Public Assessment Report

Sertraline 50mg Film-coated Tablets
Sertraline 100mg Film-coated Tablets

Sertraline Hydrochloride

PL 08553/0243-6

Dr Reddy's Laboratory (UK) Ltd

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Lay Summary

The MHRA granted market authorisations (licences) for the medicinal products Sertraline 50mg Film-coated Tablets and Sertraline 100mg Film-coated Tablets (PL 08553/0243-6) on 21/11/2008 to Dr Reddy's Laboratory (UK) Ltd. These are prescription only medicines used in the treatment of depression, anxiety with depression and obsessive-compulsive disorder.

Sertraline 50mg Film-coated Tablets and Sertraline 100mg Film-coated Tablets contain the active ingredient sertraline hydrochloride. Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake *in vitro* and *in vivo*.

The products were demonstrated to be generic medical products of the originator products, Lustral tablets (100mg), or Lustral tablets (50mg), PL 00057/0308-09, Pfizer Ltd UK.

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

Scientific Discussion

INTRODUCTION

Based on a review of the data on quality, safety and efficacy the MHRA granted UK marketing authorisations for the medicinal products Sertraline 50mg Film-coated Tablets and Sertraline 100mg Film-coated Tablets (PL 08553/0243-6). These were duplicate national abridged applications for both strengths. The medicines are available with a medical prescription.

Sertraline is indicated for the treatment of symptoms of depressive illness, including accompanying symptoms of anxiety. Following satisfactory response, continuation with Sertraline is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes, including accompanying symptoms of anxiety. Sertraline is also indicated for the treatment of obsessive compulsive disorder (OCD).

The products were demonstrated to be generic medical products of the originator products, Lustral tablets (100mg), or Lustral tablets (50mg), PL: 00057/0308-09, Pfizer Ltd UK.

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

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

International Non-proprietary Name (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

Description:	A white powder. Slightly water soluble.
Molecular formula:	C17H17NCl2.HCl
Molecular weight:	342.5

An appropriate specification has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active sertraline is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months, with no specific storage instructions.

DRUG PRODUCT
The other ingredients found in the drug product are listed below:

Tablet core:
Cellulose, Microcrystalline Ph Eur (E460)
Calcium Hydrogen Phosphate Dihydrate Ph Eur
Silica, Colloidal Anhydrous Ph Eur
Sodium Starch Glycolate (Type-A) Ph Eur
Hydroxypropyl cellulose Ph Eur (E463)
Magnesium Stearate Ph Eur (E470b)

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

All excipients are contained in the Ph. Eur. with the exception of the Opadry white OY-58900 which is controlled by an in-house monograph. Satisfactory certificates of analysis have been provided for all excipients. The applicant has confirmed that no material of human or animal origin is used in the manufacture of the drug product.

Dissolution and impurity profiles
Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The drug product is stored in aluminium foil/PVC/PVdC blisters in cartons of 28, 30 or 100 tablets which meet current requirements.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory, with no specific storage instructions.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

NON-CLINICAL ASSESSMENT

No non-clinical data were submitted with this application and none were required.

CLINICAL ASSESSMENT

Clinical Pharmacology
Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake *in vitro* and *in vivo*, but is without affinity for muscarinic, serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors.

Sertraline exhibits dose proportional pharmacokinetics over a range of 50-200mg. After oral administration of sertraline in man, peak blood levels occur at about 4.5 - 8.4 hours. Daily doses of sertraline achieve steady-state after one week. Sertraline has a plasma half-life of approximately 26 hours with a mean half-life for young and elderly adults ranging from 22-36 hours. Sertraline is approximately 98% bound to plasma proteins. The principal metabolite, N-desmethylsertraline, is inactive in *in vivo* models of depression and has a half-life of approximately 62-104 hours. Sertraline and N-desmethylsertraline are both extensively metabolised in man and the resultant metabolites excreted in faeces and urine in equal amounts. Only a small amount (<0.2%) of unchanged sertraline is excreted in the urine.

Bioequivalence Study

Randomised, 2-way, single dose, cross-over, bioequivalence study of the test Sertraline 100mg tablets versus the reference Lustral 100mg tablets in healthy adult male subjects under fasting conditions.

