ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Austria	Pfizer Corporation Austria GmbH Floridsdorfer Hauptstr 1, 1210 Wien	Tresleen 50 mg - Filmtabletten	50 mg	Film-coated tablets	Oral use	
Belgium	PFIZER S.A. Boulevard de la Plaine, 17 1050 Brussels	Serlain	50 mg 100 mg	Film-coated tablets	Oral use	
Belgium	PFIZER S.A. Boulevard de la Plaine, 17 1050 Brussels	Serlain	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Bulgaria	PFIZER EUROPE MA EEIG Ramsgate Road Sandwich Kent CT13 9NJ	Zoloft	50 mg	Film-coated tablets	Oral use	50 mg
Cyprus	Pfizer Hellas A.E., 243 Messoghion Ave., 154 51 N. Psychiko, Athens Greece	Zoloft	50 mg, 100 mg	Film Coated Tablet	Oral use	
Czech Republic	Pfizer s.r.o., Stroupežnického 17 150 00 Praha 5 Czech Republic	Zoloft 50 mg Zoloft 100 mg	50 mg 100 mg	Film-coated tablets	Oral use	
Denmark	Pfizer ApS Lautrupvang 8 DK-2750 Ballerup	Zoloft	25 mg, 50 mg, 100 mg	Film-coated tablets	Oral use	
Denmark	Pfizer ApS Lautrupvang 8 DK-2750 Ballerup	Zoloft	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Estonia	Pfizer Europe MA EEIG Ramsgate Road Sandwich	Zoloft	50 mg	Film-coated tablet	Oral use	

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
	Kent CT13 9NJ United Kingdom					
Finland	Pfizer Oy Tietokuja 4 00330 Helsinki	Zoloft	50 mg, 100 mg	Film-coated tablet	Oral use	
Finland	Pfizer Oy Tietokuja 4 00330 Helsinki	Zoloft	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
France	Pfizer Holding France 23-25 avenue du Dr Lannelongue 75014 PARIS	ZOLOFT	25 mg, 50 mg 100 mg	Capsules, hard	Oral use	
France	Pfizer Holding France 23-25 avenue du Dr Lannelongue 75014 PARIS	ZOLOFT	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ ml
France	Pfizer Holding France 23-25 avenue du Dr Lannelongue 75014 PARIS	SERTRALINE PFIZER	25 mg, 50 mg,	Capsules, hard	Oral use	
France	Pfizer Holding France 23-25 avenue du Dr Lannelongue 75014 PARIS	SERTRALINE BERAL	100 mg	Capsules, hard	Oral use	
France	Pfizer Holding France 23-25 avenue du Dr Lannelongue 75014 PARIS	SERTRALINE BERAL	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Germany	Pfizer Pharma GmbH Linkstr. 10 10785 Berlin	Zoloft 50 mg Zoloft 100 mg	50 mg. 100 mg	Film-coated tablet	Oral use	
Germany	Pfizer Pharma GmbH Linkstr. 10 10785 Berlin	Zoloft Lösungskonzentrat	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/m1
Greece	Pfizer Hellas A.E., 243 Messoghion Ave.,	Zoloft	50 mg, 100 mg	Film Coated Tablets	Oral use	

