

**SERTRALINE 50MG TABLETS  
(SERTRALINE HYDROCHLORIDE)  
PL 15413/0015**

**SERTRALINE 100MG TABLETS  
(SERTRALINE HYDROCHLORIDE)  
PL 15413/0016**

**UKPAR**

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**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Hikma Farmaceutica (Portugal) SA Marketing Authorisations (licences) for the medicinal products Sertraline 50mg Tablets (PL 15413/0015) and Sertraline 100mg Tablets (PL 15413/0016) on 25<sup>th</sup> April 2007. These are prescription-only medicines (POM) used for the treatment of depression (feelings of sadness, tearfulness, inability to sleep properly or to enjoy life as you used to).

The active ingredient, sertraline, is one of a group of antidepressant or anti-obsessional medicines known as selective serotonin reuptake inhibitors (SSRIs). Low levels of a substance called serotonin in the brain are thought to be a cause of depression and related disorders. SSRIs work by bringing the level of serotonin back up to normal. Sertraline is authorised to treat illnesses other than depression, but the details are not included in the product information for these licences.

These applications are duplicates of previously granted applications for Sertraline 50mg Tablets (PL 20532/0070) and Sertraline 100mg Tablets (PL 20532/0071), held by Aurobindo Pharma Limited. The test and reference products are identical.

No new or unexpected safety concerns arose from these simple applications and it was therefore judged that the benefits of taking Sertraline 50mg Tablets and Sertraline 100mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

The UK granted Hikma Farmaceutica (Portugal) SA Marketing Authorisations for the medicinal products Sertraline 50mg Tablets (PL 15413/0015) and Sertraline 100mg Tablets (PL 15413/0016) on 25<sup>th</sup> April 2007. The products are prescription-only medicines.

These applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended), cross-referring to the Marketing Authorisations Sertraline 50mg Tablets (PL 20532/0070) and Sertraline 100mg Tablets (PL 20532/0071), granted to Aurobindo Pharma Limited on 26<sup>th</sup> October 2005. These abridged applications had been approved as generic medicinal products of Sertraline Tablets 50mg (PL 00057/0308) and Sertraline Tablets 100mg (PL 00057/0309) respectively, granted to Pfizer Limited on 19<sup>th</sup> November 1990.

No new data was submitted nor was it necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PARs were generated for them.

Sertraline 50mg Tablets and Sertraline 100mg Tablets contain the active ingredient sertraline, as the hydrochloride. Sertraline belongs to the SSRI class of drugs, and works by bringing low levels of serotonin back up to normal. 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 50mg Tablets and Sertraline 100mg Tablets are used for the treatment of symptoms of depressive illness.

These applications for Sertraline 50mg Tablets and Sertraline 100mg Tablets were submitted at the same time and were assessed concurrently. Consequently, all sections of this Scientific Discussion refer to both products.

## **PHARMACEUTICAL ASSESSMENT**

<b>LICENCE NUMBERS:</b>	PL 15413/0015 & 0016
<b>PROPRIETARY NAME:</b>	Sertraline 50mg & 100mg Tablets
<b>ACTIVE INGREDIENTS:</b>	Sertraline hydrochloride
<b>COMPANY NAME:</b>	Hikma Farmaceutica (Portugal) SA
<b>E.C. ARTICLE:</b>	Article 10c of Directive 2001/83/EC (as amended)
<b>LEGAL STATUS:</b>	POM

### **1. INTRODUCTION**

These are simple abridged applications, submitted under Article 10c of Directive 2001/83/EC (as amended) for Sertraline 50mg Tablets and Sertraline 100mg Tablets. The proposed MA holder is 'Hikma Farmaceutica (Portugal) SA, Estrado do Rio da mo, Ferveca 2705-906 Terrugum SNT, Portugal'.

The reference products are Sertraline 50mg Tablets (PL 20532/0070) and Sertraline 100mg Tablets (PL 20532/0071), granted to Aurobindo Pharma Limited on 26<sup>th</sup> October 2005. The test and reference products are identical.

### **2. MARKETING AUTHORISATION APPLICATION FORM**

#### **2.1 Name(s)**

The proposed names of the products are Sertraline 50mg Tablets and Sertraline 100mg 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. They are to be stored in blister packs (PVC (polyvinylchloride) or PVC / PVdC (polyvinylidene chloride)) of 10, 14, 28, 30, 42, 50, 56, 84 and 100 tablets, although the MAH has stated that not all pack sizes will be marketed.

The proposed shelf-life (2 years) and storage conditions (Store in the original package) are consistent with the details registered for the cross-reference products.

#### **2.3 Legal status**

The products are available by supply through pharmacies, subject to a medical prescription.

#### **2.4 Marketing authorisation holder/Contact Persons/Company**

The proposed Marketing Authorisation holder is 'Hikma Farmaceutica (Portugal) SA, Estrado do Rio da mo, Ferveca 2705-906 Terrugum SNT, Portugal'.

The QP responsible for pharmacovigilance is stated and their CV is included.

## **2.5 Manufacturers**

The proposed manufacturing site is consistent with that registered for the cross-reference product and evidence of GMP compliance has been provided.

## **2.6 Qualitative and quantitative composition**

The proposed compositions are consistent with the details registered for the cross-reference products.