Study protocol
Thirty two healthy male volunteers aged 19-37 years, were included in this study. Statistical analysis was performed on 30 subjects. An explanation was provided for the subjects excluded.

The results from 30 subjects were presented. Each subject received a single dose (100mg tablet) of one of the sertraline formulations. For each subject there were two

dosing periods, with a washout period of 21 days. A randomisation scheme was included in the report. The following formulations were administered:

Test : Sertraline 100mg tablets (Dr Reddy's Laboratories Ltd., Andhra Pradesh, India.)

Reference : Lustral 100mg tablets (Pfizer Ltd., UK.)

The reference is registered in UK. The tablet was administered with 240ml water following a >10hr fast. Standard meals were administered from 4 hours post-dose**.** Blood samples for analysis were taken pre dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours following dosing. There followed a 21 day washout period before cross over and repeat.

Plasma samples were analysed for Sertraline concentration using a validated LC/MS/MS method. The limit of detection for Sertraline was 0.62 ng/ml and the upper limit of quantitation was 2.022 ng/ml. A validation report has been provided. $AUC_{(0\text{-}t.)}$, $AUC_{(0\text{-}inf)}$, C_{max}, t_{max} and $t_{½}$ were calculated according normal standard procedures.

Statistical evaluation was performed for $AUC_{(0\text{-}t)}$, AUC_{inf} and C_{max} with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

The study was conducted in accordance with GCP and GLP. The report is of good quality.

The 90% confidence intervals of the ratios for AUC0-t, infinity and Cmax were within the accepted limits of 80 – 125%:

Statistics	**C_{max} (ng/ml)**	**$AUC_{0\text{-}t}$ (ng.hr/ml)**	**$AUC_{0\text{-}\infty}$ (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 form 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 Sertraline product is bioequivalent with the UK reference, Lustral, is accepted.

Efficacy and Safety
Efficacy and safety are reviewed adequately in the Clinical Expert report. The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

Summary Of Product Characteristics and Patient Information Leaflet.
These are satisfactory.

Conclusion
Marketing authorisations may be granted.

Overall Conclusion and Benefit/Risk Analysis

Quality

The important quality characteristics of Sertraline 50mg and 100mg Film-coated 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 preclinical data were submitted and none are required for applications of this type.

Clinical

Bioequivalence has been demonstrated between the drug product and the originator product. Given that linear kinetics apply between the 50mg and 100mg tablets, that proportional formulae for the capsules have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 50mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the originator product.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. The risk benefit is, therefore, considered to be positive.

STEPS TAKEN DURING ASSESSMENT

1	The MHRA received the application on 18/08/2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 07/09/2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 10/04/2006 and 26/11/2007.
4	The applicant provided further information in regard to the quality assessment on 02/04/2007 and 27/02/2008.
5	The application was determined on 21/11/2008.

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

A list of all non-safety variations of clinical relevance that are presented as annexes at the end of this PAR are listed below.

Date submitted	**Application type**	**Scope**	**Outcome**
21/01/2013	IB	To update sections 4.1, 5.1 - 5.3 of the SmPCs to bring them in line with UK reference product Lustral 50mg and 100mg Tablets. As a consequence, the PIL has been updated.	Granted 04/03/2013

SUMMARY OF PRODUCT CHARACTERISTICS

The current Summaries of Product Characteristics are available on the MHRA website.

PATIENT INFORMATION LEAFLET

The current Patient Information Leaflet is available on the MHRA website.

LABELLING

BN: 0000

Sertraline 50mg film-coated Tablets
Dr . Reddy's Laboratories (UK) Ltd

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Sertraline 50mg film-coated Tablets
Dr . Reddy's Laboratories (UK) Ltd