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
	154 51 N. Psychiko Athens Greece					
Hungary	Pfizer Kft. 1123 Budapest Alkotás u. 53. MOM Park F Épület	Zoloft 50 mg film tabletta	50 mg	Film-coated tablets	Oral use	
Hungary	Pfizer Kft. 1123 Budapest Alkotás u. 53. MOM Park F Épület	Zoloft 20 mg/ml oldat	20 mg/ml	Concentrate for oral Solution	Oral use	20 mg/ml
Iceland	Pfizer ApS Lautrupvang 8 DK-2750 Ballerup	Zoloft	25 mg, 50 mg, 100 mg	Film-coated tablets	Oral use	
Iceland	Pfizer ApS Lautrupvang 8 DK-2750 Ballerup	Zoloft	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Ireland	Pfizer Healthcare Ireland 9 Riverwalk National Digital Park Citywest Business Campus Dublin 24 Ireland	Lustral	50 mg, 100 mg	Film-coated Tablet	Oral use	
Italy	Pfizer Italia S.r.l. S.S. 156, Km 50 04010 Borgo San Michele (LT)	ZOLOFT	25 mg, 50 mg 100 mg	film-coated tablets	Oral use	
Italy	Pfizer Italia S.r.l. S.S. 156, Km 50 04010 Borgo San Michele (LT)	ZOLOFT	50 mg	Capsules, hard	Oral use	
Italy	Pfizer Italia S.r.l. S.S. 156, Km 50	ZOLOFT	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
	04010 Borgo San Michele (LT)					
Italy	Bioindustria Farmaceutici S.r.l. S.S. 156, Km 50 04010 Borgo San Michele (LT)	TATIG	50 mg 100 mg	film-coated tablets	Oral use	
Italy	Bioindustria Farmaceutici S.r.l. S.S. 156, Km 50 04010 Borgo San Michele (LT)	TATIG	50 mg	Capsules, hard	Oral use	
Italy	Bioindustria Farmaceutici S.r.l. S.S. 156, Km 50 04010 Borgo San Michele (LT)	TATIG	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Latvia	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	ZOLOFT	50 mg	Film-coated tablets	Oral use	
Lithuania	Pfizer Limited, UK, Ramsgate Road, Sandwich Kent CT13 9NJ United Kingdom	Zoloft	50 mg	Film-coated tablets	Oral use	
Luxembourg	PFIZER S.A Boulevard de la Plaine, 17 1050 Brussels	Serlain	50 mg 100 mg	Film-coated tablets	Oral use	
Luxembourg	PFIZER S.A. Boulevard de la Plaine, 17 1050 Brussels	Serlain	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Malta	Pfizer Hellas A.E., 243 Messoghion Ave., 154 51 N. Psychiko Athens Greece	Lustral	50 mg, 100 mg	Film-Coated Tablets	Oral use	

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Netherlands	Pfizer bv Rivium Westlaan 142 2909 LD Capelle a/d IJssel	Zoloft 50	50 mg	Film-Coated tablet	Oral use	
Netherlands	Pfizer bv Rivium Westlaan 142 2909 LD Capelle a/d IJssel	Zoloft 20 mg/ml	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Norway	Pfizer AS POBox 3 1324 Lysaker Norway	Zoloft	25 mg, 50 mg, 100 mg	Film-coated tablets	Oral use	
Norway	Pfizer AS POBox 3 1324 Lysaker Norway	Zoloft	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Poland	Pfizer Europe MA EEIG Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	Zoloft	50 mg, 100 mg	Film-coated tablets	Oral use	
Poland	Pfizer Europe MA EEIG Ramsgate Road Sandwich Kent CT13 9 NJ United Kingdom	Zoloft	20 mg/ml	Concentrate for Oral solution	Oral use	20 mg/ml
Portugal	Laboratórios Pfizer Lda. Lagoas Park Edifício 10 2740-271 Porto Salvo Portugal	Zoloft	50 mg 100 mg	Film-coated tablet	Oral use	

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Portugal	Laboratórios Pfizer Lda. Lagoas Park Edifício 10 2740-271 Porto Salvo Portugal	Zoloft	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Romania	Pfizer Europe MA EEIG Ramsgate Road Sandwich Kent CT13 9 NJ United Kingdom	Zoloft 50 mg Zoloft 100 mg	50 mg, 100 mg	Film-coated tablets	Oral use	
Romania	Pfizer Europe MA EEIG Ramsgate Road Sandwich Kent CT13 9 NJ United Kingdom	Zoloft	20 mg/ml	Concentrate for Oral solution	Oral use	20 mg/ml
Slovak Republic	Pfizer Europe MA EEIG Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	Zoloft	50 mg 100 mg	Film-coated tablets	Oral use	
Slovak Republic	Pfizer Europe MA EEIG Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	Zoloft OC	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Slovenia	Pfizer Luxembourg SARL Rond-Point du Kirchberg 51 Avenue J.F. Kennedy L-1855 Luxembourg	Zoloft	50 mg 100 mg	film coated tablets	Oral use	
Slovenia	Pfizer Luxembourg SARL Rond-Point du Kirchberg 51	Zoloft	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml

