Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Sertraline 50 mg/5 ml Oral Suspension

(sertraline hydrochloride)

PL 41344/0064

Colonis Pharma Ltd

LAY SUMMARY

Sertraline 50 mg/5 ml Oral Suspension (sertraline hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Sertraline 50 mg/5 ml Oral Suspension. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Sertraline Oral Suspension in this lay summary for ease of reading.

For practical information about using Sertraline Oral Suspension, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Sertraline Oral Suspension and what is it used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the United Kingdom (UK) called Lustral 50 mg film-coated tablets.

Sertraline Oral Suspension can be 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).

Depression is a clinical illness with symptoms like feeling sad, unable to sleep properly or to enjoy life as a person used to.

OCD and panic disorders are illnesses linked to anxiety with symptoms like being constantly troubled by persistent ideas (obsessions) that make a person carry out repetitive rituals (compulsions).

PTSD is a condition that can occur after a very emotionally traumatic experience and has some symptoms that are similar to depression and anxiety.

Social anxiety disorder (social phobia) is an illness linked to anxiety. It is characterised by feelings of intense anxiety or distress in social situations (for example: talking to strangers, speaking in front of groups of people, eating or drinking in front of others or worrying that one might behave in an embarrassing manner).

How does Sertraline Oral Suspension work?
Sertraline Oral Suspension contains the active substance sertraline (as sertraline hydrochloride). Sertraline is one of a group of medicines called Selective Serotonin Re-uptake Inhibitors (SSRIs); these medicines are used to treat depression and/or anxiety disorders.

How is Sertraline Oral Suspension used?
The pharmaceutical form of this medicine is an oral suspension and the route of administration is oral (taken by mouth).

The recommended dose is:
Adults:
Depression and OCD
For depression and OCD, the usual effective dose is 50 mg/day (5 ml/day). The daily dose may be increased in 50 mg (5 ml) increments and at intervals of at least one week over a period of weeks.

The maximum recommended dose is 200 mg/day (20 ml/day).

Panic disorder, Social anxiety disorder and PTSD
For panic disorder, social anxiety disorder and post traumatic stress disorder, treatment should be started at 25 mg/day (2.5 ml/day) and increased to 50 mg/day (5 ml/day) after one week.

The daily dose then may be increased in 50 mg (5 ml) increments over a period of weeks.

The maximum recommended dose is 200 mg/day (20 ml/day).

Use in children and adolescents
Sertraline Oral Suspension must only be used to treat children and adolescents suffering from OCD aged 6-17 years old.

OCD
Children aged 6 to 12: the recommended starting dose is 25 mg (2.5 ml) daily.
After one week, the patient's doctor may increase this to 50 mg (5 ml) daily.

The maximum dose is 200 mg (20 ml) daily.

Adolescents aged 13 to 17: the recommended starting dose is 50 mg (5 ml) daily.

The maximum dose is 200 mg (20 ml) daily.

If the patient has liver or kidney problems, they should tell their doctor and follow the doctor's instructions.

Method of administration
Sertraline 50 mg/5 ml oral suspension should be administered with a glass of water and may be taken with or without food.

The patient should take their medication once daily either in the morning or evening.

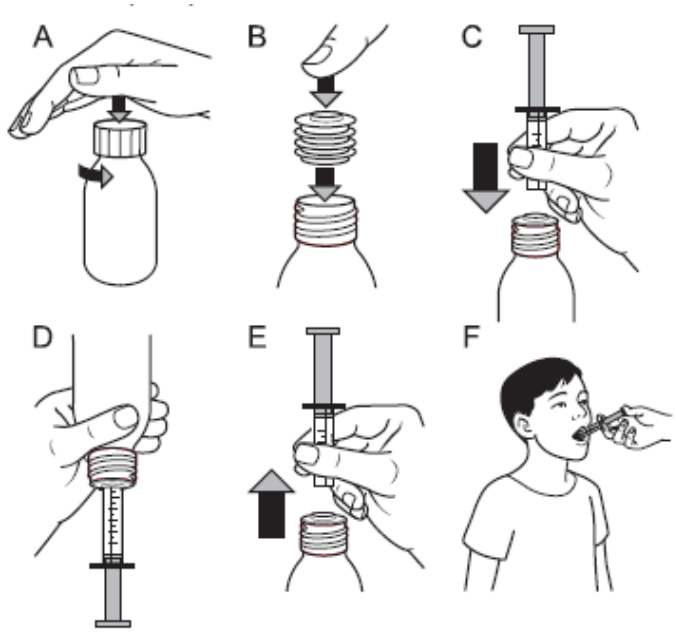
The doctor will advise their patient on how long to take this medication for. This will depend on the nature of the patient's illness and how well the patient is responding to the treatment.