EXP: 00 0000

BN: 0000

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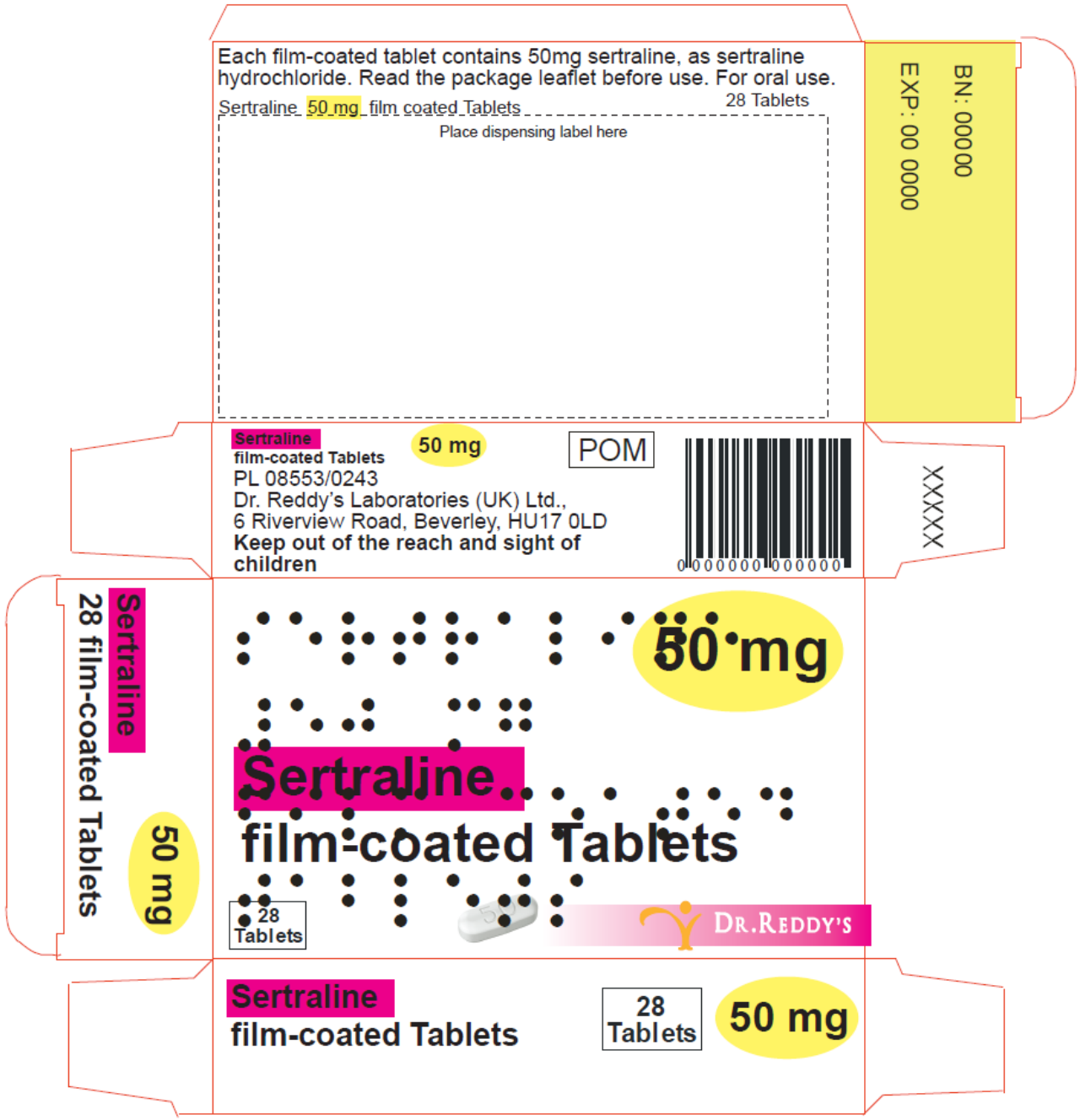
Sertraline 100mg film-coated Tablets
Dr Reddy's Laboratories (UK) Ltd

EXP: 00 0000


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
28 Tablets
Place dispensing label here
BN: 00000
EXP: 00 0000
Sertraline
film-coated Tablets
50 mg
POM
PL 08553/0243
Dr. Reddy's Laboratories (UK) Ltd.,
6 Riverview Road, Beverley, HU17 0LD
Keep out of the reach and sight of children
0 000000 000000
XXXXX
Sertraline
28 film-coated Tablets
50 mg
50 mg
Sertraline
film-coated Tablets
28 Tablets
DR.REDDY'S
Sertraline
film-coated Tablets
28 Tablets
50 mg


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: 00000
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


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
XXXXX
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
XXXXX
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
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Tablets

Annex 1

Reference(s): PL 08553/0243 & 0244 - 0011
Product(s): Sertraline 50mg & 100mg 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