## **2.7 Manufacturing process**

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

## **2.8 Finished product/shelf-life specification**

The proposed finished product specifications are in line with the details registered for the cross-reference products.

## **2.9 Drug substance specification**

The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

## **2.10 TSE Compliance**

No materials of animal or human origin are included in the products.

## **3. EXPERT REPORTS**

Satisfactory expert reports and curriculum vitae of experts are provided.

## **4. PRODUCT NAME & APPEARANCE**

See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

## **5. SUMMARY OF PRODUCT CHARACTERISTICS**

The approved SmPCs are consistent with the details registered for the cross-reference products.

## **6. PATIENT INFORMATION LEAFLET (PIL) / CARTON**

### PIL

The patient information leaflet has been prepared in the user tested format and in line with the details registered for the cross-reference products. The approved PIL is satisfactory.

Cartons

The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In line with current legislation the applicant has included the name of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

**7. CONCLUSIONS**

The grounds for these applications are considered adequate. It is recommended that Marketing Authorisations are granted for these applications.

## **PRECLINICAL ASSESSMENT**

The applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended).

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



## **CLINICAL ASSESSMENT**

The applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended).

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

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The data for these applications are consistent with that previously assessed for the cross-reference products 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**

Medicinal products containing sertraline have been available in the UK for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

These applications are identical to the cross-reference products Sertraline 50mg Tablets (PL 20532/0070) and Sertraline 100mg Tablets (PL 20532/0071), which were demonstrated to be generic medicinal products of the innovator products Sertraline Tablets 50mg (PL 00057/0308) and Sertraline Tablets 100mg (PL 00057/0309) respectively, granted to Pfizer Limited on 19<sup>th</sup> November 1990.

No new or unexpected safety concerns arise from these applications.

### **PRODUCT LITERATURE**

The approved SPCs, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

### **RISK BENEFIT ASSESSMENT**

The quality of the products 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 hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

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**STEPS TAKEN FOR ASSESMENT**

- 1 The MHRA received the marketing authorisation applications on 5<sup>th</sup> June 2006
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 16<sup>th</sup> August 2006
- 3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 27<sup>th</sup> October 2006
- 4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 2<sup>nd</sup> February 2007
- 5 The applications were determined on 25<sup>th</sup> April 2007

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Sertraline 50mg Tablets is as follows:

### 1 NAME OF THE MEDICINAL PRODUCT

Sertraline 50mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains sertraline hydrochloride equivalent to 50 mg sertraline. For excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Film-coated tablets.

White, capsule shaped, film coated tablets debossed with 'A' on one side and score line in between '8' and '1' on the other side.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Sertraline tablets are indicated for the treatment of symptoms of depressive illness. Following satisfactory response, continuation with Sertraline tablets therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes.

Sertraline tablets are not indicated for use in children and adolescents under the age of 18 years with Major Depressive Disorder.

#### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The lowest effective dose should be used.

The maximum recommended dose (200mg daily) should not be exceeded.

In the event that treatment with sertraline is to be discontinued, the dose should be tapered gradually over a period of several weeks, according to the patient's need, to minimise withdrawal reactions on stopping SSRIs.

#### **Withdrawal symptoms seen on discontinuation of sertraline**

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 section 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.

#### **Adults**

**Depression** The starting dose is 50mg daily and the usual antidepressant dose is 50mg daily. In some patients, doses higher than 50mg may be required. In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50mg increments over a period of weeks to a maximum of 200mg daily.

Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level. Dosage during prolonged maintenance therapy should be kept at the lowest effective level, with subsequent adjustments depending on therapeutic response. The onset of therapeutic effect may be seen within 7 days, although 2-4 weeks are usually necessary for full activity.

### *Children*

The efficacy and safety of Sertraline tablets in children and adolescents under the age of 18 years with Major Depressive Disorder have not been established. Controlled clinical studies failed to demonstrate efficacy and do not support the use of Sertraline tablets in the treatment of children and adolescents with Major Depressive Disorder.

### *Use in the elderly*

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

Sertraline tablets are for oral administration only.

## 4.3 CONTRAINDICATIONS

Sertraline tablets are contra-indicated 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 vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Sertraline tablets should not be used in combination with a MAOI. Sertraline tablets 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 least 14 days should elapse after discontinuing Sertraline tablets treatment before starting a MAOI or RIMA.

***Use in hepatic impairment:*** There is insufficient clinical experience in patients with significant hepatic dysfunction and accordingly Sertraline tablets should not be used in such patients.

Concomitant use in patients taking pimozone is contra-indicated (see section 4.5 - Interaction with other medicaments and other forms of interaction).

Sertraline tablets should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be carefully and frequently monitored in the early stages of treatment, particularly if a patient experiences worsening of symptoms or if new symptoms arise after starting treatment.

The possibility of an adverse reaction to the drug should be considered if a patient is not doing well after starting treatment. Patients should be monitored for signs of restlessness or agitation, particularly at the beginning of treatment. Increasing the dose in these circumstances may be detrimental.

Patients should be monitored particularly carefully around the time of dose changes for any new symptoms or worsening of disease.

To minimise withdrawal reactions on stopping SSRIs, the dose should be tapered gradually over a period of several weeks, according to the patient's need.

Young adults are at a higher background risk of suicidal behaviour than older adults, so as a precautionary measure, young adults treated with SSRIs should be closely monitored.

