Safeguarding public health

MHRA

Public Assessment Report

SERTRALINE 50 MG TABLETS
SERTRALINE 100 MG TABLETS

(SERTRALINE HYDROCHLORIDE)

PL 20658/0001-2

Medicines and Healthcare products Regulatory Agency

SERTRALINE TABLETS

(sertraline hydrochloride) PL 20658/0001-2

UKPAR

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SERTRALINE 50 AND 100 MG TABLETS
(SERTRALINE HYDROCHLORIDE)
PL 20658/0001-2

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Torrent Pharma GmbH Marketing Authorisation (licence) for the medicinal products Sertraline 50 mg and 100 mg Tablets (PL 20658/0001-2). Sertraline tablets are indicated for treatment of symptoms of depressive illness, including the accompanying symptoms of anxiety.
This is a prescription only medicine [POM].

The clinical data presented to the MHRA, before licensing, demonstrated that sertraline tablets are bioequivalent to the reference product, Lustral Tablets, first approved in the United Kingdom on 19th November 1990 (PLs 00057/0308 and 0309).
Based on the information provided, sertraline tablets from Torrent Pharma are interchangeable with Lustral Tablets.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using sertraline tablets outweigh the risks; hence a Marketing Authorisation has been granted.

SERTRALINE 50 AND 100 MG TABLETS

(SERTRALINE HYDROCHLORIDE)

PL 20658/0001-2

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products sertraline tablets (PL 20658/0001-2) to Torrent Pharma GmbH on 23rd March 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC as amended, claiming essential similarity to Lustral Tablets (Pfizer) first approved in The United Kingdom on 19th November 1990.

The product contains the active ingredient sertraline hydrochloride. 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 to 200 mg. After oral administration of sertraline in man, peak blood levels occur within 4.5 to 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 to 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 to 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 (less than 0.2%) of unchanged sertraline is excreted in the urine.

PHARMACEUTICAL ASSESSMENT

LICENCE NO:	PL 20658/0001-2
PROPRIETARY NAME:	Sertraline 50mg and 100mg Tablets
ACTIVE(S):	Sertraline
COMPANY NAME:	Torrent Pharmaceuticals Limited
E.C. ARTICLE:	Article 10.1 [formerly Article 10.1(a)(iii) of Directive 2001/83/EC]
LEGAL STATUS:	POM

1. INTRODUCTION

1.1 Legal Basis

These national abridged, complex and standard applications for oral immediate release tablets containing 50 and 100mg of sertraline are submitted under Article 10.1 [formerly Article 10.1(a)(iii)], claiming essential similarity to Lustral Tablets, which were first authorised in the UK on 19th November 1990 (PLs 00057/0308 and 0309). In support of these applications, Torrent has provided a bioequivalence study performed by Vulm a.s of Slovakia using Zoloft (brand name in Germany, Austria and Denmark) 100 mg tablets, manufactured by Pfizer, Germany as the reference product. Hence, the 10 year rule is complied with.

1.2 Use

The active, Sertraline hydrochloride, is a naphthaleneamine derivative, is a selective serotonin re-uptake inhibitor with actions and uses similar to those of fluoxetine. It is administered by mouth and in the treatment of depression, the usual initial dose is 50 mg daily, increased, if necessary, in increments of 50 mg at intervals of at least a week to a maximum of 200 mg daily.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Sertraline 50 mg and 100 mg Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain Sertraline hydrochloride equivalent to 50mg and 100mg of Sertraline respectively. The tablets are packed into a white opaque blister of PVC film coated with PVdc and aluminium foil coated with heat sealable lacquer of vinyl monochlorohexane (VMCH). The proposed shelf-life (24 months) and storage conditions (This medicinal product does not require any special storage conditions) are consistent with the details registered for the cross-reference products.

2.3 Legal status

These products will be subject to a medical prescription.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is Torrent Pharma GmbH, Gregor-Umhof-Strasse 11, 76694 Forst, Germany.
The Qualified Person responsible for pharmacovigilance is stated and their CV is included.

2.5 TSE

The applicant has provided a declaration that no materials of animal origin are used in manufacture of the finished product. Supporting statements to the same effect have been provided from suppliers of the following excipients: Magnesium stearate, propylene glycol and polysorbate 80. This is acceptable.

DRUG SUBSTANCE

The manufacturer and the site of manufacture is Torrent Pharmaceuticals Limited (TPL), Ahmdebad Mehsana Highway post office – Indrad, Taluka Kadi, District: Mehana – 382 721, Gujarat, India.

The finished product manufacturer has also provided a drug substance specification. Certificates of Analysis (CoAs) for batches of the drug substance tested on receipt have been provided.

Analytical Procedures

Analytical procedures are described.

Validation of Analytical Procedures

Satisfactory validation data are provided for the analytical procedures.

Batch Analysis

Results of industrial scale batches of sertraline are within specification.

Reference standards

Satisfactory primary and working reference standards are identified.

Stability

Batches stored under ICH real time conditions show compliance with set limits during the approved retest period.

DOSAGE FORM

Composition

The composition is satisfactory and tabulated below.

Name of constituents	Function	Reference to Standards
Active constituent		
Sertraline Hydrochloride	Active	Ph. Eur
Other constituents		
Microcrystalline Cellulose		Ph. Eur
Sodium Starch Glycollate (Type A)		Ph. Eur
Calcium Hydrogen Phosphate Dihydrate		Ph. Eur
Hydroxypropyl Cellulose		Ph. Eur
Polysorbate		Ph. Eur
Magnesium Stearate		Ph. Eur
Hypromellose 6 CPS	Coat	Ph. Eur
Propylene Glycol	Coat	Ph. Eur
Titanium Dioxide	Coat	Ph. Eur

PHARMACEUTICAL DEVELOPMENT

Excipients

The formulation is film-coated tablets, comprising of excipients that comply with Ph. Eur. The function and concentration of the excipients used is standard and accepted.
The applicant has stated that each batch of excipients is fully tested according to the proposed specifications upon receipt. Raw materials are not tested prior to use in the finished product provided the raw material is still within its retest period. This is acceptable.

Pharmacokinetic studies

Satisfactory CoAs are provided for the biobatches.

Container Closure System

Sertraline tablets are packed in blisters of white opaque PVC film (coated with 90 GSM PVDC film on one side) sealed with printed aluminium lidding foil with VMCH heat seal lacquer.

Each blister strip contains 10 tablets. The blister strips are packed in printed cartons containing a total of 30 tablets (3 strips of 10).
Data are provided for the primary packaging to show compliance with EU food safety requirements

Microbiological Attributes

The microbiological attributes are controlled in the finished product specification to Ph. Eur. 5.1.4 category 3A and accepted.

Compatibility
Stated ‘not relevant’ but can be inferred from the product stability data, and accepted.

MANUFACTURE

GMP Statement and Manufacturing Chain
The manufacturing site for the product is Torrent Pharmaceuticals Limited, Mehsana 382 721, Gujarat, India. Responsibilities at this site also include assembly and packaging. A satisfactory copy of the German manufacturing licence/GMP report is provided. The site of batch release is Biokanol Pharma GmbH, Kehler Strasse 7, Rastatt D-76437, Germany, for which a satisfactory of the Marketing Authorisation is provided.

Description of the Manufacturing Process
A satisfactory formula and description of manufacture are provided.
There are no re-processing required for manufacture.

Critical phases of the manufacturing process have been satisfactorily identified and appropriate in-process controls are in place.

The analytical methods and limits are the same as those used in finished product testing and comply with current guidelines and accepted. The tablets are blister packed with satisfactory in-process controls.

In-process batch data for validation batches are satisfactory. The validation results demonstrate homogeneity of blends and consistent manufacture.

The validation protocol provided is considered adequate for the purpose.

Control of Excipients
The list of excipients, complying with Ph. Eur. requirements, is given under “Composition of the medicinal product” above.

Satisfactory Certificates of Analysis have been provided for each excipient and are accepted. The compendial methodology is used in testing.

Specifications
A satisfactory finished product specification is provided.

Analytical Procedures
Satisfactory validation data are provided.

Batch data
Satisfactory data are provided for batches manufactured at the proposed site and are considered representative of the product to be marketed. Dissolution data including standard deviations and profiles are reported.

Characterisation of Impurities
This is satisfactory.

Reference Samples
Reference samples are identified.

Container Closure System
Satisfactory details of supplier specification, product construction, standards and compliance statements are provided. In-house specification giving details of tests performed on receipt are provided.

Standard Storage Conditions
Based on stability data at real time and accelerated conditions. The data support the product shelf-life of 24 months with no special storage conditions.

The samples provided for stability studies are representative of the product to be marketed in the proposed pack.

The programme is ongoing. The stability programme is satisfactory as the applicant has agreed to place the first three commercial/production batches on stability.

Bioanalytical Methods and Validation
Satisfactory methodology and validation data are provided.

Quality Overall Summary
This is satisfactory.