It may take several weeks before the patient symptoms begin to improve.

Treatment of depression should usually continue for 6 months after improvement.

A 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and a “press-in” syringe/bottle adapter are provided with the product.

1. Shake the bottle well, before use.
2. Open the bottle and at first use insert the “Press-In” Bottle Adapter (PIBA) (see pictures A-B).
3. Insert the syringe into the PIBA and draw out the required volume from the inverted bottle (see pictures C-D).
4. Remove the filled syringe from the bottle in the upright position (see picture E).
5. Discharge the syringe contents into the mouth (see picture F). Repeat steps 3 to 5 as needed to achieve the required dose.
6. Rinse the syringe and replace the cap on the bottle (PIBA remains in place).



For further information on how Sertraline Oral Suspension is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

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

What benefits of Sertraline Oral Suspension have been shown in studies?
As Sertraline Oral Suspension is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. 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 Oral Suspension?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

As Sertraline Oral Suspension is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Sertraline Oral Suspension approved?
It was concluded that, Sertraline Oral Suspension has been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Sertraline Oral Suspension?
A Risk Management Plan (RMP) has been developed to ensure that Sertraline Oral Suspension is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, 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 Oral Suspension
A Marketing Authorisation was granted in the UK on 11 October 2021.

The full PAR for Sertraline Oral Suspension follows this summary.

This summary was last updated in December 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Sertraline 50 mg/5 ml Oral Suspension (PL 41344/0064) could be approved.

The product is approved for the following indications:
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).

The active substance, sertraline (as 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.

This application was approved under Regulation 51B of The Human Medicines Regulations 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Lustral 50 mg film-coated tablets, that has been licensed within the United Kingdom (UK) for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence studies were conducted in line with current Good Clinical Practice (GCP).

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 20 June 2019 because major objections were raised with respect to quality and clinical aspects of the dossier. The Committee provisionally concluded that further information on quality aspects should be requested before the products could be approved. In response to the CHM advice,

the applicant provided additional data, including a bioequivalence study and detailed clarification of the points that had been raised. Following consideration of the responses and further data that were submitted, the approval of the Marketing Authorisation was recommended.

A national Marketing Authorisation was granted in the UK on 11 October 2021.

II QUALITY ASPECTS

II.1 Introduction

This product contains of 50 mg sertraline (as sertraline hydrochloride) in 5 ml of oral suspension.

In addition to sertraline hydrochloride, this product also contain the excipients citric acid (E330), disodium phosphate, polysorbate 80 (E433), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), simeticone 30 % emulsion, propylene glycol (E1520), saccharin sodium (E954) and strawberry flavour (including traces of ethanol, (E1510) and propylene glycol, E1520), xanthan gum (E415), glycerol (E422) and purified water.

The finished product is packaged in amber, type III glass bottles of 150 ml nominal capacity, each safely closed with a high density polyethylene (HDPE), child-resistant, tamper-evident screw cap with a low density polyethylene (LDPE) liner.

A 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and a “press-in” syringe/bottle adapter are also provided in each pack.

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

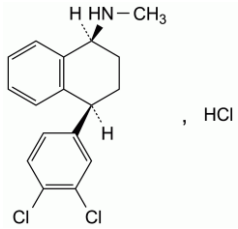
II.2 ACTIVE SUBSTANCE

rINN: **Sertraline hydrochloride**

Chemical Name: (1*S*,4*S*)-4-(3,4-Dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride

Molecular Formula: $C_{17}H_{18}Cl_3N$

Chemical Structure:



Molecular Weight: 342.7 g/mol

Appearance: White or almost white, crystalline powder.

Solubility: Slightly soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, slightly soluble in acetone and in 2-propanol.

Sertraline hydrochloride is the subject of a European Pharmacopoeia monograph.