**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 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 in the early stages of recovery. Further more 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 precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorder.

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 a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

**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 subjectively 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 sertraline**

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 they 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 2 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' in the section 4.2 Posology and Method of Administration).

***Monoamine oxidase inhibitors*** See 'Contra-indications'.

***Use in patients with renal or hepatic impairment:*** As with many other medications, sertraline should be used with caution in patients with renal and hepatic impairment (see 'Contra-indications').

Since sertraline is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 20-50ml/min) or severe renal impairment (creatinine clearance <20ml/min), single dose pharmacokinetic parameters were reported to be not significantly different compared with controls. However, steady state pharmacokinetics of sertraline have not been adequately studied in this patient population and caution is advised when treating patients with renal impairment.

Sertraline is extensively metabolised by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and approximately three-fold greater AUC and  $C_{max}$  in comparison with normal subjects. There were no significant differences in plasma protein binding observed 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:** In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may be needed to be adjusted.

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

**Electroconvulsive therapy (ECT):** Since there is little clinical experience of concurrent administration of Sertraline tablets and ECT, caution is advisable.

**Mania:** Sertraline tablets should be used with caution in patients with a history of mania/hypomania. Sertraline tablets should be discontinued in any patient entering a manic phase.

**Suicide:** As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved and it is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

**Haemorrhage:** There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (*e.g.* atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders.

**Use in the elderly:** Several hundred elderly patients have participated in clinical studies with Sertraline tablets. The pattern and incidence of adverse reactions in the elderly is similar to that in younger patients.

**Use in Children:** The efficacy of Sertraline tablets in paediatric patients with depression has not been demonstrated in controlled trials. Safety and effectiveness in paediatric patients below the age of 6 have not been established.

There is limited knowledge with respect to an effect on sexual development in children.

#### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

**Monoamine oxidase inhibitors:** See 'Contra-indications'.

**Centrally active medication:** Caution is advised if Sertraline tablets are 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 the SSRIs in the extent to which they inhibit the activity of CYP2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered drug. In formal interaction studies, chronic dosing

with sertraline 50mg daily showed minimal elevation (mean 23-37%) of steady state plasma desipramine levels (a marker of CYP2D6 isoenzyme activity).

**Pimozide**– In a controlled study of a single dose (2mg) of pimozide, 200mg sertraline (once daily) coadministered to steady state was associated with a mean increase in pimozide AUC and  $C_{max}$  of about 40%, but was not associated with any changes in ECG. Since the recommended therapeutic dose of pimozide is higher and this has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters of pimozide at doses higher than 2mg at this time are not known. While the mechanism of this interaction is unknown, concomitant administration of sertraline and pimozide is contraindicated due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide (see section 4.3 Contraindications).

**Alcohol:** In 11 healthy subjects administered Sertraline tablets (200mg daily) for 9 days, no adverse effect on cognitive or psychomotor performance relative to placebo, following a single dose of 500mg/kg alcohol has been reported. However, the concomitant use of Sertraline tablets and alcohol in depressed patients is not recommended.

**Lithium and Tryptophan:** Co-administration of Sertraline tablets and lithium did not significantly alter lithium pharmacokinetics in placebo-controlled trials in normal volunteers. However, co-administration of Sertraline tablets with lithium resulted in an 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 the optimal timing of switching from other antidepressant or antiobsessional drugs to Sertraline. Care and prudent medical judgement 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 are available, serotonergic drugs, such as tramadol, sumatriptan or fenfluramine, should not be used concomitantly with Sertraline tablets, due to a possible enhancement of 5-HT associated effects.

**St John's Wort:** Concomitant use of the herbal remedy St John's wort (*Hypericum perforatum*) in patients receiving SSRIs should be avoided since there is a possibility of serotonergic potentiation.

**Drugs that affect platelet function, such as NSAIDs:** See 'Special warnings and special precautions for use (*Haemorrhage*)'.

**Other drug interactions:** Since Sertraline is bound to plasma proteins, the potential of Sertraline tablets to interact with other plasma protein bound drugs should be borne in mind.

Formal drug interaction studies have been performed with Sertraline. Co-administration of Sertraline (200mg daily) with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters.

Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction with Sertraline (200mg daily) was observed with glibenclamide or digoxin.

Co-administration of Sertraline (200mg daily) with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Accordingly, prothrombin time should be carefully monitored when Sertraline tablets therapy is initiated or stopped.

Sertraline (200mg 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. As with all drugs Sertraline tablets should only be used in pregnancy if the potential benefits of 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 tablets 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, since antidepressant or antiobsessional drugs may impair the abilities required to perform potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly. Sertraline tablets should not be administered with benzodiazepines or other tranquillizers in patients who drive or operate machinery.

#### 4.8 UNDESIRABLE EFFECTS

##### **Withdrawal symptoms seen on discontinuation of sertraline**

Discontinuation of sertraline (particularly when abrupt) commonly leads to withdrawal symptoms. 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 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 Special Precautions for use).

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 (principally ejaculatory delay in males).

The following adverse reactions of sertraline have been reported:

**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.

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

Rarely, psychomotor restlessness/akathisia have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

**Convulsions (Seizures):** Sertraline tablets should be discontinued in any patient who develops seizures (See 'Special warnings and special precautions for use').