Essential Similarity
The following data support essential similarity:

a) Acceptable choice of test and reference products
b) Acceptable bioequivalence between test and reference product
c) Comparative dissolution profiles are provided for test and reference product
d) The impurity profile of the test product is comparable with that of the reference product and considered satisfactory
e) The active substance comply with relevant principles in ICH guidelines

PRODUCT PARTICULARS

Product Brand Name
This is considered satisfactory.

Summary of Product Characteristics
Satisfactory SPC provided.

Patient Information Leaflet
Satisfactory coloured mock-ups are provided**.** The applicant has until 1st July 2008 to amend the order in which the information appears in the leaflet and provide user testing

data (both parts of Article 59, Directive 2004/27/EC must be complied with at the same time).

Labelling
Satisfactory.

MARKETING AUTHORISATION APPLICATION (MAA) form
This is satisfactory.

ADDITIONAL DATA REQUIREMENTS
Satisfactory.

CONCLUSION
A product licence may be granted for this product.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND

These are generic application for sertraline tablets claiming essential similarity to Lustral Tablets (Pfizer, UK)

2. INDICATIONS

Satisfactory

3. DOSE & DOSE SCHEDULE

Satisfactory

4. TOXICOLOGY

No new data.

5. CLINICAL PHARMACOLOGY

The applicant presents data from a randomised comparative single dose two treatment two period two way cross-over study of test 100 mg tablets vs originator 100 mg tablets.

Results:

Parameter	Mean	St.dev.	Mean (geometric)
AUC_t(ng.hr/ml)	961.53	247.43	929.91
AUC (ng.hr/ml)	1035.16	260.50	1003.22
C_{max} (ng/ml)	41.19	7.39	40.41
T_{max} (hrs)	4.89	0.83	4.82
MRT (hrs)	41.00	7.95	40.26
K_{e1}(1/hrs)	0.024	0.006	0.023
$T_{1/2}$(hrs)	31.37	9.75	30.13

Parameter	Mean	St.dev.	Mean (geometric)
AUC_t(ng.hr/ml)	956.44	242.46	924.51
AUC (ng.hr/ml)	1028.88	238.23	1000.52
C_{max} (ng/ml)	41.33	8.01	40.44
T_{max} (hrs)	4.74	0.92	4.65
MRT (hrs)	41.53	6.28	41.08
K_{e1}(1/hrs)	0.023	0.006	0.023
$T_{1/2}$(hrs)	31.00	11.53	31.48

Parameter	ANOVA latin square confidence intervals on ln transformed data		
	Point estimate	90%	Result
AUC_t(ng.hr/ml)	1.006	0.969 – 1.044	Bioequivalent
AUC (ng.hr/ml)	1.003	0.963 – 1.044	Bioequivalent
C_{max} (ng/ml)	0.999	0.979 – 1.020	Bioequivalent

6. EFFICACY
No new data.

7. SAFETY
No new data.

8. EXPERT REPORT
A Clinical Overview has been provided in CTD Module 2.5.
A Clinical Summary has not been provided in CTD Module 2.7.
Information about the Clinical Expert is provided in CTD Module 1.4.3.

9. SUMMARY OF PRODUCT CHARACTERISTICS
The SPCs are considered satisfactory and are consistent with the SPC for the reference product.

10. PATIENT INFORMATION LEAFLET
The PILs are considered satisfactory and are consistent with the PIL for the reference product.

11. LABELLING
The labelling is considered satisfactory.

12. DISCUSSION
The 90% CI for ratios of AUC test:reference and C_{max} test:reference both fall within the guideline range 80 - 125%. The claim of essential similarity is justified.

12. CONCLUSIONS
Marketing authorisation is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

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

EFFICACY

Sertraline is a well known drug and has been used as treatment for symptoms of depressive illnesses for many years. Bioequivalence has been demonstrated between the applicant's and the innovator product. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with sertraline is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

SERTRALINE 50 AND 100 MG TABLETS (SERTRALINE HYDROCHLORIDE)
PL 20658/0001-2

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 11th November 2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 12th December 2003
3	Medical assessment started on 2nd March 2004
4	The MHRA requested further Medical information on 2nd March 2004
5	The applicant responded to the MHRA's requests, providing further information on 24th March 2004
6	Pharmaceutical assessment started on 4th August 2004
7	The MHRA requested further Pharmaceutical information on 16th August 2004
8	The applicant responded to the MHRA's requests, providing further information on 22nd October 2004
9	Following assessment of the companies response the MHRA requested additional Pharmaceutical information on 22nd October 2004
10	Additional information was received from by the MHRA on 26th July 2005
11	A final request for additional information was produced on the 27th July 2005
12	The applicant responded to the MHRA's final requests and the assessment was completed on 20th of March 2006
13	The application was determined on 23rd March 2006

SERTRALINE 1.25, 2.5, 5 AND 10MG TABLETS

(SERTRALINE HYDROCHLORIDE)

PL 20658/0001-2

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

SERTRALINE 50 MG TABLETS (SERTRALINE HYDROCHLORIDE)
PL 20658/0001

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sertraline 50mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains sertraline hydrochloride equivalent to 50mg sertraline.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Sertraline 50mg Tablets are white to off white, capsule shaped, biconvex, film-coated tablets with bisecting line on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Sertraline 50mg tablets are indicated for treatment of symptoms of depressive illness, including the accompanying symptoms of anxiety.

Following satisfactory response, continuation of sertraline therapy is useful in preventing relapse of an initial episode of depression or recurrence of further depressive episodes, including accompanying symptoms of anxiety.

Sertraline 50mg tablets are also indicated for treatment of obsessive compulsive disorder (OCD). Following a satisfactory initial response, sertraline has been related to effective, safe and tolerable maintenance therapy for treatment of OCD up to two years.

Sertraline is also indicated for treatment of paediatric patients with OCD.

Whilst clinical trials showed efficacy in treatment of post-traumatic stress disorder (PTSD) in females, so far there has been no evidence for the same in males. Therefore, Sertraline 50mg tablets are normally not recommended for male patients with PTSD. Should a therapeutic trial in males be justified, treatment should only continue subsequently if a clear therapeutic benefit is evident.

Sertraline is not indicated for use in children and adolescents under the age of 18 years with major depressive disorder.

In particular, controlled clinical studies failed to show efficacy and do not justify the use of sertraline in treatment of children and adolescents with major depressive disorder (see also sections 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

4.2. Posology and method of administration

Sertraline 50mg tablets should be given as a single daily dose; administered with or without food. Sertraline 50mg tablets are only for oral administration.

Adults

DEPRESSION (including accompanying symptoms of anxiety)
Sertraline treatment is initiated at a dose of 50 mg once daily. The usual antidepressant dose is 50 mg daily; however some patients may require higher doses.

OBSESSIVE COMPULSIVE DISORDER (OCD)
The starting dose of sertraline is 50 mg once daily. The therapeutic dose range is 50 to 200 mg daily.

POST-TRAUMATIC STRESS DISORDER (PTSD)
Treatment of patients with PTSD should be initiated with a dose of 25 mg per day. After one week, the daily dose should be increased to 50 mg. Dosing should be periodically reviewed for response as PTSD is a heterogeneous condition and some patients meeting the criteria of PTSD may not appear to be responsive to sertraline therapy. The treatment should be withdrawn if there is no clear evidence of efficacy.

DEPRESSION (including accompanying symptoms of anxiety), OCD AND PTSD
Some patients may require daily doses higher than 50 mg. For patients showing an incomplete response but good toleration to lower doses, dosage adjustments should be made in 50 mg increments over a period of weeks, up to a maximum of 200 mg daily.

After achieving the optimal therapeutic response the dose should be reduced, depending on therapeutic response, to the lowest effective level. Patients requiring prolonged maintenance therapy should be maintained at the lowest effective level with subsequent adjustments depending on the therapeutic response to the treatment. The onset of the therapeutic effect of sertraline may be seen within 7 days, although it usually takes 2 to 4 weeks (and even longer in OCD) to obtain full activity. In case of therapeutic trial in PTSD a longer treatment period (beyond 12 weeks in some cases) may be required.

Use in children aged 6-17 years

Treatment should be initiated by specialists only. The safety and efficacy of sertraline has been established in paediatric (6-17 years) OCD patients. The administration of sertraline to paediatric OCD patients between 13 and 17 years of age should be initiated with 50 mg per day; the therapy for paediatric OCD patients between 6 and 12 years of age should be initiated with 25 mg per day and then increased to 50 mg per day after one week. Subsequent dosages may be increased (in case there is no response) in 50mg/day increments up to 200 mg daily as needed. However, in advancing the doses from 50 mg care should be taken to avoid excessive dosing by taking into consideration the lower body weights of the children compared to adults.

Due to the 24 hour elimination half-life of sertraline dose changes should not occur at intervals of less than one week.