Member State EU/EEA	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
	Avenue J.F. Kennedy L-1855 Luxembourg					
Spain	Pfizer S.A. Avda. de Europa, 20 B Parque Empresarial La Moraleja 28108 Alcobendas (Madrid) SPAIN	Besitran	50 mg, 100 mg	Film-coated tablet	Oral use	
Spain	Pfizer S.A. Avda. de Europa, 20 B Parque Empresarial La Moraleja 28108 Alcobendas (Madrid) SPAIN	Besitran	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
Spain	Pfizer S.A. Avda. de Europa, 20 B Parque Empresarial La Moraleja 28108 Alcobendas (Madrid) SPAIN	Sertralina Pfizer	50 mg, 100 mg	Film-coated tablet	Oral use	
Sweden	Pfizer AB Vetenskapsvägen 10 191 90 Sollentuna Sweden	Zoloft	25 mg 50 mg 100 mg 25 + 50 mg (initiation pack)	Film-coated tablets	Oral use	
Sweden	Pfizer AB Vetenskapsvägen 10 191 90 Sollentuna Sweden	Zoloft	20 mg/ml	Concentrate for oral solution	Oral use	20 mg/ml
United Kingdom	Pfizer Ltd Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	Lustral	50 mg, 100 mg	Film-coated tablets	Oral use	

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ZOLOFT AND ASSOCIATED NAMES (SEE ANNEX I)

The active compound of Zoloft and associated names is sertraline, a selective serotonin reuptake inhibitor (SSRI). Sertraline is approved for the treatment of depression and in addition, the product is approved in some Member States for the treatment of social anxiety disorder, panic disorder (with or without agoraphobia disorder), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). In some Member States, OCD is also indicated in children and adolescents (aged 6-17). Zoloft was included in the list of products for Summary of Products Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended.

Section 4.1 – Indications: Panic disorder with or without agoraphobia disorder

The MAH provided details of the clinical programme supporting this indication, consisting of four multi-centre, double blind, placebo-controlled clinical trials and one randomised withdrawal study. The primary efficacy variable was defined based on the average number of panic attacks during the last two weeks of treatment. The results indicated that with respect to the primary efficacy endpoint, three of the studies demonstrated statistically significant improvement in panic disorders compared to placebo, while the fourth study did not. For the randomised withdrawal study, patients were recruited from the short-term studies described above and from another 10 week study. The primary endpoint was the proportion of subjects with a relapse. The results submitted indicated that only 6 patients relapsed during the withdrawal phase of this study, 6% in placebo and 1% in the sertraline arm. The low occurrence of relapse in this study suggest that relapse prevention after 1 year of treatment may not be necessary but the study did not provide information regarding the need for relapse prevention after acute treatment (12 weeks).

The CHMP concluded that short-term efficacy has been demonstrated, but that concerns remain over the lack of evidence with respect to relapse prevention. In addition, the relapse prevention study did not provide evidence with respect to the necessity to continue treatment after an acute treatment phase (of about 10-12 weeks). Therefore it is considered that insufficient evidence was provided to support the duration of treatment in panic disorders.

The safety profile of sertraline is acceptable and the CHMP concluded that the overall recommendation is to grant an indication for the treatment of panic disorder with the following wording:

"Sertraline is indicated for the treatment of panic disorder, with or without agoraphobia".

The CHMP implemented the following text in section 4.2 of the SPC, to indicate that the need for continued treatment should be regularly evaluated:

"Continued treatment in panic disorder and OCD should be evaluated regularly, as relapse prevention has not been shown for these disorders".