**Musculoskeletal:** Arthralgia, myalgia.

**Hepatic/pancreatic:** Rarely, 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 200mg 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:** Hyperprolactinemia, galactorrhoea, menstrual irregularities, anorgasmy.

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

**Metabolic:** Rare cases of hyponatremia have been reported and 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 unclear whether sertraline had a causative role. See also 'Special warnings and special precautions for use'.

**General:** Malaise.

**Others:** Withdrawal reactions have been reported with Sertraline tablets. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with Sertraline tablets should be avoided. The majority of symptoms experienced on withdrawal of Sertraline tablets are non-serious and self-limiting.

## 4.9 OVERDOSE

On the evidence available, Sertraline has a wide margin of safety in overdose. Overdoses of Sertraline alone of up to 8g have 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 such as 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. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive 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

ATC code: N06AB06

Category: Selective serotonin reuptake inhibitor

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 observed to produce physical or psychological dependence.

## 5.2 PHARMACOKINETIC PROPERTIES

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

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 tablets.

## 5.3 PRECLINICAL SAFETY DATA

Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Sertraline tablets include the following excipients:

#### *Core tablets:*

Calcium hydrogen phosphate dihydrate  
Cellulose microcrystalline  
Hydroxypropylcellulose  
Sodium starch glycollate (Type A)  
Magnesium stearate

#### *Film coating:*

Opadry White OY-S-7355 containing -  
Titanium dioxide (E171)  
Hypromellose  
Macrogol 400  
Polysorbate-80

### 6.2 INCOMPATIBILITIES

None

### 6.3 SHELF LIFE

2 years

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package.

This medicinal product does not require any special storage conditions

**6.5 NATURE AND CONTENTS OF CONTAINER**

- (i) White opaque PVC – Aluminium blister
- (ii) White opaque PVdC – PVC Aluminium blister

Packs of 10, 14, 28, 30, 42, 50, 56, 84, 100 tablets

Not all packs are marketed.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements

**7 MARKETING AUTHORISATION HOLDER**

Hikma Farmaceutica,  
Estrada do Rio da mo,  
No8, 8A e 8B,  
Ferveca 2705-906 Terrugum SNT  
Portugal

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 15413/0015

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

25/04/2007

**10 DATE OF REVISION OF THE TEXT**

25/04/2007

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Sertraline 100mg Tablets is as follows:

### 1 NAME OF THE MEDICINAL PRODUCT

Sertraline 100mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains sertraline hydrochloride equivalent to 100 mg sertraline. For excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Film-coated tablets.

White, capsule shaped, film coated tablets debossed with 'A' on one side and '82' on the other side.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Sertraline tablets are indicated for the treatment of symptoms of depressive illness. Following satisfactory response, continuation with Sertraline tablets therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depressive episodes.

Sertraline tablets are not indicated for use in children and adolescents under the age of 18 years with Major Depressive Disorder.

#### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The lowest effective dose should be used.

The maximum recommended dose (200mg daily) should not be exceeded.

In the event that treatment with sertraline is to be discontinued, the dose should be tapered gradually over a period of several weeks, according to the patient's need, to minimise withdrawal reactions on stopping SSRIs.

#### **Withdrawal symptoms seen on discontinuation of sertraline**

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 section 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.

#### **Adults**

**Depression** The starting dose is 50mg daily and the usual antidepressant dose is 50mg daily. In some patients, doses higher than 50mg may be required.

In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50mg increments over a period of weeks to a maximum of 200mg daily. Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level. Dosage during prolonged maintenance therapy should be kept at the lowest effective level, with subsequent adjustments depending on therapeutic response. The onset of therapeutic effect may be seen within 7 days, although 2-4 weeks are usually necessary for full activity.

### *Children*

The efficacy and safety of Sertraline tablets in children and adolescents under the age of 18 years with Major Depressive Disorder have not been established. Controlled clinical studies failed to demonstrate efficacy and do not support the use of Sertraline tablets in the treatment of children and adolescents with Major Depressive Disorder.

### *Use in the elderly*

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

Sertraline tablets are for oral administration only.

## 4.3 CONTRAINDICATIONS

Sertraline tablets are contra-indicated 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 vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Sertraline tablets should not be used in combination with a MAOI. Sertraline tablets 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 least 14 days should elapse after discontinuing Sertraline tablets treatment before starting a MAOI or RIMA.

***Use in hepatic impairment:*** There is insufficient clinical experience in patients with significant hepatic dysfunction and accordingly Sertraline tablets should not be used in such patients.

Concomitant use in patients taking pimozone is contra-indicated (see section 4.5 - Interaction with other medicaments and other forms of interaction).

Sertraline tablets should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be carefully and frequently monitored in the early stages of treatment, particularly if a patient experiences worsening of symptoms or if new symptoms arise after starting treatment.

The possibility of an adverse reaction to the drug should be considered if a patient is not doing well after starting treatment. Patients should be monitored for signs of restlessness or agitation, particularly at the beginning of treatment. Increasing the dose in these circumstances may be detrimental.

Patients should be monitored particularly carefully around the time of dose changes for any new symptoms or worsening of disease.

To minimise withdrawal reactions on stopping SSRIs, the dose should be tapered gradually over a period of several weeks, according to the patient's need.