The efficacy and safety of sertraline in children and adolescents under the age of 18 years with major depressive disorder have not been established. Controlled clinical studies failed to show efficacy and do not justify the use of sertraline in treatment of children and adolescents with major depressive disorder (see also sections 4.3 Contraindications 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

Children aged less than 6 years

Sertraline is not recommended in children below 6 years of age as its safety and efficacy have not been established. See also section 5 Pharmacological properties.

Use in the elderly

No special precautions are required. The usual adult dose is recommended in the elderly. The incidence and pattern of adverse reactions in the elderly population is similar to that in younger patients.

Withdrawal symptoms seen on discontinuation of SSRI

Abrupt discontinuation should be avoided. When stopping treatment with sertraline the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 Special warnings and special precautions for use and section 4.8 Undesirable effects). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3. Contraindications

Sertraline 50mg tablets are contraindicated in patients with a known hypersensitivity to sertraline.

MONOAMINE OXIDASE INHIBITORS
Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA) moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of a drug interaction with a MAOI include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of the vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Sertraline should not be used in combination with a MAOI. Sertraline may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA) moclobemide. At minimum a period of 14 days should elapse after discontinuing sertraline treatment before starting a MAOI or RIMA.

USE IN HEPATIC IMPAIRMENT
There is insufficient clinical experience available in patients with significant hepatic dysfunction and therefore sertraline should not be used in such patients.

Concomitant use of sertraline in patients receiving pimozide is contraindicated; see section 4.5 Interaction with other medicaments and other forms of interaction.

Sertraline should not be used in children and adolescents under the age of 18 years with major depressive disorder (see section 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

4.4. Special warnings and precautions for use

MONOAMINE OXIDASE INHIBITORS
See section 4.3 Contraindications.

USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT
Sertraline should be used with caution in patients with renal and hepatic impairment (see also Contraindications).
Sertraline is extensively metabolized and hence urinary excretion of unchanged drug is a minor route of elimination. Single dose pharmacokinetic parameters in patients with mild to moderate or severe renal impairment (creatinine clearance 20-50 ml/min and less than 20 ml/min, respectively) were not significantly different compared with control. However, steady state pharmacokinetics of sertraline

have not been adequately studied in this patient population and Sertraline 50mg tablets should be used with caution when treating patients with renal impairment.
Sertraline is extensively metabolized by the liver. In patients with mild, stable cirrhosis a prolongation in the elimination half life and about a three fold increase in C_{max} and AUC was observed in comparison with normal subjects during a multiple dose pharmacokinetic study. There were no significant differences observed in plasma protein binding between the two groups. The use of sertraline in patients with hepatic disease should be approached with caution; a lower or less frequent dose should be used in patients with hepatic impairment.

DIABETES
Treatment with an SSRI in patients with diabetes may alter the glycaemic control, possibly due to improvement of depressive symptoms. Dosage of insulin and/or oral hypoglycaemic dugs may need to be adjusted.

SEIZURES
Seizures are a potential risk with antidepressant and antiobsessional drugs. The drug should be discontinued in any patient who develops seizures. Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued if an increase in seizure frequency occurs.

ELECTROCONVULSIVE THERAPY (ECT)
Since there is little clinical experience of concurrent administration of sertraline and ECT, caution is advisable.

MANIA
Sertraline should be used with caution in patients with a history of mania/hypomania and therapy should be discontinued in any patient entering a manic phase.

SUICIDE/SUICIDAL THOUGHTS
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of the treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.
Other psychiatric conditions for which sertraline is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precaution is observed when treating patients with other psychiatric disorders.
Patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Patients, (and caregivers of patients) should be alerted to the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

HAEMORRHAGE
There have been reports of cutaneous bleeding abnormalities such as purpura and ecchymoses with SSRIs.
Caution is advised in patients on SSRI therapy, particularly in concomitant administration with drugs known to affect platelet function e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs); also in patients with a history of bleeding disorders.

PSYCHOMOTOR RESTLESSNESS
The use of sertraline has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjective unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of sertraline.

WITHDRAWAL SYMPTOMS SEEN ON DISCONTINUATION OF SSRI TREATMENT

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 20% of patients treated with sertraline.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation, or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients the may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within two weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that sertraline should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal symptoms seen on discontinuation of sertraline", section 4.2 Posology and method of administration).

USE IN THE ELDERLY

The incidence and pattern of adverse reaction in the elderly population is similar to that in younger patients.

USE IN CHILDREN AND ADOLESCENTS UNDER 18 YEARS OF AGE

The safety profile of sertraline in paediatric patients (children above 6 years of age) with OCD and in adolescents under 18 years of age with OCD (more than 250 patients in various studies) is comparable to that observed in the adult OCD studies. Safety and effectiveness in paediatric patients below 6 years of age have not been established.

Except for patients with OCD as above, sertraline tablets should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken the patient should be carefully monitored for the appearance of suicidal symptoms.

In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

4.5. Interactions with other medicinal products and other forms of interaction

MONOAMINE OXIDASE INHIBITORS

See section 4.3 Contraindications.

CENTRALLY ACTIVE MEDICATION

Sertraline should be used with caution when administered with other centrally active medication. In particular, SSRIs have the potential to interact with tricyclic antidepressants leading to an increase in plasma levels of the tricyclic antidepressant. A possible mechanism for this interaction is the inhibitory effect of SSRIs on the CYP2D6 isoenzyme. There is variability among SSRIs in the extent to which they inhibit the activity of CYP2D6. The clinical significance of this interaction depends on the degree of inhibition and the therapeutic index of the co-administered drug. In formal interaction studies chronic dosing with sertraline 50 mg daily showed minimal increase (mean 23-37%) of steady state plasma desipramine levels (a marker of CYP2D6 activity).

Pimozide: Increased pimozide levels have been demonstrated in a study with single low dose pimozide (2 mg) with co-administered sertraline. The increase in pimozide levels were not linked to any changes in ECG. The mechanism of this interaction is not known but due to the narrow therapeutic index of pimozide, concomitant use of sertraline and pimozide is contraindicated.

ALCOHOL

No adverse effect was found on cognitive or psychomotor performance (relative to placebo) when healthy subjects taking 200 mg sertraline per day for 9 days were given a single dose of 550 mg/kg

alcohol. However, concomitant use of sertraline and alcohol in depressed patients is not recommended.

LITHIUM AND TRYPTOPHAN
Co-administration of sertraline and lithium did not significantly alter lithium pharmacokinetics (in a placebo controlled trial in normal volunteers).
However, co-administration of sertraline with lithium did result in increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. There have been other reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of SSRIs with these drugs should be undertaken with caution.

SEROTONERGIC DRUGS
There is limited controlled experience regarding optimal timing of switching from other antidepressant or antiobsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Until further data available, serotonergic drugs, such as tramadol, sumatriptan or fenfluramine, should not be used concomitantly with sertraline, due to a possible enhancement of 5-HT associated effects.

ST JOHN'S WORT (Hypericum perforatum)
Since there is a possibility of serotonergic potentiation, concomitant use of herbal remedy St John's wort in patients receiving SSRIs should be avoided.

DRUGS THAT AFFECT PLATELET FUNCTION, SUCH AS NSAIDs
See section 4.4 Special warnings and special precautions for use (haemorrhage).

OTHER DRUG INTERACTIONS
Sertraline is bound to plasma proteins; the potential of interaction with other plasma protein bound drugs should be borne in mind.

Formal drug interaction studies that have been performed with sertraline are as follows: -

Co-administration of sertraline (200 mg daily) with diazepam or tolbutamide resulted in small but statistically significant changes in some pharmacokinetic parameters.

Co-administration with cimetidine caused a substantial decrease in the sertraline clearance. The clinical significance of these changes is unknown.

Sertraline had no effect on beta-adrenergic blocking ability of atenolol.

No interaction was observed between sertraline and glibenclamide or digoxin.

Co-administration of sertraline with warfarin caused a small yet statistically significant increase in prothrombin time; the clinical significance of this effect is unknown. Therefore, prothrombin time should be monitored carefully when sertraline therapy is initiated or terminated.

Sertraline (200 mg daily) did not potentiate the effects of carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects.

4.6. Pregnancy and lactation

PREGNANCY
Although animal studies did not provide any evidence of teratogenicity, the safety of sertraline during human pregnancy has not been established. Sertraline should be used during pregnancy only if the potential benefits of the treatment to the mother outweigh the possible risks to the developing foetus.

LACTATION
Sertraline is known to be excreted in breast milk; its effects on the nursing infant have not yet been established. If treatment with sertraline is considered necessary, discontinuation of breast feeding should be considered.

4.7. Effects on ability to drive and use machines

Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However as antidepressant or anti-obsessional drugs may impair the abilities required performing potentially hazardous tasks such as driving a car or operating machinery, patients such be cautioned accordingly. Sertraline should not be administered with benzodiazepines or other tranquillizers in patients who drive or operate machinery.