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

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

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

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

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months for the unopened product, with the storage conditions ‘Store below 25°C’ for the unopened product, is acceptable.

The product should be used within 2 months of first opening.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of sertraline 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.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of sertraline hydrochloride are well-known. With the exception of data from three bioequivalence studies, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence studies.

Bioequivalence Study 1 (Pilot study, single-dose, fasting conditions)
This study was an open-label, randomised, single-dose, three-treatment, three-sequence, three-period, crossover, comparative bioavailability study of two test batches of Sertraline 50 mg/5 ml oral Suspension (Test-1 and Test-2) and the reference product Lustral (sertraline) 50 mg Film-coated tablets in healthy, adult, human, subjects under fasting conditions.

After an overnight fast for at least 10 hours, subjects were administered a single dose (50 mg) of either the test (5 ml of 50 mg/5 ml oral suspension) or reference product (1 x 50 mg tablet) with approximately 240 ml of dosing water.

Blood samples were taken pre-dose and up to 72 hours post-dose in each period. A washout period of 18 and 19 days was maintained between study periods.

A summary of the pharmacokinetic results is presented below:

For Test (T1) vs. Reference (R):

PK Parameters (Units)	Geometric Least Squares Means and its ratio (N=12)			Intra-subject CV (%)	90% Confidence Interval	Power (%)
	Test Product (T1)	Reference Product (R)	(T1/R) (%)			
C_{max} (ng/mL)	15.373	14.825	103.70	11.53	95.64% - 112.43%	99.67
AUC_{0-72} (hr*ng/mL)	420.475	418.001	100.59	9.50	94.10% - 107.54%	99.97

For Test (T2) vs. Reference (R):

PK Parameters (Units)	Geometric Least Squares Means and its ratio (N=12)			Intra-subject CV (%)	90% Confidence Interval	Power (%)
	Test Product (T2)	Reference Product (R)	(T2/R) (%)			
C_{max} (ng/mL)	15.896	14.825	107.22	11.53	98.89% - 116.26%	99.67
AUC_{0-72} (hr*ng/mL)	438.807	418.001	104.98	9.50	98.20% - 112.22%	99.97

Bioequivalence Study 2 (pivotal, single-dose, fasting conditions)
This study was an open-label, randomised, single-dose, two-treatment, two-sequence, two-period, crossover, comparative bioavailability study of the test product Sertraline 50 mg/5 ml Oral Suspension (Test-1 and Test-2) and the reference product Lustral (sertraline) 50 mg Film-coated tablets in healthy, adult, human, subjects under fasting conditions.

Blood samples were taken pre-dose and up to 72 hours post-dose in each period. A washout period of 18 days was maintained between study periods.

A summary of the pharmacokinetic results is presented below:

Parameters (Units)	Geometric Least Squares Means and it's ratio (N = 28)			ISCV (%)	90 % Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (ng/mL)	14.271	13.045	109.40	18.36	100.68 % - 118.86 %	99.61
AUC_{0-72} (hr*ng/mL)	409.695	394.984	103.72	13.87	97.40 % - 110.46 %	99.99

Conclusion of Bioequivalence Study 1 and Study 2
Although the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test products and the reference product, the applicant's conclusion of bioequivalence between the test products and the reference product is not accepted. The use of the 50 mg dose strength is not acceptable as the reference product is available as a 100 mg strength and the posology of the drug product covers a 100 mg. In accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/14001/98 Rev1, the highest strength tablet (Lustral 100 mg film coated tablets) should have been used to demonstrate bioequivalence. Higher strengths have better discriminatory power to detect any potential differences between the test and reference products.

In response to the raised major clinical objection, the applicant submitted the results of the below bioequivalence study. The study was performed to detect the differences between Test products (Test 1 and Test 2) and Reference product (R). Test 2 used in this bioequivalence study was one of the registration batches submitted in the dossier with the same composition as the product used in the previous bioequivalence study against the 50 mg strength of the reference product (Bioequivalence study 2). Test 1 was a second formulation with a different composition to Test 2, which was not relevant to this application. Therefore, only the pharmacokinetic results pertaining to the Test 2 test product and the reference product (R) are discussed in this report.