Section 4.1 – Indications: Post-traumatic Stress Disorder (PTSD)

The MAH submitted data from the clinical programme for the indication PTSD, consisting of four short term double blind, placebo controlled clinical trials and two long term efficacy and safety studies. The four short-term placebo controlled studies were conducted in patients with PTSD and consisted of 1/2 weeks single-blind placebo run-in, followed by 12 week double-blind treatment. One study recruited male military veterans, in which the primarily cause of PTSD was largely combat related and exhibiting longstanding PTSD. In the other three short term studies, most patients were

females with PTSD due to domestic abuse or sexual/physical trauma. The primary efficacy variable was the CAPS-2 (Clinician-Administered PTSD scale) total severity score. The results show that only two of the four studies demonstrated efficacy while the remaining two studies were negative. Regarding the demonstration of the efficacy of sertraline, the CHMP considered the results of the study in war veterans (known to be a treatment resistant population) to be explained, but the reason for the negative effect in the second study unexplained, although likely to be linked to the unexpectedly high performance of the placebo group. Furthermore, the CHMP was of the opinion that the effect of sertraline on PTSD is at least partly due to its effect on depression (HAMD). A direct effect on PTSD while controlling for the effect on depression was not demonstrated. The effects obtained in the short-term studies seem limited to women while no effect could be demonstrated in men and the CHMP considered this to be due to differences in baseline variables between males and females. Another concern is the effect on depression and the chronicity effect, as only subgroups defined by <5 year or >5years chronicity were examined while chronic PTSD according to DSM criteria starts at >3 months. Therefore, is it still not clear if the efficacy results can be extrapolated to patients with a more recent onset, with acute PTSD (< 3months) and on patients with chronic PTSD (> 3months).

Regarding safety, the incidence of AEs in the PTSD dossier is within the range reported in studies for other indications and SAEs were not considered to be related to the study medication. There was one suicide attempt and one reported case of sertraline overdose, but no death occurred in the studies. The CHMP agreed that overall, the safety of sertraline in the treatment of PTSD is similar to that of major depressive disorder) MDD and does not present any new issues.

In conclusion, the lack of consistent efficacy and the unknown origin of the low response in the negative study are of concern. The interference of depressive symptoms and their effect on PTSD is still a concern because this was not sufficiently controlled for. However, the CHMP considered that the two positive studies allow to conclude on efficacy and adopted the following indication:

"Sertraline is indicated for the treatment of post traumatic stress disorder (PTSD)",

provided the following text concerning PTSD is inserted in section 5.1:

"Combined data from the 3 studies of PTSD in the general population found a lower response rate in males compared to females. In the two positive general population trials, the male and female sertraline vs. placebo responder rates were similar (females: 57.2% vs 34.5%; males: 53.9% vs 38.2%). The number of male and female patients in the pooled general population trials was 184 and 430, respectively and hence the results in females are more robust and males were associated with other baseline variables (more substance abuse, longer duration, source of trauma etc) which are correlated with decreased effect."

Section 4.1 – Indications: Social Anxiety Disorder

The clinical programme for the indication social anxiety disorder consisted of two short term double blind, randomized, placebo controlled clinical trials and two long term efficacy and safety studies. The two short-term placebo controlled studies were conducted in patients with social anxiety disorder. The primary efficacy variables in the different studies were the Liebowitz Social anxiety Symptom Scale (LSAS) and the Duke Brief Social Anxiety disorder Scale (BSPS). The submitted results showed that the improvement on the primary outcome variable was statistically significantly greater in the sertraline versus the placebo arm. The provided results also indicate that relapse rates in the sertraline/sertraline arm are significantly lower compared to the rates in sertraline/placebo and placebo/placebo arms. The positive results that were obtained in two studies with respect to mean improvements on social anxiety scales and with respect to responders appear sufficiently robust to support short-term efficacy. The assessment of the evidence for long-term efficacy and relapse prevention indicates the studies were not performed strictly according to guidelines and the long-term (24 weeks) study does suggest efficacy of long term treatment but includes exposure therapy arms

which may have interfered with the interpretation of the results. Overall, the results of the two studies combined are suggestive of maintenances of effect over the long-term.