4.8. Undesirable effects

The side-effects which occurred significantly more frequently with sertraline than placebo in multiple dose studies were nausea, diarrhoea/loose stools, anorexia, dyspepsia, tremor, dizziness, insomnia, somnolence, increased sweating, dry mouth and sexual dysfunction (primarily delayed ejaculation in males).

The side-effect profile commonly observed in double-blind, placebo-controlled studies in patients with OCD and PTSD was similar to that observed in patients with depression.

In paediatric patients with OCD the following side-effects occurred significantly more frequently with sertraline than placebo: headache, insomnia, agitation, anorexia, tremor. Most of those side effects were of mild to moderate severity.

Post-marketing spontaneously reports have included the following side-effects:

Cardiovascular: Blood pressure disturbances including postural hypotension, tachycardia.

Eye disorders: Abnormal vision.

Gastro-intestinal: Vomiting, abdominal pain.

Nervous system: Amnesia, headache, drowsiness, movement disorders, paraesthesia, hypoaesthesia, depressive symptoms, hallucinations, aggressive reaction, agitation, anxiety, psychosis, depersonalisation, nervousness, panic reaction and signs and symptoms associated with serotonin syndrome which include fever, rigidity, confusion, agitation, diaphoresis, tachycardia, hypertension and diarrhoea.

Psychomotor restlessness/akathisia has been reported rarely (see section 4.4 Special warnings and precautions for use).

There have also been reports of manic reaction; although this phenomenon may be part of the underlying disease.

Convulsions (seizures): Sertraline should be discontinued in any patient who develops seizures. See section 4.4 Special warnings and special precautions for use.

Musculoskeletal: Arthralgia, myalgia.

Hepatic/pancreatic: Rare reports of pancreatitis and serious liver events (including hepatitis, jaundice and liver failure). Asymptomatic elevations in serum transaminases (SGOT and SGPT) have been reported in association with sertraline administration (0.8-1.3%); with an increased risk associated with the 200 mg daily dose. The abnormalities usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Renal & urinary disorders: Urinary retention.

Reproductive disorders: Hyperprolactinemia, galactorrhoea, menstrual irregularities, anorgasmy.

Skin and allergic reactions: Rash (including rare reports of erythema multiforme, photosensitivity), angioedema, ecchymoses, pruritus and anaphylactoid reactions.

Metabolic: There have been rare reports of hyponatremia, which appeared to be reversible when sertraline was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients, and patients taking diuretics or other medications.

Haematologic: There have been rare reports of altered platelet function and/or abnormal clinical laboratory results in patients taking sertraline. While there have been reports of thrombocytopenia, abnormal bleeding or purpura in several patients taking sertraline it is not clear whether sertraline had a causative role. See also section 4.4 Special warnings and special precautions for use.

General: Malaise.

Withdrawal symptoms seen on discontinuation of SSRI treatment: Discontinuation of sertraline (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation and anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when sertraline treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use).

Adverse events from paediatric clinical trials
In paediatric clinical trials in depression the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: dry mouth (2.1% vs. 0.5%), hyperkinesia (2.6% vs. 0.5%), tremor (2.1% vs. 0%), diarrhoea (9.5% vs. 1.6%), vomiting (4.2% vs. 1.1%), agitation (6.3% vs. 1.1%), anorexia (5.3% vs. 1.1%) and urinary incontinence (2.1% vs. 0%).

Suicidal thoughts and suicide attempts were mainly observed in clinical trials with major depressive disorder.

4.9. Overdose

On the evidence available sertraline has a wide margin of safety in overdose with overdoses of sertraline alone up to 8 g having been reported. Deaths involving overdoses of sertraline in combination with other drugs and/or alcohol have been reported; therefore any overdosage should be treated aggressively.

Symptoms of overdose include serotonin-mediated side-effects like somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness. Less frequently reported was coma.

No specific therapy is recommended and there are no specific antidotes to sertraline. Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. It is recommended monitoring cardiac and vital signs along with general and symptomatic measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group
Selective serotonin reuptake inhibitors

ATC code
N06AB06

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 is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals.

Unlike tricyclic antidepressants, no weight gain is observed with treatment for depression.

Sertraline has not been found to produce physical or psychological dependence.

Sertraline has been evaluated in paediatric OCD patients aged 6 to 17 in a 12 week placebo-controlled study. Therapy for paediatric OCD patients (aged 6-12) commenced at 25 mg per day increasing to 50 mg/day after one week. Side-effects which occurred significantly more frequently with sertraline than placebo were: insomnia, anorexia, tremor (13-17 years). There is limited evidence of efficacy and safety beyond 12 weeks of treatment.

5.2. Pharmacokinetic properties

Sertraline exhibits dose proportional pharmacokinetics over a range of 50 to 200 mg. After oral administration of sertraline in man, peak blood levels occur within 4.5 to 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 to 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 to 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 (less than 0.2%) of unchanged sertraline is excreted in the urine.

The pharmacokinetics of sertraline in paediatric OCD patients have been shown to be comparable with adults, although paediatric patients metabolise sertraline with slightly higher efficiency. However, lower doses may be advisable for paediatric patients given their lower body weights (especially 6-12 years), in order to avoid excessive plasma levels.

A clear relationship between sertraline concentration and the magnitude of therapeutic response has not been established.

The pharmacokinetics of sertraline in elderly patients are similar to younger adults.

Food does not significantly change the bioavailability of sertraline.

5.3. Preclinical safety data

Extensive chronic safety evaluation studies in animals demonstrate that sertraline is generally well tolerated at considerable multiple levels of the clinically effective doses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core
Microcrystalline cellulose (E460)
Sodium starch glycollate (type A)
Calcium hydrogen phosphate dihydrate (E341)
Hydroxypropyl cellulose (E463)
Polysorbate 80 (E433)
Magnesium stearate (E572)

Coat
Hypromellose 6 cp (E464)
Propylene glycol (E1520)
Titanium dioxide (E171)

6.2. Incompatibilities

None

6.3. Shelf life

24 months

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Sertraline tablets are packed in blisters of white opaque PVC film (coated with 90 GSM PVDC film on one side) sealed with printed aluminium lidding foil with VMCH heat seal lacquer.

Each blister strip contains 10 tablets. The blister strips are packed in printed cartons containing a total of 30 tablets (3 strips of 10).

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Torrent Pharma GmbH
Gregor-Umhof-Strasse 11,
76694 Forst
Germany

8. MARKETING AUTHORISATION NUMBER

PL 20658/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/03/2006

10 DATE OF REVISION OF THE TEXT

23/03/2006

SERTRALINE 100 MG TABLETS (sertraline hydrochloride)
PL 20658/0002

1. NAME OF THE MEDICINAL PRODUCT

Sertraline 100mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains sertraline hydrochloride equivalent to 100mg sertraline.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Sertraline 100mg Tablets are white to off white, capsule shaped, biconvex, film-coated tablets with bisecting line on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Sertraline 100mg tablets are indicated for treatment of symptoms of depressive illness, including the accompanying symptoms of anxiety.

Following satisfactory response, continuation of sertraline therapy is useful in preventing relapse of an initial episode of depression or recurrence of further depressive episodes, including accompanying symptoms of anxiety.

Sertraline 100mg tablets are also indicated for treatment of obsessive compulsive disorder (OCD). Following a satisfactory initial response, sertraline has been related to effective, safe and tolerable maintenance therapy for treatment of OCD up to two years.

Sertraline is also indicated for treatment of paediatric patients with OCD.

Whilst clinical trials showed efficacy in treatment of post-traumatic stress disorder (PTSD) in females, so far there has been no evidence for the same in males. Therefore, Sertraline 50mg tablets are normally not recommended for male patients with PTSD. Should a therapeutic trial in males be justified, treatment should only continue subsequently if a clear therapeutic benefit is evident.

Sertraline is not indicated for use in children and adolescents under the age of 18 years with major depressive disorder.

In particular, controlled clinical studies failed to show efficacy and do not justify the use of sertraline in treatment of children and adolescents with major depressive disorder (see also sections 4.3 Contraindications 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

4.2. Posology and method of administration

Sertraline 100mg tablets should be given as a single daily dose; administered with or without food.

Sertraline 100mg tablets are only for oral administration.
Adults

DEPRESSION (including accompanying symptoms of anxiety)
Sertraline treatment is initiated at a dose of 50 mg once daily. The usual antidepressant dose is 50 mg daily; however some patients may require higher doses.

OBSESSIVE COMPULSIVE DISORDER (OCD)
The starting dose of sertraline is 50 mg once daily. The therapeutic dose range is 50 to 200 mg daily.

POST-TRAUMATIC STRESS DISORDER (PTSD)
Treatment of patients with PTSD should be initiated with a dose of 25 mg per day. After one week, the daily dose should be increased to 50 mg. Dosing should be periodically reviewed for response as PTSD is a heterogeneous condition and some patients meeting the criteria of PTSD may not appear to be responsive to sertraline therapy. The treatment should be withdrawn if there is no clear evidence of efficacy.