Bioequivalence Study 3
This study was an open-label, randomised, single-dose, three-treatment, six-sequence, three-period, crossover, comparative bioavailability study of two different test formulations (Test 1 and Test 2) of Sertraline 50 mg/5 ml Oral Suspension (100 mg) with the reference product Lustral (sertraline) 100 mg Film-coated Tablets, in healthy, adult, human subjects under fasting conditions.

After an overnight fast for at least 10 hours, subjects were administered a single dose (100 mg) of either the test (10 ml of 50 mg/5 ml oral suspension) or reference product (1 x 100 mg tablet) with approximately 240 ml of dosing water.

For the test products, subjects were instructed to open the mouth and the investigational product was administered using syringe. The syringe was rinsed thrice with dosing water and given to the subject followed by the remaining amount of 240 ± 2 ml dosing water.

Blood samples were taken pre-dose and up to 72 hours post-dose in each period. A washout period of 24 days was kept between period 1 and period 2 dosing and 19 days was kept between period 2 and period 3 dosing.

A summary of the pharmacokinetic results for Test 2 versus the reference product is presented below:

Bioequivalence data – Test 2

Pharmacokinetic parameter	Geometric Mean Ratio Test 2/Ref	Confidence Intervals	CV %[1]
$AUC_{(0-72)}$[2]	102.23	95.08 % - 109.91 %	16.86
C_{max}	108.28	98.87 % - 118.57 %	21.24

[1]Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV % using only the reference product data.
[2]In some cases $AUC_{(0-72)}$

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product (Test 2) and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

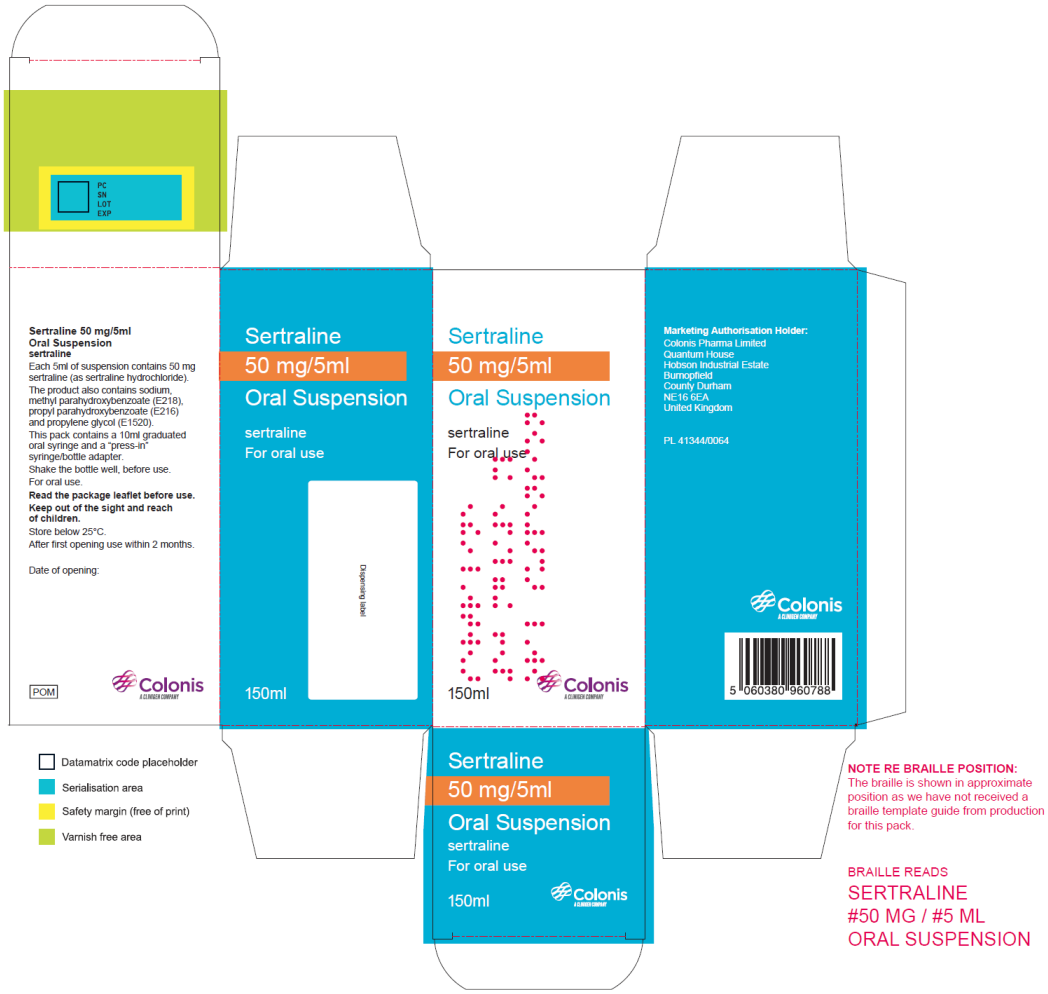
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sertraline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