Regarding safety, the incidence of all adverse events is within the range reported for the application of sertraline in major depression and the post-marketing experience does not indicate any adverse events which deserve special attention or concern in the application for this indication. Therefore, the overall results of the sertraline studies are supportive of short- and long-term efficacy and, as no unexpected safety issues emerged against the known safety profile of sertraline in the treatment of depression, the CHMP considered the benefit/risk balance for the indication social anxiety disorder to be positive, and approved the following indication:

"Sertraline is indicated for the treatment of social anxiety disorder".

Section 4.1 – Indications: Obsessive Compulsive Disorder (OCD) (In adults)

The MAH submitted the clinical programme for the indication OCD, consisting of five short term double blind, placebo controlled clinical trials; one short term double blind non-placebo controlled study with an active comparator and two long term efficacy and safety studies. All studies included patients with Obsessive Compulsive Disorder (OCD) according to DSM-III or III-R. The results of the short-term studies show that 3 of the 5 placebo controlled studies demonstrated statistically significant results and that these results are supported by responders analysis that indicate a higher proportion of responders in the active arms compared to placebo. The other 2 studies were negative. The CHMP was of the opinion that overall, modest short-term efficacy was demonstrated in these studies. In previous applications, the MAH had submitted data from a placebo-controlled withdrawal study (relapse prevention study) in which responders to 1 year open label treatment were randomised to treatment with sertraline or placebo for a duration of 28 weeks and the results from that study were considered. The CHMP was of the opinion that the second relapse definition used in this study, based on only the investigators judgement rather than on objective measures of OCD, cannot be considered to be an acceptable relapse definition as it is not objective and not necessarily based on disorder specific symptoms. Therefore the CHMP considered that long-term efficacy (maintenance of effect) has not been demonstrated.

In conclusion, the CHMP was of the opinion that sertraline demonstrates a modest short-term effect and that the safety seems acceptable. However, concerns remain about the lack of evidence with respect to relapse prevention. The two long-term studies were not designed to assess relapse prevention and the significant results that were obtained were with respect to subjectively defined relapse, which is not acceptable. Therefore the CHMP considers that insufficient evidence was provided to support the duration of treatment in OCD. The recommendation derived from the evidence regarding efficacy and safety is to grant the following indication for the treatment of OCD:

"Sertraline is indicated for the treatment of obsessive compulsive disorder (OCD) in adults",

provided the lack of long-term efficacy results is reflected in the SPC section 4.2, indicating the need for regular assessment of treatment continuation with the following wording:

"Continued treatment in panic disorder and OCD should be evaluated regularly, as relapse prevention has not been shown for these disorders".

Section 4.1 – Indications: Obsessive Compulsive Disorder (In paediatric patients)

One single study was submitted in support of the paediatric indication, a 12 week randomised double blind study with a sertraline and a placebo arm. The study included children and adolescents aged 6-17. Two previous additional open label extension studies (that were not submitted within the context of this dossier) showed serious AEs, some of which were possibly related to study drug, including severe aggressive reactions, nervousness and paranoid reactions, two severe grand mal seizures,

exacerbated suicidal ideation and homicidal ideation. Moreover, with respect to safety, no data was submitted on endocrine parameters, effects on cognition and other maturation parameters. Efficacy and safety were not investigated with respect to long-term safety, long-term effects on endocrine parameters, on sexual, cognitive and emotional development and other maturation parameters. The CHMP considered that the lack of any evidence suggesting a difference between children and adults is not equivalent to establishing that the disorder is identical in the 2 groups. Paediatric-onset OCD shares important similarities with the adult disorder but also shows important differences. The presented double-blind 12 week study in 187 children (6-17 years) supports the efficacy of sertraline but there was no justification for the dose in children and the clinical relevance of the results has not been established. The CHMP considered that open label studies are not appropriate to demonstrate long term efficacy for regulatory purposes, and that a single study cannot be sufficient to support a paediatric indication.