DEPRESSION (including accompanying symptoms of anxiety), OCD AND PTSD
Some patients may require daily doses higher than 50 mg. For patients showing an incomplete response but good toleration to lower doses, dosage adjustments should be made in 50 mg increments over a period of weeks, up to a maximum of 200 mg daily.

After achieving the optimal therapeutic response the dose should be reduced, depending on therapeutic response, to the lowest effective level. Patients requiring prolonged maintenance therapy should be maintained at the lowest effective level with subsequent adjustments depending on the therapeutic response to the treatment. The onset of the therapeutic effect of sertraline may be seen within 7 days, although it usually takes 2 to 4 weeks (and even longer in OCD) to obtain full activity. In case of therapeutic trial in PTSD a longer treatment period (beyond 12 weeks in some cases) may be required.

Use in children aged 6-17 years

Treatment should be initiated by specialists only. The safety and efficacy of sertraline has been established in paediatric (6-17 years) OCD patients. The administration of sertraline to paediatric OCD patients between 13 and 17 years of age should be initiated with 50 mg per day; the therapy for paediatric OCD patients between 6 and 12 years of age should be initiated with 25 mg per day and then increased to 50 mg per day after one week. Subsequent dosages may be increased (in case there is no response) in 50mg/day increments up to 200 mg daily as needed. However, in advancing the doses from 50 mg care should be taken to avoid excessive dosing by taking into consideration the lower body weights of the children compared to adults.

Due to the 24 hour elimination half-life of sertraline dose changes should not occur at intervals of less than one week.

The efficacy and safety of sertraline in children and adolescents under the age of 18 years with major depressive disorder have not been established. Controlled clinical studies failed to show efficacy and do not justify the use of sertraline in treatment of children and adolescents with major depressive disorder (see also sections 4.3 Contraindications 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

Children aged less than 6 years

Sertraline is not recommended in children below 6 years of age as its safety and efficacy have not been established. See also section 5 Pharmacological properties.

Use in the elderly

No special precautions are required. The usual adult dose is recommended in the elderly. The incidence and pattern of adverse reactions in the elderly population is similar to that in younger patients.

Withdrawal symptoms seen on discontinuation of SSRI

Abrupt discontinuation should be avoided. When stopping treatment with sertraline the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 Special warnings and special precautions for use and section 4.8 Undesirable effects). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3. Contraindications

Sertraline 100mg tablets are contraindicated in patients with a known hypersensitivity to sertraline.

MONOAMINE OXIDASE INHIBITORS
Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA) moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of a drug interaction with a MAOI include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of the vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Sertraline should not be used in combination with a MAOI. Sertraline may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA) moclobemide. At minimum a period of 14 days should elapse after discontinuing sertraline treatment before starting a MAOI or RIMA.

USE IN HEPATIC IMPAIRMENT
There is insufficient clinical experience available in patients with significant hepatic dysfunction and therefore sertraline should not be used in such patients.

Concomitant use of sertraline in patients receiving pimozide is contraindicated; see section 4.5 Interaction with other medicaments and other forms of interaction.

Sertraline should not be used in children and adolescents under the age of 18 years with major depressive disorder (see section 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

4.4. Special warnings and precautions for use

MONOAMINE OXIDASE INHIBITORS
See section 4.3 Contraindications.

USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT
Sertraline should be used with caution in patients with renal and hepatic impairment (see also Contraindications).
Sertraline is extensively metabolized and hence urinary excretion of unchanged drug is a minor route of elimination. Single dose pharmacokinetic parameters in patients with mild to moderate or severe renal impairment (creatinine clearance 20-50 ml/min and less than 20 ml/min, respectively) were not significantly different compared with control. However, steady state pharmacokinetics of sertraline have not been adequately studied in this patient population and Sertraline 50mg tablets should be used with caution when treating patients with renal impairment.
Sertraline is extensively metabolized by the liver. In patients with mild, stable cirrhosis a prolongation in the elimination half life and about a three fold increase in C_{max} and AUC was observed in comparison with normal subjects during a multiple dose pharmacokinetic study. There were no significant differences observed in plasma protein binding between the two groups. The use of sertraline in patients with hepatic disease should be approached with caution; a lower or less frequent dose should be used in patients with hepatic impairment.

DIABETES
Treatment with an SSRI in patients with diabetes may alter the glycaemic control, possibly due to improvement of depressive symptoms. Dosage of insulin and/or oral hypoglycaemic dugs may need to be adjusted.

SEIZURES
Seizures are a potential risk with antidepressant and antiobsessional drugs. The drug should be discontinued in any patient who develops seizures. Sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued if an increase in seizure frequency occurs.

ELECTROCONVULSIVE THERAPY (ECT)
Since there is little clinical experience of concurrent administration of sertraline and ECT, caution is advisable.

MANIA
Sertraline should be used with caution in patients with a history of mania/hypomania and therapy should be discontinued in any patient entering a manic phase.

SUICIDE/SUICIDAL THOUGHTS
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of the treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.
Other psychiatric conditions for which sertraline is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precaution is observed when treating patients with other psychiatric disorders.
Patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Patients, (and caregivers of patients) should be alerted to the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

HAEMORRHAGE
There have been reports of cutaneous bleeding abnormalities such as purpura and ecchymoses with SSRIs.
Caution is advised in patients on SSRI therapy, particularly in concomitant administration with drugs known to affect platelet function e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs); also in patients with a history of bleeding disorders.

PSYCHOMOTOR RESTLESSNESS
The use of sertraline has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjective unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of sertraline.

WITHDRAWAL SYMPTOMS SEEN ON DISCONTINUATION OF SSRI TREATMENT
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 20% of patients treated with sertraline.
The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation, or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally

these symptoms are mild to moderate, however, in some patients the may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within two weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that sertraline should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal symptoms seen on discontinuation of sertraline", section 4.2 Posology and method of administration).

USE IN THE ELDERLY
The incidence and pattern of adverse reaction in the elderly population is similar to that in younger patients.

USE IN CHILDREN AND ADOLESCENTS UNDER 18 YEARS OF AGE
The safety profile of sertraline in paediatric patients (children above 6 years of age) with OCD and in adolescents under 18 years of age with OCD (more than 250 patients in various studies) is comparable to that observed in the adult OCD studies. Safety and effectiveness in paediatric patients below 6 years of age have not been established.
Except for patients with OCD as above, sertraline tablets should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken the patient should be carefully monitored for the appearance of suicidal symptoms.
In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

4.5. Interactions with other medicinal products and other forms of interaction

MONOAMINE OXIDASE INHIBITORS
See section 4.3 Contraindications.

CENTRALLY ACTIVE MEDICATION
Sertraline should be used with caution when administered with other centrally active medication. In particular, SSRIs have the potential to interact with tricyclic antidepressants leading to an increase in plasma levels of the tricyclic antidepressant. A possible mechanism for this interaction is the inhibitory effect of SSRIs on the CYP2D6 isoenzyme. There is variability among SSRIs in the extent to which they inhibit the activity of CYP2D6. The clinical significance of this interaction depends on the degree of inhibition and the therapeutic index of the co-administered drug. In formal interaction studies chronic dosing with sertraline 50 mg daily showed minimal increase (mean 23-37%) of steady state plasma desipramine levels (a marker of CYP2D6 activity).
Pimozide: Increased pimozide levels have been demonstrated in a study with single low dose pimozide (2 mg) with co-administered sertraline. The increase in pimozide levels were not linked to any changes in ECG. The mechanism of this interaction is not known but due to the narrow therapeutic index of pimozide, concomitant use of sertraline and pimozide is contraindicated.

ALCOHOL
No adverse effect was found on cognitive or psychomotor performance (relative to placebo) when healthy subjects taking 200 mg sertraline per day for 9 days were given a single dose of 550 mg/kg alcohol. However, concomitant use of sertraline and alcohol in depressed patients is not recommended.

LITHIUM AND TRYPTOPHAN
Co-administration of sertraline and lithium did not significantly alter lithium pharmacokinetics (in a placebo controlled trial in normal volunteers).
However, co-administration of sertraline with lithium did result in increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. There have been other reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of SSRIs with these drugs should be undertaken with caution.

SEROTONERGIC DRUGS
There is limited controlled experience regarding optimal timing of switching from other antidepressant or antiobsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Until further data available, serotonergic drugs, such as tramadol, sumatriptan or fenfluramine, should not be used concomitantly with sertraline, due to a possible enhancement of 5-HT associated effects.

ST JOHN'S WORT (Hypericum perforatum)
Since there is a possibility of serotonergic potentiation, concomitant use of herbal remedy St John's wort in patients receiving SSRIs should be avoided.

DRUGS THAT AFFECT PLATELET FUNCTION, SUCH AS NSAIDs
See section 4.4 Special warnings and special precautions for use (haemorrhage).

