Hypromellose 5cps (E464)
Macrogol 400
Polysorbate 80

The finished products are packaged in aluminium/polyvinyl chloride/polyvinylidene chloride blisters in cartons containing 28, 30 or 100 tablets.

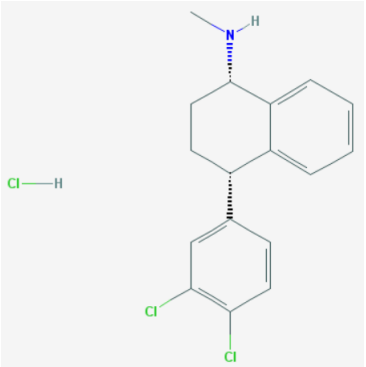
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Sertraline Hydrochloride

Chemical name: 1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1 -naphthyl(methyl)amine hydrochloride
(1S-Cis)-4-(3,4-dichlorophenyl)-1,2,3,4,tetrahydro N-methyl-1-naphthalenamine hydrochloride

Structure:



Molecular formula:	$C_{17}H_{17}NCl_2.HCl$
Molecular weight:	342.5
Solubility:	Slightly soluble in water
Appearance:	A white powder

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture, control, packaging and stability of the active substance.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate stable products that could be considered generic medicinal products of the currently licensed products, Lustral 50 mg and 100 mg tablets (PL 00057/0308-09; Pfizer Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the test and reference products.

With the exception of the tablet coating, which is controlled to an in-house standard, all excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients are sourced from animal or human origin. These products do not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on batches of each strength of finished product. The results are satisfactory.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of both strengths of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 3 years, with no special storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Sertraline 50 mg and 100 mg film-coated Tablets.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of sertraline hydrochloride are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As these products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to sertraline hydrochloride is anticipated. Thus, the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Sertraline 50 mg and 100 mg film-coated Tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction

With the exception of the bioequivalence study detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence study:

A randomised, 2-way, single dose, cross-over, bioequivalence study comparing the pharmacokinetics of the test product, Sertraline 100 mg film-coated Tablets, to those of the reference product, Lustral 100 mg tablets (Pfizer Limited, UK), in healthy, adult, human subjects, under fasting conditions.

Volunteers were given each treatment after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 144 hours post dose. Each treatment was separated by a washout period of 21 days.

A summary of the main pharmacokinetic results is presented in the table below:

Statistics	C_{max} (ng/ml)	AUC_{0-t} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)
Least Square Means Estimate (Anti log Values)			
Test (A)	30.421	946.866	1112.070
Reference (B)	29.643	914.527	1045.709
Ratio (Test/Reference)-%	102.62	103.54	106.35
90% Confidence Interval			
Lower- 90% C.I.(%)	93.30	93.41	95.86
Upper- 90% C.I.(%)	112.87	114.76	117.98

The multiple strengths exemption criterion for linear pharmacokinetics over the therapeutic range is met and the results from the bioequivalence study at the 100mg strength can be expected to apply to the 50mg strength tablet also:

a. The pharmacokinetics are linear
b. The qualitative composition is the same
c. The ratio between active substance and the excipients in both strengths of the test product is the same
d. The dissolution rate of the highest strength of the test product *in-vitro* is similar to that of the lower strength, and the dissolution rate of both of the strengths of the test product *in vitro* is similar to the dissolution rates of the corresponding strengths of the reference product.

The claim that the test product, Sertraline 100 mg film-coated Tablets, is bioequivalent with the UK reference, Lustral 100 mg tablets, is accepted.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy

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

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type.
No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

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.

The MAH has provided suitable justification for not submitting a RMP.

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Sertraline 50 mg and 100 mg film-coated Tablets.