The CHMP considered that because no placebo was used, it is difficult to put the observed adverse events into perspective. Regarding the dosage, there are no reasons to believe that dose-response effects would be evident in children and adolescents, and subsequently disappear in adulthood and the CHMP considered that there is no evidence to support the minimum effective dose in children and in adolescents. In order to provide long-term safety evidence, the MAH proposed to augment the current Data Capture Aid (DCA) and to monitor all reported paediatric (less than 18 years of age) adverse events (AEs) in the pharmacovigilance safety database and look in more detail for AEs of interest in these cases. The CHMP concluded that the safety in children and adolescents has not sufficiently been established and that a commitment to further investigate safety in paediatric patients is required.

The MAH therefore committed to providing a long-term safety study looking at aspects of growth, sexual maturation, cognitive and emotional development and submitted a study synopsis for evaluation by the CHMP. The CHMP agreed to the general aspects of the proposed study but requested the inclusion of a control group, consisting for instance of patients not treated with SSRIs or treated by psychotherapy alone. The MAH submitted a revised study synopsis, now including a sertraline-unexposed control group and following the evaluation of this synopsis, the study proposal was supported. The CHMP was of the opinion that based on the previous discussion within the committee and given the revised study synopsis submitted by the MAH, the OCD indication in paediatric patients is now also considered acceptable and therefore adopted the following indication:

"Sertraline is indicated for the treatment of obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years."

With the condition that the following text is inserted in section 5.1 of the SPC:

"Long-term efficacy data are lacking for this paediatric population, however, clinical trials for up to 64 weeks have been conducted and the safety profile is consistent with that of adults. No data is available for children under 6 years of age".

Provided that the following commitment is agreed upon by the MAH:

"The MAH has committed to undertake a long-term safety study looking at aspects of growth, sexual maturation, cognitive and emotional development to support the paediatric OCD indication in paediatric patients aged 6-17 years old. This study includes a comparison group consisting of paediatric patients receiving psychotherapy alone."

Section 4.1 – Indications: Depression (MDD)

In total, 13 short term RCTs were carried out in support of the MDD indication, in addition to one randomised withdrawal study and several other long-term studies. The results of these studies indicate a positive benefit/risk balance for MDD. The evidence in support of the MDD indication was considered acceptable, and the CHMP focused on the assessment of the evidence supporting the additional indication: "*including depression accompanied by symptoms of anxiety, in patients with or*

without a history of mania". A review of the trials included in this dossier indicated that there were two trials that included patients with a bipolar disorder and one with depression accompanied by symptoms of anxiety. The CHMP was of the opinion that the results of these three trials do not support the addition of "*including depression accompanied by symptoms of anxiety, in patients with or without a history of mania"* to the Major Depressive Episodes (MDD) indication. The data submitted to support the additional indication anxiety treatment indication proposed by the MAH consisted of various studies showing that the sertraline groups consistently had a greater reduction in the Ham-D Factor for anxiety and somatisation than the placebo group. The CHMP considered that because anxiety is an inherent part of the depression disorder, a decrease in Hamilton anxiety can not be seen as separate due to possible interactions with improvement of depression. The effect on anxiety is considered to be part of the antidepressant effect, and the indication can therefore not be granted. In addition, the improvements in anxiety presented by the MAH are far from impressive and not significant. Prevention of relapse and recurrence was not initially requested by the MAH but proposed during the assessment by the CHMP. Noting that MDD is considered to be a chronic or chronic intermittent condition where treatment is aimed at amelioration and possibly interruption of the natural course of the episode, the CHMP considered it unnecessary to accept this separate indication. In conclusion, the recurrence study is the first recurrence-prevention study in a trial with depressive patients who had experienced at least three documented episodes of major depressive disorder within the last 4 years. The design is largely adequate but because this trial is performed in patients with recurrent depressive episodes, the adequate wording of the SPC should mention the description of patient populations and previous episodes in section 5.1. In summary, the CHMP adopted the following harmonised wording:

"Sertraline is indicated for the treatment of major depressive episodes. Prevention of recurrence of major depressive episodes".