OTHER DRUG INTERACTIONS
Sertraline is bound to plasma proteins; the potential of interaction with other plasma protein bound drugs should be borne in mind.

Formal drug interaction studies that have been performed with sertraline are as follows: -

Co-administration of sertraline (200 mg daily) with diazepam or tolbutamide resulted in small but statistically significant changes in some pharmacokinetic parameters.

Co-administration with cimetidine caused a substantial decrease in the sertraline clearance. The clinical significance of these changes is unknown.

Sertraline had no effect on beta-adrenergic blocking ability of atenolol.

No interaction was observed between sertraline and glibenclamide or digoxin.

Co-administration of sertraline with warfarin caused a small yet statistically significant increase in prothrombin time; the clinical significance of this effect is unknown. Therefore, prothrombin time should be monitored carefully when sertraline therapy is initiated or terminated.

Sertraline (200 mg daily) did not potentiate the effects of carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects.

4.6. Pregnancy and lactation

PREGNANCY
Although animal studies did not provide any evidence of teratogenicity, the safety of sertraline during human pregnancy has not been established. Sertraline should be used during pregnancy only if the potential benefits of the treatment to the mother outweigh the possible risks to the developing foetus.

LACTATION
Sertraline is known to be excreted in breast milk; its effects on the nursing infant have not yet been established. If treatment with sertraline is considered necessary, discontinuation of breast feeding should be considered.

4.7. Effects on ability to drive and use machines

Clinical pharmacology studies have shown that sertraline has no effect on psychomotor performance. However as antidepressant or anti-obsessional drugs may impair the abilities required performing potentially hazardous tasks such as driving a car or operating machinery, patients such

be cautioned accordingly. Sertraline should not be administered with benzodiazepines or other tranquillizers in patients who drive or operate machinery.

4.8. Undesirable effects

The side-effects which occurred significantly more frequently with sertraline than placebo in multiple dose studies were nausea, diarrhoea/loose stools, anorexia, dyspepsia, tremor, dizziness, insomnia, somnolence, increased sweating, dry mouth and sexual dysfunction (primarily delayed ejaculation in males).

The side-effect profile commonly observed in double-blind, placebo-controlled studies in patients with OCD and PTSD was similar to that observed in patients with depression.

In paediatric patients with OCD the following side-effects occurred significantly more frequently with sertraline than placebo: headache, insomnia, agitation, anorexia, tremor. Most of those side effects were of mild to moderate severity.

Post-marketing spontaneously reports have included the following side-effects:

Cardiovascular: Blood pressure disturbances including postural hypotension, tachycardia.

Eye disorders: Abnormal vision.

Gastro-intestinal: Vomiting, abdominal pain.

Nervous system: Amnesia, headache, drowsiness, movement disorders, paraesthesia, hypoaesthesia, depressive symptoms, hallucinations, aggressive reaction, agitation, anxiety, psychosis, depersonalisation, nervousness, panic reaction and signs and symptoms associated with serotonin syndrome which include fever, rigidity, confusion, agitation, diaphoresis, tachycardia, hypertension and diarrhoea.

Psychomotor restlessness/akathisia has been reported rarely (see section 4.4 Special warnings and precautions for use).

There have also been reports of manic reaction; although this phenomenon may be part of the underlying disease.

Convulsions (seizures): Sertraline should be discontinued in any patient who develops seizures. See section 4.4 Special warnings and special precautions for use.

Musculoskeletal: Arthralgia, myalgia.

Hepatic/pancreatic: Rare reports of pancreatitis and serious liver events (including hepatitis, jaundice and liver failure). Asymptomatic elevations in serum transaminases (SGOT and SGPT) have been reported in association with sertraline administration (0.8-1.3%); with an increased risk associated with the 200 mg daily dose. The abnormalities usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Renal & urinary disorders: Urinary retention.

Reproductive disorders: Hyperprolactinemia, galactorrhoea, menstrual irregularities, anorgasmy.

Skin and allergic reactions: Rash (including rare reports of erythema multiforme, photosensitivity), angioedema, ecchymoses, pruritus and anaphylactoid reactions.

Metabolic: There have been rare reports of hyponatremia, which appeared to be reversible when sertraline was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients, and patients taking diuretics or other medications.

Haematologic: There have been rare reports of altered platelet function and/or abnormal clinical laboratory results in patients taking sertraline. While there have been reports of thrombocytopenia, abnormal bleeding or purpura in several patients taking sertraline it is not clear whether sertraline had a causative role. See also section 4.4 Special warnings and special precautions for use.

General: Malaise.

Withdrawal symptoms seen on discontinuation of SSRI treatment: Discontinuation of sertraline (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation and anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when sertraline treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use).

Adverse events from paediatric clinical trials
In paediatric clinical trials in depression the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: dry mouth (2.1% vs. 0.5%), hyperkinesia (2.6% vs. 0.5%), tremor (2.1% vs. 0%), diarrhoea (9.5% vs. 1.6%), vomiting (4.2% vs. 1.1%), agitation (6.3% vs. 1.1%), anorexia (5.3% vs. 1.1%) and urinary incontinence (2.1% vs. 0%).

Suicidal thoughts and suicide attempts were mainly observed in clinical trials with major depressive disorder.

4.9. Overdose

On the evidence available sertraline has a wide margin of safety in overdose with overdoses of sertraline alone up to 8 g having been reported. Deaths involving overdoses of sertraline in combination with other drugs and/or alcohol have been reported; therefore any overdosage should be treated aggressively.

Symptoms of overdose include serotonin-mediated side-effects like somnolence, gastrointestinal disturbances (such as nausea and vomiting), tachycardia, tremor, agitation and dizziness. Less frequently reported was coma.

No specific therapy is recommended and there are no specific antidotes to sertraline. Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. It is recommended monitoring cardiac and vital signs along with general and symptomatic measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group
Selective serotonin reuptake inhibitors

ATC code
N06AB06

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 is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals.

Unlike tricyclic antidepressants, no weight gain is observed with treatment for depression.

Sertraline has not been found to produce physical or psychological dependence.

Sertraline has been evaluated in paediatric OCD patients aged 6 to 17 in a 12 week placebo-controlled study. Therapy for paediatric OCD patients (aged 6-12) commenced at 25 mg per day increasing to 50 mg/day after one week. Side-effects which occurred significantly more frequently with sertraline than placebo were: insomnia, anorexia, tremor (13-17 years). There is limited evidence of efficacy and safety beyond 12 weeks of treatment.

5.2. Pharmacokinetic properties

Sertraline exhibits dose proportional pharmacokinetics over a range of 50 to 200 mg. After oral administration of sertraline in man, peak blood levels occur within 4.5 to 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 to 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 to 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 (less than 0.2%) of unchanged sertraline is excreted in the urine.

The pharmacokinetics of sertraline in paediatric OCD patients have been shown to be comparable with adults, although paediatric patients metabolise sertraline with slightly higher efficiency. However, lower doses may be advisable for paediatric patients given their lower body weights (especially 6-12 years), in order to avoid excessive plasma levels.

A clear relationship between sertraline concentration and the magnitude of therapeutic response has not been established.

The pharmacokinetics of sertraline in elderly patients are similar to younger adults.

Food does not significantly change the bioavailability of sertraline.

5.3. Preclinical safety data

Extensive chronic safety evaluation studies in animals demonstrate that sertraline is generally well tolerated at considerable multiple levels of the clinically effective doses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core
Microcrystalline cellulose (E460)
Sodium starch glycollate (type A)
Calcium hydrogen phosphate dihydrate (E341)
Hydroxypropyl cellulose (E463)
Polysorbate 80 (E433)
Magnesium stearate (E572)

Coat
Hypromellose 6 cp (E464)
Propylene glycol (E1520)
Titanium dioxide (E171)

6.2. Incompatibilities

None

6.3. Shelf life

24 months

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Sertraline tablets are packed in blisters of white opaque PVC film (coated with 90 GSM PVDC film on one side) sealed with printed aluminium lidding foil with VMCH heat seal lacquer.

Each blister strip contains 10 tablets. The blister strips are packed in printed cartons containing a total of 30 tablets (3 strips of 10).

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Torrent Pharma GmbH
Gregor-Umhof-Strasse 11,
76694 Forst
Germany

8. MARKETING AUTHORISATION NUMBER

PL 20658/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/03/2006

10 DATE OF REVISION OF THE TEXT

23/03/2006

SERTRALINE 50 AND 100 MG TABLETS
(SERTRALINE HYDROCHLORIDE)
PL 20658/0001-2

PRODUCT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET xxxxxxxxxxxxx

SERTRALINE 50 mg or 100 mg TABLETS

Please read this leaflet carefully before you start to take your medicine.
This leaflet does not contain the complete information about your medicine, but tells you some of the more important things you should know about taking sertraline tablets. Ask your doctor or pharmacist if you have any questions or wish to know more. **Please keep this leaflet – you may need to read it again.**

What's in your medicine?
Each film-coated tablet contains either 50 mg or 100 mg of sertraline (the active substance) as sertraline hydrochloride. They also contain microcrystalline cellulose (E460), sodium starch glycollate, calcium hydrogen phosphate dihydrate (E341), hydroxypropylcellulose (E463), polysorbate 80 (E433) and magnesium stearate (E572). The tablet coating contains hypromellose (E464), propylene glycol (E1520) and titanium dioxide (EI71).
Sertraline 50 mg tablets are capsule shaped, white to off white, film-coated tablets. The tablets have a single score line on one side whilst the other side is plain with no markings.
Sertraline 100 mg tablets are capsule shaped, white to off white, film-coated tablets. The tablets have a single score line on one side whilst the other side is plain with no markings.
Sertraline tablets are available in packs of 30 tablets.