V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

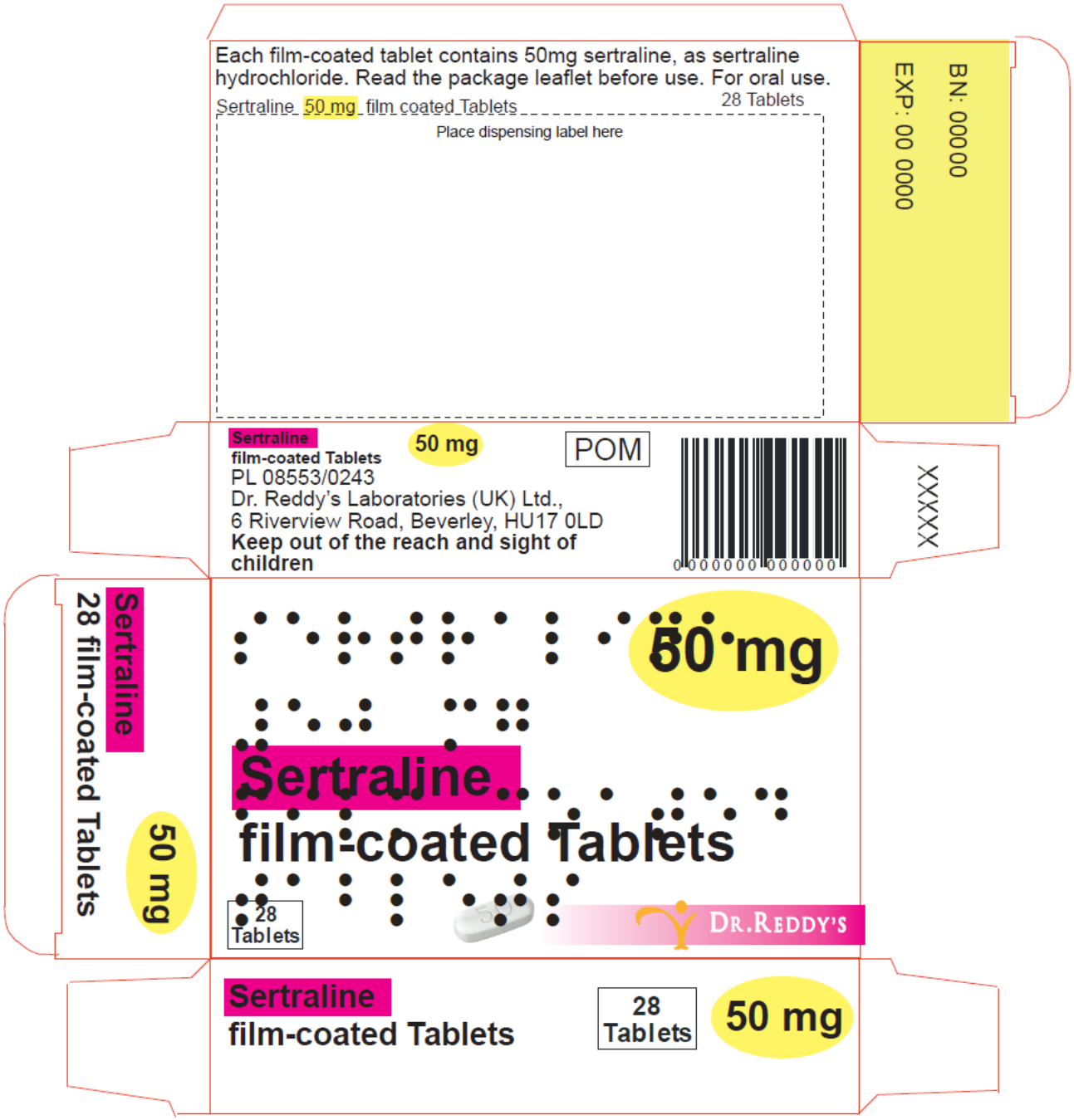
VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's products and the reference products are interchangeable. Extensive clinical experience with sertraline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

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

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

The approved labelling for Sertraline 50 mg and 100 mg film-coated Tablets is presented below:




Each film-coated tablet contains 50mg sertraline, as sertraline hydrochloride. Read the package leaflet before use. For oral use.
Sertraline 50 mg film-coated tablets 100 Tablets
Place dispensing label here
POM
BN: 0000
EXP: 00 0000
Sertraline
Film-coated Tablets
50 mg
xxxx
PL 08553/0243
Dr. Reddy's Laboratories (UK) Ltd, 6 Riverview Road, Beverley, HU17 0LD
Keep out of the reach and sight of children
Sertraline
100 film-coated Tablets
50 mg
50 mg
Sertraline
film-coated Tablets
100 Tablets
DR.REDDY'S
Sertraline
film-coated Tablets
50 mg
100 Tablets