Young adults are at a higher background risk of suicidal behaviour than older adults, so as a precautionary measure, young adults treated with SSRIs should be closely monitored.

**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 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 in the early stages of recovery. Further more 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 precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorder.

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 a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

**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 subjectively 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 sertraline**

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 they 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 2 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' in the section 4.2 Posology and Method of Administration).

***Monoamine oxidase inhibitors*** See 'Contra-indications'.

***Use in patients with renal or hepatic impairment:*** As with many other medications, sertraline should be used with caution in patients with renal and hepatic impairment (see 'Contra-indications').

Since sertraline is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 20-50ml/min) or severe renal impairment (creatinine clearance <20ml/min), single dose pharmacokinetic parameters were reported to be not significantly different compared with controls. However, steady state pharmacokinetics of sertraline have not been adequately

studied in this patient population and caution is advised when treating patients with renal impairment.

Sertraline is extensively metabolised by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and approximately three-fold greater AUC and  $C_{max}$  in comparison with normal subjects. There were no significant differences in plasma protein binding observed 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:** In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may be needed to be adjusted.

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

**Electroconvulsive therapy (ECT):** Since there is little clinical experience of concurrent administration of Sertraline tablets and ECT, caution is advisable.

**Mania:** Sertraline tablets should be used with caution in patients with a history of mania/hypomania. Sertraline tablets should be discontinued in any patient entering a manic phase.

**Suicide:** As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved and it is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

**Haemorrhage:** There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (*e.g.* atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders.

**Use in the elderly:** Several hundred elderly patients have participated in clinical studies with Sertraline tablets. The pattern and incidence of adverse reactions in the elderly is similar to that in younger patients.

**Use in Children:** The efficacy of Sertraline tablets in paediatric patients with depression has not been demonstrated in controlled trials. Safety and effectiveness in paediatric patients below the age of 6 have not been established.

There is limited knowledge with respect to an effect on sexual development in children.

#### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

**Monoamine oxidase inhibitors:** See 'Contra-indications'.

**Centrally active medication:** Caution is advised if Sertraline tablets are 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 the SSRIs in the extent to which they inhibit the activity of CYP2D6. The clinical significance of this depends on the extent of inhibition and the therapeutic index of the co-administered drug. In formal interaction studies, chronic dosing with sertraline 50mg daily showed minimal elevation (mean 23-37%) of steady state plasma desipramine levels (a marker of CYP2D6 isoenzyme activity).



**Pimozide**– In a controlled study of a single dose (2mg) of pimozide, 200mg sertraline (once daily) coadministered to steady state was associated with a mean increase in pimozide AUC and  $C_{max}$  of about 40%, but was not associated with any changes in ECG. Since the recommended therapeutic dose of pimozide is higher and this has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters of pimozide at doses higher than 2mg at this time are not known. While the mechanism of this interaction is unknown, concomitant administration of sertraline and pimozide is contraindicated due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide (see section 4.3 Contraindications).

**Alcohol:** In 11 healthy subjects administered Sertraline tablets (200mg daily) for 9 days, no adverse effect on cognitive or psychomotor performance relative to placebo, following a single dose of 500mg/kg alcohol has been reported. However, the concomitant use of Sertraline tablets and alcohol in depressed patients is not recommended.

**Lithium and Tryptophan:** Co-administration of Sertraline tablets and lithium did not significantly alter lithium pharmacokinetics in placebo-controlled trials in normal volunteers. However, co-administration of Sertraline tablets with lithium resulted in an 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 the optimal timing of switching from other antidepressant or antiobsessional drugs to Sertraline. Care and prudent medical judgement 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 are available, serotonergic drugs, such as tramadol, sumatriptan or fenfluramine, should not be used concomitantly with Sertraline tablets, due to a possible enhancement of 5-HT associated effects.

**St John's Wort:** Concomitant use of the herbal remedy St John's wort (*Hypericum perforatum*) in patients receiving SSRIs should be avoided since there is a possibility of serotonergic potentiation.

**Drugs that affect platelet function, such as NSAIDs:** See 'Special warnings and special precautions for use (*Haemorrhage*)'.

**Other drug interactions:** Since Sertraline is bound to plasma proteins, the potential of Sertraline tablets to interact with other plasma protein bound drugs should be borne in mind.

Formal drug interaction studies have been performed with Sertraline. Co-administration of Sertraline (200mg daily) with diazepam or tolbutamide resulted in small, statistically significant changes in some pharmacokinetic parameters.

Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction with Sertraline (200mg daily) was observed with glibenclamide or digoxin.

Co-administration of Sertraline (200mg daily) with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Accordingly, prothrombin time should be carefully monitored when Sertraline tablets therapy is initiated or stopped.

Sertraline (200mg 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. As with all drugs Sertraline tablets should only be used in pregnancy if the potential benefits of 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 tablets 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, since antidepressant or antiobsessional drugs may impair the abilities required to perform potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly. Sertraline tablets should not be administered with benzodiazepines or other tranquillizers in patients who drive or operate machinery.

#### 4.8 UNDESIRABLE EFFECTS

##### **Withdrawal symptoms seen on discontinuation of sertraline**

Discontinuation of sertraline (particularly when abrupt) commonly leads to withdrawal symptoms. 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 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 Special Precautions for use).

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 (principally ejaculatory delay in males).