Product licence holder and manufacturer;
Product Licence holder: Torrent Pharma GmbH, Gregor-Umhof-Strasse 11, 76694 Forst, Germany.
Manufacturer: Biokanol Pharma GmbH, Kehler Strasse 7, 76347 Rastatt, Germany.

What your medicine is, and what it is used for;
Sertraline belongs to a group of anti-depressant medicines called Selective Serotonin Reuptake Inhibitors (SSRIs). In adults it is used to treat depression and any connected feelings of anxiety, Obsessive Compulsive Disorder (OCD) and females with Post Traumatic Stress Disorder (PTSD).
It is also used to treat OCD in children aged 6 years or more; **however it should not be used to treat depression in children and adolescents under 18 years.** For further information regarding the use of sertraline in children please refer to the section at the end of this leaflet 'Use of sertraline in children and adolescents'.
Depression is a common medical illness often caused by a decrease in the brain of a substance called serotonin. Sertraline treats depression by bringing the levels of serotonin in the brain back to normal.
OCD is an illness whereby a persistent (obsessive) unpleasant thought, feeling or action causes anxiety and may make you carry out a repetitive impulse (compulsion). PTSD is an anxiety disorder caused by the major personal stress of a serious, frightening or traumatic event. Sertraline may help you if suffer from either OCD or PTSD.
Ask your doctor if you are still unsure why you have been prescribed this medicine.

Before taking your medicine;
Do not take sertraline tablets if you;
- Are allergic to sertraline, or any of the other tablet ingredients.
- Are taking, or have taken at any time within the last two weeks, any medicines known as monoamine oxidase inhibitors (also known as MAOIs).
- Have any serious liver problems.
- Are taking a medicine called pimozide.
- Are a child under 6 years old who suffers from obsessive-compulsive disorder symptoms.
- Are under 18 years of age and are suffering from depression.

Before taking sertraline tablets tell your doctor or pharmacist if you;
- Are pregnant or thinking of becoming pregnant.
- Are breastfeeding.
- Have any liver problems (as your dose or frequency of dosing may have to be reduced).
- Have any kidney problems.
- Have epilepsy, or have had a fit in the past (as sertraline may increase the risk of a fit).
- Are diabetic (as you may need to adjust your dose of insulin or other antidiabetic medication).
- Are having ECT (electro-convulsive therapy) treatment.
- Are a child under 16 years old suffering from panic symptoms.
- Are a male adult suffering from (PTSD) Post Traumatic Stress Disorder (as your treatment will need to be monitored).
- Have ever had thoughts about killing or harming yourself (as you may need additional monitoring during treatment, particularly during the first few weeks).
- Have a history of bleeding disorders.
- Are taking any other medicines, but especially;
  - Lithium, tryptophan, or another antidepressant or antiobsessional drug?
  - Tramadol (a painkiller), sumatriptan (for migraine), fenfluramine (for suppressing appetite).
  - Warfarin (used to thin the blood), diazepam (for anxiety relief), tolbutamide (for diabetes), or cimetidine (for ulcers).
  - Aspirin or NSAIDs (non-steroidal anti-inflammatory drugs) including those that may have been bought without a prescription.
  - St. Johns Wort (a herbal remedy).

Alcohol should be avoided whilst taking this medicine.
You should also note that like most antidepressants sertraline may affect your ability to perform skilled tasks such as driving or operating machinery. If at any stage you feel affected in this way do not drive or use machinery.

Harmful or suicidal thoughts;
Sometimes people suffering from depression and/or anxiety disorders have thoughts about harming or killing themselves, particularly young adults or people who have previously experienced suicidal or harmful thoughts. These thoughts may increase when you first start taking anti-depressants as it takes a few weeks or more for this medicine to start to work.
If at any time you experience any thoughts of suicide or self-harm you should tell your doctor or go to your local hospital straight away.

Taking your medicine;
Dosage
Your doctor will tell you how much you should take and how often. **Always follow your doctor's instructions exactly, and those printed on the pharmacy label.**
The usual dosages are listed below. If you have been prescribed a dose that is different from that below you should discuss it with your doctor, if you haven't already done so.
Adults:
Depression and Obsessive compulsive disorder (OCD):
The usual dose at the start of treatment is 50 mg daily, however your doctor may decide to increase the dose 50 mg at a time, up to a maximum of 200 mg daily.
Post-traumatic stress disorder (PTSD):
The usual dose at the start of treatment is 25 mg (half a 50 mg tablet) daily, increasing after one week to 50 mg daily. Larger doses may also be prescribed, up to a maximum of 200 mg daily.
Adults with poor liver function:
If you have impaired liver function your doctor may prescribe a lower dosage of sertraline than the usual stated above, or prescribe a less frequent dose.
Children:
In children 6-12 years of age treatment normally starts at a dose of 25 mg (half a 50 mg tablet) daily, which may be increased to 50 mg daily after one week. For children 13-17 years of age treatment normally starts with a dose of 50 mg daily. Depending on treatment response doses in 6-17 year olds may be increased up to a maximum of 200 mg daily.
How to take your medicine
Each dose should be swallowed with a drink of water, with or without food. Do not chew or crush the tablets. To help you to remember to take your medicine regularly it is recommended that you try and take each dose at the same time each day.
What to do if you miss a dose
If you forget to take a dose do not worry. Leave out the missed dose completely and take your next dose at the usual time. Do not take two doses at the same time to make up for a forgotten dose.
What to do if you take too much medicine
Always take your medicine as recommended by your doctor. If you take too much medicine tell your doctor or go to your local hospital emergency department immediately, taking the pack of this medicine with you.
After starting to take your medicine
You may need to take sertraline tablets for up to 2-4 weeks before you start to feel better and for the full antidepressant effect of this medicine to become noticeable. During this time the symptoms of depression, which may include thoughts of suicide or self-harm, may remain or increase. Tell you doctor immediately or go to your local hospital emergency department if you have any distressing thoughts or experiences.
Keep taking your medicine for as long as it is prescribed by your doctor, as you may need to keep taking the tablets to stay well even when if you start to feel better.

Stopping treatment with your medicine;
Do not stop taking this medicine until your doctor tells you to, since this may be harmful. When stopping treatment with this medicine your doctor should gradually reduce your dose over a number of weeks or months in order to minimise the chance of withdrawal reactions. For most people any symptoms of withdrawal are mild and usually go away within two weeks, however for some people these symptoms may be more severe or may last longer.
Possible symptoms of withdrawal;
- Feeling dizzy
- Shakiness (tremors)
- Nervous system disturbances, such as tingling sensations (pins and needles)
- Headaches
- Feeling agitated or anxious
- Vomiting or feeling sick
- Sleep disturbances (inability to go to sleep or intense dreams)

Occasionally these symptoms may occur if a dose is missed, therefore it is important that you take your medicine as prescribed by your doctor.
Please tell your doctor immediately should you suffer from withdrawal effects especially if they are severe or long lasting. He or she may ask you to start taking your tablets again and then reduce your dose over a longer period of time.

Possible side-effects;
All medicines sometimes cause unwanted side-effects in some people. Tell your doctor if you think your medicine is making you feel unwell or if you get any of the following side-effects;
An allergic reaction which may occur as;
- Swelling of the eyelids, lips, face, mouth, hands or feet.
- A rash on your skin (which might be severe).
- Sudden wheeziness or tightness in the chest.
- Unexplained fever.
- Skin lumps and hives.

These serious side-effects are rare, **but if you think you are having an allergic reaction stop taking your tablets IMMEDIATELY and tell your doctor or go to your local hospital emergency department as severe allergic reactions may require emergency treatment.**
- Convulsions or fits.
- Mental or physical restlessness or an inability to sit or stand still, particularly during the first few weeks of treatment.
- Liver disorders (including abnormal liver function tests) or jaundice (yellowing of the skin and whites of the eyes).
- Severe pain in the stomach and/or back (which may be caused by an inflamed pancreas).
- Faster heart beat or changes to your blood pressure, including low blood pressure (which may cause you to feel dizzy or unsteady).
- Blood disorders, including an increase in the number of platelets, abnormal bleeding, change in platelet functioning and abnormal blood tests.
- A collection of symptoms called "Serotonin syndrome" which can include fever, sweating, faster heartbeat, high blood pressure, diarrhoea and feelings of confusion, agitation or anxiety,
- Psychological effects such as hallucinations, confusion, anxiety, aggression, psychosis (loss of contact with reality), depersonalisation (a feel of being detached from yourself), nervousness or panic.
- Abnormal vision.
- Lowering of blood sodium levels (which may make you tired, weak, achy or stiff).