BN: 0000
EXP: 00 0000
Sertraline 50mg film-coated Tablets
Dr . Reddy's Laboratories (UK) Ltd


Each film-coated tablet contains 100mg sertraline, as sertraline hydrochloride. Read the package leaflet before use. For oral use.
Sertraline 100 mg film-coated Tablets 28 Tablets
Place dispensing label here
BN: 00000
EXP: 00 0000
PL 08553/0244
Dr. Reddy's Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD
Keep out of the reach and sight of children
POM
XXXX
Sertraline
28 film-coated Tablets
100 mg
100 mg
Sertraline
film-coated Tablets
28 Tablets
DR.REDDY'S
Sertraline
film-coated Tablets
28 Tablets
100 mg


Each film-coated tablet contains 100mg sertraline, as sertraline hydrochloride. Read the package leaflet before use. For oral use.
Sertraline 100 mg film-coated tablets
100 film-Coated Tablets
Place dispensing label here
POM
ML 59/RR/AP/97/F/R
BN: 00000
EXP: 00 0000
Sertraline
film-coated Tablets
100 mg
xxxx
PL 08553/0244
Dr. Reddy's Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD
Keep out of the reach and sight of children
Sertraline
100 film-coated Tablets
100 mg
Sertraline
film-coated Tablets
100 mg
100 Tablets
DR.REDDY'S
Sertraline
film-coated Tablets
100 mg
100 Tablets


BN: 0000
EXP: 00 0000
Sertraline 100mg film-coated Tablets
Dr Reddy's Laboratories (UK) Ltd

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)

Scope	**Procedure number**	**Product information affected**	**Date of start of procedure**	**Date of end of procedure**	**Approval / Non-approval**	**Assessment report attached Y/N (version)**
To update sections 4.1, 5.1 – 5.3 of the SmPC and consequentially the PIL in line with the reference products.	PL 08553/0243 and 0244 - 0011	SmPC and PIL	21/01/2013	04/03/2013	Approval	Y (Annex 1)
To update sections 4.8 and 5.2 of the SmPC and consequentially the PIL in line with the reference products In addition, to add the updated national reporting system in line with Annex V of the current QRD template.	PL 08553/0243 – 0030 PL 08553/0244 – 0029	SmPC and PIL	28/02/2018	18/04/2018	Approval	Y (Annex 2)

Annex 1

Reference: PL 08553/0243 & 0244 - 0011
Product: Sertraline 50 mg & 100 mg film-coated Tablets
Marketing Authorisation Holder: Dr Reddy's Laboratory (UK) Limited
Active Ingredient(s): Sertraline hydrochloride

Reason:
To update sections 4.1, 5.1-5.3 of the SmPCs to bring them in line with UK reference products Lustral 50mg and 100mg Tablets. As a consequence, the PIL has been updated.

Supporting Evidence
Updated sections 4.1 and 5.1-5.3 of each SmPC have been provided.

Evaluation
The updated SmPC sections are satisfactory and in-line with the reference products.

Decision – Granted 04/03/2013

Annex 2

Reference: PL 08553/0243 – 0029
PL 08553/0244 - 0030
Product: Sertraline 50 mg & 100 mg film-coated Tablets
Marketing Authorisation Holder: Dr Reddy's Laboratory (UK) Limited
Active Ingredient(s): Sertraline hydrochloride

Reason:
To update sections 4.8 and 5.2 of the SmPCs to bring them in line with UK reference products, Lustral 50mg and 100mg Tablets.

In addition, to add the updated national reporting system information to communicate adverse reactions (side effects) in line with Annex V of the current QRD template.

Consequently, the PIL has been updated.

Supporting Evidence
Updated sections 4.8 and 5.2 of each SmPC and a revised PIL have been provided.

Evaluation
The updated SmPC sections and revised PIL are satisfactory and in-line with the reference products.

The current SmPC and PIL are available on the MHRA website.

Decision – Granted 18/04/2018