The following adverse reactions of sertraline have been reported:

**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.

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

Rarely, psychomotor restlessness/akathisia have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

**Convulsions (Seizures):** Sertraline tablets should be discontinued in any patient who develops seizures (See 'Special warnings and special precautions for use').

**Musculoskeletal:** Arthralgia, myalgia.

**Hepatic/pancreatic:** Rarely, 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 200mg 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:** Hyperprolactinemia, galactorrhoea, menstrual irregularities, anorgasmy.

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

**Metabolic:** Rare cases of hyponatremia have been reported and 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 unclear whether sertraline had a causative role. See also 'Special warnings and special precautions for use'.

**General:** Malaise.

**Others:** Withdrawal reactions have been reported with Sertraline tablets. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with Sertraline tablets should be avoided. The majority of symptoms experienced on withdrawal of Sertraline tablets are non-serious and self-limiting.

## 4.9 OVERDOSE

On the evidence available, Sertraline has a wide margin of safety in overdose. Overdoses of Sertraline alone of up to 8g have 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 such as 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. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive 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

ATC code: N06AB06

Category: Selective serotonin reuptake inhibitor

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 observed to produce physical or psychological dependence.

## 5.2 PHARMACOKINETIC PROPERTIES

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

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 tablets.

## 5.3 PRECLINICAL SAFETY DATA

Extensive chronic safety evaluation studies in animals show that sertraline is generally well tolerated at doses that are appreciable multiples of those that are clinically effective.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Sertraline tablets include the following excipients:

*Core tablets:*

Calcium hydrogen phosphate dihydrate  
Cellulose microcrystalline  
Hydroxypropylcellulose  
Sodium starch glycollate (Type A)  
Magnesium stearate

*Film coating:*

Opadry White OY-S-7355 containing -  
Titanium dioxide (E171)  
Hypromellose  
Macrogol 400  
Polysorbate-80

### 6.2 INCOMPATIBILITIES

None

### 6.3 SHELF LIFE

2 years

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package.

This medicinal product does not require any special storage conditions

**6.5 NATURE AND CONTENTS OF CONTAINER**

- (i) White opaque PVC – Aluminium blister
- (ii) White opaque PVdC – PVC Aluminium blister

Packs of 10, 14, 28, 30, 42, 50, 56, 84, 100 tablets

Not all packs are marketed.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements

**7 MARKETING AUTHORISATION HOLDER**

Hikma Farmaceutica,  
Estrada do Rio da mo,  
No8, 8A e 8B,  
Ferveca 2705-906 Terrugum SNT  
Portugal

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 15413/0016

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

25/04/2007

**10 DATE OF REVISION OF THE TEXT**

25/04/2007

## PATIENT INFORMATION LEAFLET

Package Leaflet : Information for the user

Sertraline 50 & 100mg Tablets  
(Sertraline)

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

- 1) What are Sertraline tablets and what are they used for
- 2) Before you take Sertraline tablets
- 3) How to take Sertraline tablets
- 4) Possible side effects
- 5) How to store Sertraline tablets
- 6) Further information

### 1) What are Sertraline tablets and what are they used for

Sertraline tablets contain the active ingredient sertraline and are used to treat depression.

Sertraline belongs to a group of antidepressant drugs called Selective Serotonin Re-uptake inhibitors.

These tablets are not sleeping tablets or tranquillizers.

If you have been feeling sad, tearful, unable to sleep properly or to enjoy life as you used to, Sertraline tablets may help you to feel better. If you are not sure why you are taking these tablets, ask your doctor.

Sertraline, which is the active ingredient in Sertraline tablets, is also authorised to treat other illnesses, which are not mentioned in this leaflet. Ask your doctor, pharmacist or other healthcare professional if you have any further questions and always follow their instructions.

### 2) Before you take Sertraline tablets

**Do not take Sertraline tablets:**

- If you are allergic to sertraline or any other ingredients of Sertraline tablets.
- If you have any liver and kidney problems.
- If you are taking other antidepressant medicines like MAOIs and Pimozide
- If you are under 18 years

**Take special care with Sertraline tablets:**

Tell your doctor if:

- You are pregnant or think you might be pregnant
- You are breast feeding
- You are suffering from diabetes
- You have ever had an epileptic fit
- You are being treated with electroconvulsive therapy (ECT)
- You have any bleeding disorder

**Taking other medicines**

Please tell your doctor if you are taking or have recently taken the following medicines or any other medicines including medicines obtained without a prescription.

- Lithium or any other anti obsessive drug
- Tryptophan, sumatriptan, fenfluramine, warfarin, diazepam, tolbutamide or cimetidine
- Aspirin or other pain killers known as NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) or another strong painkiller called Tramadol
- Herbal remedy St. John's Wort (*Hypericum perforatum*)

#### **Taking Sertraline tablets with food and drink**

You can take Sertraline tablets with or without meals. Swallow the tablets with water.

Do not consume alcohol during the treatment with Sertraline tablets.

#### **Pregnancy and breast feeding**

The possible effects of Sertraline tablets on unborn child are unknown. You must tell your doctor if you are pregnant or if you think you are pregnant. The doctor will decide if Sertraline tablets are right for you.

The effects of Sertraline tablets on nursing infants are unknown. You must tell your doctor if you are breast feeding so that the doctor can decide if Sertraline tablets are right for you.