PC
SN
LOT
EXP
Sertraline 50 mg/5ml Oral Suspension
sertraline
Each 5ml of suspension contains 50 mg sertraline (as sertraline hydrochloride).
The product also contains sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and propylene glycol (E1520).
This pack contains a 10ml graduated oral syringe and a "press-in" syringe/bottle adapter.
Shake the bottle well, before use.
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C.
After first opening use within 2 months.
Date of opening:
POM
Colonis
Sertraline
50 mg/5ml
Oral Suspension
sertraline
For oral use
Opening date
150ml
Sertraline
50 mg/5ml
Oral Suspension
sertraline
For oral use
150ml
Colonis
Marketing Authorisation Holder:
Colonis Pharma Limited
Quantum House
Hobson Industrial Estate
Burnopfield
County Durham
NE16 6EA
United Kingdom
PL 41344/0064
Colonis
5 060380 960788
Sertraline
50 mg/5ml
Oral Suspension
sertraline
For oral use
150ml
Colonis
Datamatrix code placeholder
Serialisation area
Safety margin (free of print)
Varnish free area
NOTE RE BRAILLE POSITION:
The braille is shown in approximate position as we have not received a braille template guide from production for this pack.
BRAILLE READS
SERTRALINE
#50 MG / #5 ML
ORAL SUSPENSION

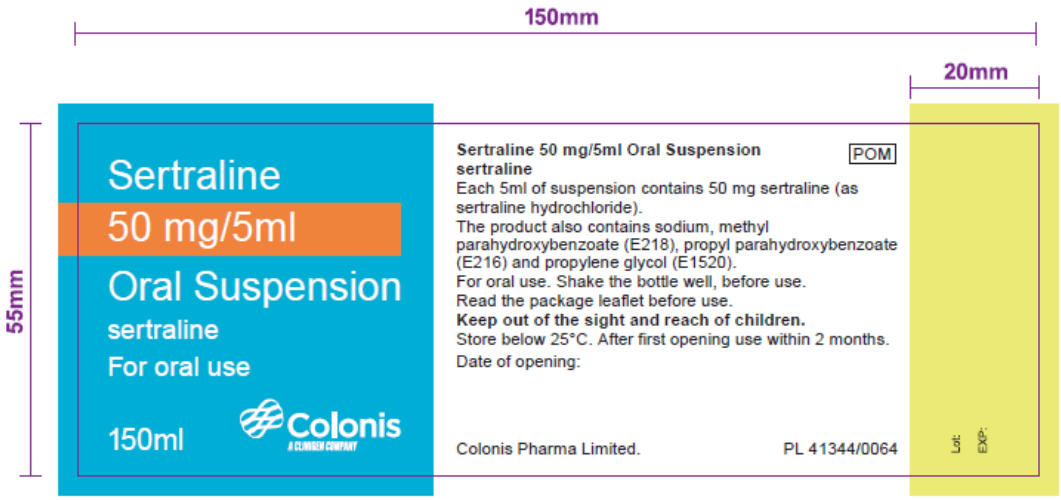

150mm
20mm
55mm
Sertraline
50 mg/5ml
Oral Suspension
sertraline
For oral use
150ml
Colonis
Sertraline 50 mg/5ml Oral Suspension
sertraline
POM
Each 5ml of suspension contains 50 mg sertraline (as sertraline hydrochloride).
The product also contains sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and propylene glycol (E1520).
For oral use. Shake the bottle well, before use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C. After first opening use within 2 months.
Date of opening:
Colonis Pharma Limited.
PL 41344/0064
Lot:
EXP:

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**