These are serious side-effects – **tell your doctor immediately or go to your local hospital emergency department, as you may need medical attention.**
- Sweating.
- Headache.
- Tiredness.
- Dry mouth.
- Vomiting or feeling sick.
- Feeling dizzy or shaky (tremors).
- Loss of appetite, stomach upsets or diarrhoea.
- Inability to go to sleep (insomnia) or sleepiness.
- Urinary retention (not being able to pass water).
- Change in sexual function (e.g. ejaculatory delay in men).
- Tingling sensations (pins and needles) or loss of the sense of touch.
- Skin problems including skin rash, itching, easy bruising, and sensitivity to sunlight.
- Menstrual irregularities and an increase in the hormone prolactin that can lead to abnormal production of breast milk in men and women.

These are mild side-effects, however you should tell your doctor as soon as possible if the effects are troublesome or continue for more than a few days.
Tell your doctor or pharmacist if you experience any other unusual or unexpected side-effects.

Use of sertraline in children and adolescents under 18 years of age
Sertraline should normally not be used for children and adolescents under 18 years except for patients with Obsessive-Compulsive Disorder who are 6 years of age and above.
The most commonly occurring side-effects in children treated for Obsessive-Compulsive Disorder are reported as headache, anorexia, insomnia, tremor and agitation.
When children and adolescents under 18 years of age were treated for depression in clinical trials the following side-effects occurred most commonly with a frequency of at least 2 in 100 patients: hyperactivity, dry mouth, tremor, diarrhoea, vomiting, loss of appetite, agitation and loss of bladder control. Suicide attempts and suicidal thoughts were mainly observed in clinical trials with children and adolescents with depression.
Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe sertraline for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed sertraline for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any symptoms listed above develop or worsen when patients under 18 are taking sertraline. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of sertraline in this age group have not yet been demonstrated.

Storing your medicine
Store in the original package.
This medicinal product does not require any special storage conditions.
Do not use this medicine after the expiry date printed on the pack.
ALWAYS KEEP YOUR MEDICINE OUT OF THE REACH AND SIGHT OF CHILDREN.
Unless your doctor advises otherwise, any unused medicine should be returned to your local pharmacist for safe disposal.
Remember: This medicine is only for you. Never give it to others, even if they have the same symptoms as you it, as it may harm them.
This leaflet was last approved on: January 2006
Distributed by; ©

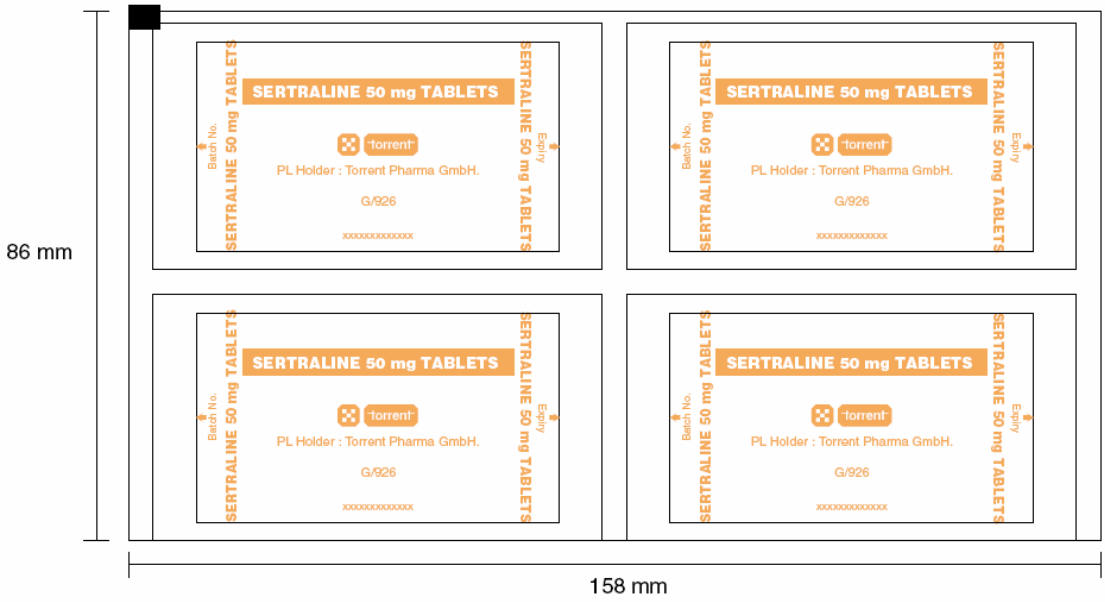
Size : 480 x 130 mm UK F/B

SERTRALINE 50 MG TABLETS (SERTRALINE HYDROCHLORIDE)
PL 20658/0001

CARTON LABELLING

SERTRALINE 50 MG TABLETS (SERTRALINE HYDROCHLORIDE)
PL 20658/0001

BLISTER LABELLING



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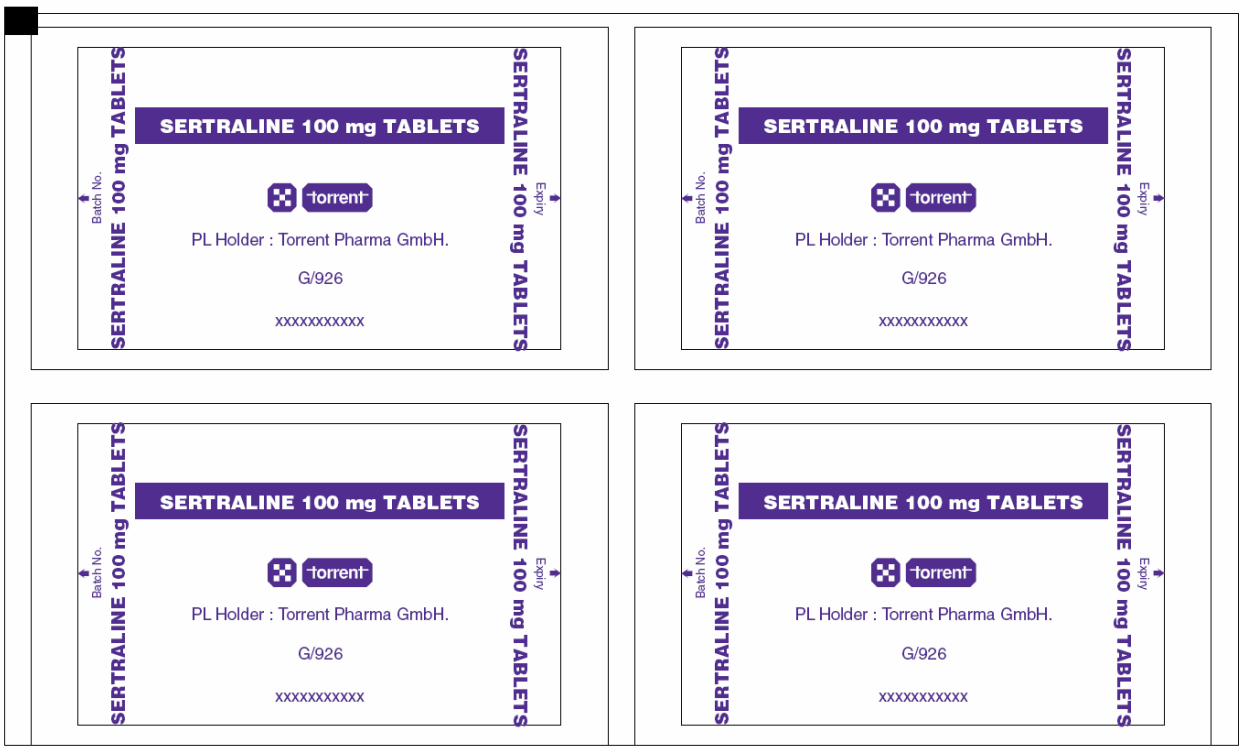
DIMENSIONS (MM) :	158 mm		Reviewed By	Pkg.Dev			
ART WORK SIZE :	S/S			RA			
DATE :	04-08-2005		Approved By	CQA			

SERTRALINE 100 MG TABLETS (SERTRALINE HYDROCHLORIDE)
PL 20658/0002

CARTON LABELLING

SERTRALINE 100 MG TABLETS (SERTRALINE HYDROCHLORIDE)
PL 20658/0002

BLISTER LABELLING



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ART WORK SIZE :	S/S			RA				
DATE :	04-08-2005		Approved By	CQA				