#### **Driving and using machines**

You must consult your doctor if you intend to drive or use machinery while taking Sertraline tablets.

### **3) How to take Sertraline tablets**

Always take Sertraline tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Swallow the tablets with a drink of water. Do not crush or chew your tablets. It is best to take them at the same time each day with or without a meal. Keep taking your tablets everyday. The day is written on the pack to help you to remember.

The usual dose of Sertraline tablets for most patients is 50 mg once daily. Doctors may recommend you a higher dose upto a maximum of 200 mg daily. Your doctor will determine the dose that is most suitable for you.

You may need to take Sertraline tablets for up to 2-4 weeks before you start to feel better. Your doctor will want to monitor your progress closely during this period.

You must keep taking Sertraline tablets to help you get better. See your doctor before your tablets run out. Even if you begin to feel better, keep taking your tablets. You may need to keep taking them to stay well.

Thoughts of suicide or self harm can be part of your illness and may even occur or increase as you start to get better. This should improve as your treatment continues. Tell your doctor immediately if you have any distressing thoughts or experiences.

#### **If you take more Sertraline tablets than you should**

Too many tablets at once can be dangerous. If you take too many tablets tell your doctor. If you are unable to contact your doctor, go to your local hospital casualty department at once.

**If you forget to take Sertraline tablets**

If you forget to take your medicine, do not worry and take the next dose at the right time. Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Sertraline tablets**

Do not stop taking Sertraline tablets on your own. Your doctor will advise you when to discontinue the treatment.

Symptoms such as dizziness, tingling, headache, anxiety and nausea may occur if the treatment is stopped too quickly. These symptoms are generally non-serious and disappear within a few days. If you experience symptoms on stopping treatment, contact your doctor.

If you have any further questions on the use of this product ask your doctor or pharmacist.

**4) Possible side effects**

Like all medicines, Sertraline tablets can cause side effects, although not everybody gets them. The frequency of the side effects can be classified as follows:

Very common:	affecting more than 1 in 10 patients treated
Common:	affecting fewer than 10 in 100 patients treated
Uncommon:	affecting fewer than 10 in 1000 patients treated
Rare:	affecting fewer than 10 in 10,000 patients treated

**Gastrointestinal (Stomach) disorders**

Very common	:	Nausea, diarrhoea (loose stools)
Common	:	indigestion (dyspepsia), vomiting, flatulence, abdominal pain, loss of appetite (anorexia)

**Cardiac (Heart) disorders**

Common	:	Palpitations (rapid heart beat)
Uncommon	:	Changes to blood pressure including postural hypotension, dizziness on standing

**Nervous system disorders**

Very common	:	Dry mouth, headache, dizziness, tremor (shaky feeling)
Common	:	Increased sweating, uncontrollable twitching, jerking or writhing movements, tingling sensation (paresthesia), confusion.
Uncommon	:	Movement disorders
Rare:	:	Convulsions

**Psychiatric disorders**

Very common	:	Insomnia (not being able to sleep), somnolence (excessive sleepiness)
Common	:	Agitation, nervousness, anxiety
Uncommon	:	aggressive reaction, amnesia, depressive symptoms, hallucinations, abnormal thinking, mania, panic reactions, loss of feeling of identity, inability to react normally to everyday situations, suicide attempt (including suicidal ideation)

**Skin and allergic reactions**



Common	:	Rash, hot flushes
Rare:	:	Sensitivity to sunlight, erythema multiforme, swelling, severe itching, difficulty in breathing, sudden wheeziness

**Musculoskeletal (Rheumatic) disorders**

Common	:	Joint pains
Uncommon	:	Muscle pain, muscle weakness, rigidity

**Reproductive system**

Uncommon	:	Menstrual disorders
Rare:	:	Breast enlargement, abnormal production of breast milk, change in sex drive or function e.g. ejaculatory delay, inability to experience orgasm.

**Urinary disorders**

Common	:	Urinary retention (inability to pass urine)
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**General disorders**

Very common	:	Fatigue
Common	:	Fever, thirst, weakness, abnormal vision
Uncommon	:	Discomfort (malaise)

Abnormalities in liver function tests, jaundice, inflammation of pancreas or liver, abnormal bleeding, lower sodium content, abnormal tests have also been reported rarely.

Most undesirable effects are usually mild and tend to wear off as you take the tablets for longer. If they cause you discomfort or are long lasting, check with your doctor or pharmacist.

All medicines can cause allergic reactions. Serious allergic reactions are very rare. Any sudden wheeziness, difficulty in breathing, swelling, rash or itching (especially affecting the whole body) should be reported to a doctor immediately.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5) How to store Sertraline tablets**

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Store in the original package.

Do not use Sertraline tablets after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

**6) Further information**

What Sertraline tablets contain:

The active substance is Sertraline. Each film coated tablet contains Sertraline Hydrochloride equivalent to 50 or 100mg Sertraline.

The other ingredients in the tablets are:

*Core:*

Cellulose microcrystalline, Sodium starch glycolate (Type A), Hydroxypropylcellulose, Calcium hydrogen phosphate dihydrate, Magnesium stearate.

*Coating:*

Hypromellose, Macrogol 400, Polysorbate 80 and Titanium dioxide (E171).

**What Sertraline tablets look like and contents of the pack**

Sertraline tablets are Film-coated tablets.

Sertraline 50mg tablets are white capsule shaped, film coated tablets marked with 'A' on one side and with '8' and '1' on the other side.

Sertraline 100mg tablets are white capsule shaped, film coated tablets marked with 'A' on one side and with '82' on the other side.

Sertraline 50 & 100 mg tablets are available in packs of 10, 14, 28, 30, 42, 50, 56, 84 and 100 tablets. Not all packs may be marketed.

**Marketing Authorisation Holder**

Hikma Farmaceutica,  
Estrada do Rio da mo,  
Ferveca 2705-906 Terrugum SNT  
Portugal  
Tel: +351 (0) 21 960 84 10  
Fax: +352 (0) 21 961 51 02

**Manufacturer**

Aurex Generics Limited,  
65 Delamere Road, Hayes,  
Middlesex, UB4 0NN, UK  
Tel: +44 (0) 20 8756 1333  
Fax: +44 (0) 20 8756 1444

This leaflet was last approved in MM/YYYY

**LABELLING**

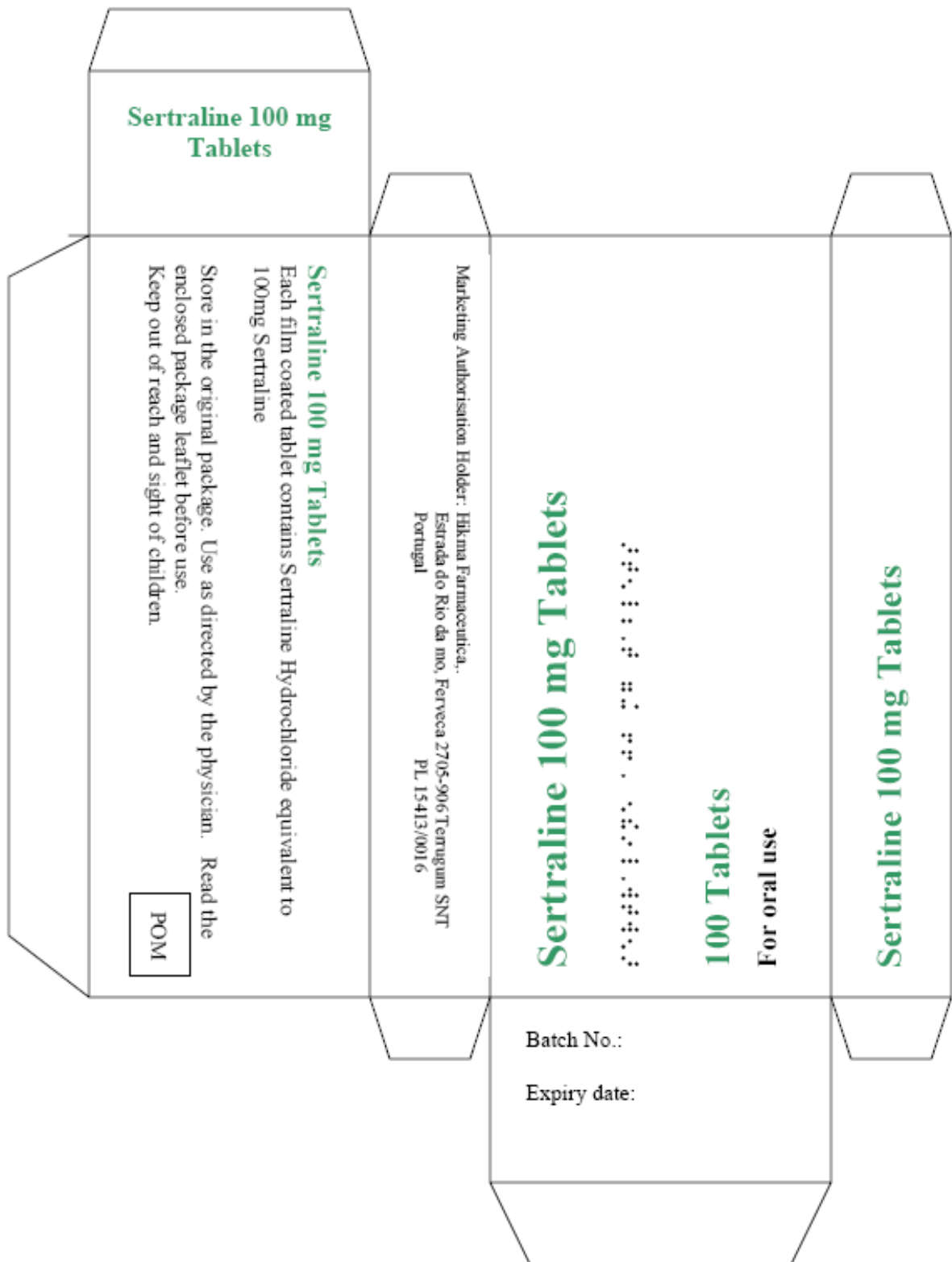
**Sertraline 50mg Tablets**

Carton for blisters, with braille (same design for all pack sizes marketed)



### Sertraline 100mg Tablets

Carton for blisters, with braille (same design for all pack sizes marketed)



**Blister foils**

**Sertraline 50mg Tablets**

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**Sertraline 100mg Tablets**

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