Section 4.2 - Posology and Method of Administration

According to the MAH, differences in this section are related to differences in the formulations that have been approved. The MAH submitted data from a number of studies to support the proposed harmonised text for this section. In general, the CHMP considered the wordings proposed by the MAH to be acceptable. Regarding the dosing of paediatric patients with OCD, the CHMP requested the insertion of a warning in section 4.4 and adopted the following wording:

"Subsequent doses may be increased in case of less than desired response in 50 mg increments over a period of some weeks, as needed. The maximum dosage is 200 mg daily. However, the generally lower body weights of children compared to those of adults should be taken into consideration when increasing the dose from 50 mg. Dose changes should not occur at intervals of less than one week."

Regarding the use of sertraline in Hepatic Insufficiency and in Renal Insufficiency, the CHMP agreed with the wording proposed by the MAH for harmonisation.

Section 4.3 - Contraindications

In general, the harmonised wording proposed by the MAH was accepted by the CHMP. Regarding pimozide, the CHMP agreed to the MAH proposal: *"Concomitant intake of pimozide is contraindicated (see section 4.5)"* and regarding hepatic impairment, the CHMP considered that patients with significant hepatic impairment are not strictly contraindicated with sertraline and that appropriate warnings about the recommended use of sertraline in patients with hepatic impairment are provided in section 4.2 and section 4.4 of the proposed harmonised SPC. In both sections, caution is advised and a lower or less frequent dose should be used in patients with hepatic impairment.

In addition, the MAH proposed harmonised wordings for sections 4.4, 4.5, 4.6, 4.7, 4.8 and 4.9 as well as for sections 5.1, 5.2 and 5.3. The texts proposed by the MAH were in general accepted by the CHMP, with some occasional minor amendments. Comments were also made to the remaining

sections of the SPC, and for all sections, the labelling and the package leaflet were revised accordingly.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet.

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

- commitments "*to undertake a long-term safety study looking at aspects of growth, sexual maturation, cognitive and emotional development to support the paediatric OCD indication in paediatric patients aged 6-17 years old. This study includes a comparison group consisting of paediatric patients receiving psychotherapy alone*" and also "*to provide the relevant non-clinical data on juvenile animal toxicity available in the public domain, in order to justify why no further data needs to be generated in this field*" were obtained from the Marketing Authorisation Holder,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Zoloft and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zoloft and associated names (see Annex I) 25 mg film coated tablets
Zoloft and associated names (see Annex I) 50 mg film coated tablets
Zoloft and associated names (see Annex I) 100 mg film coated tablets

Zoloft and associated names (see Annex I) 25 mg hard capsules
Zoloft and associated names (see Annex I) 50 mg hard capsules
Zoloft and associated names (see Annex I) 100 mg hard capsules

Zoloft and associated names (see Annex I) 20 mg/ml concentrate for oral solution

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sertraline is indicated for the treatment of:

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

4.2 Posology and method of administration

Sertraline should be administered once daily, either in the morning or evening.
Sertraline tablet can be administered with or without food
Sertraline capsule should be administered with food.
Sertraline concentrate for oral solution can be administered with or without food.
Sertraline concentrate for oral solution must be diluted before use (see section 6.6).

Initial treatment

Depression and OCD
Sertraline treatment should be started at a dose of 50 mg/day.

Panic Disorder, PTSD, and Social Anxiety Disorder
Therapy should be initiated at 25 mg/day. After one week, the dose should be increased to 50 mg once daily. This dosage regimen has been shown to reduce the frequency of early treatment emergent side effects characteristic of panic disorder.

Titration

Depression, OCD, Panic Disorder, Social Anxiety Disorder and PTSD
Patients not responding to a 50 mg dose may benefit from dose increases. Dose changes should be made in steps of 50 mg at intervals of at least one week, up to a maximum of 200 mg/day. Changes in dose should not be made more frequently than once per week given the 24-hour elimination half life of sertraline.

The onset of therapeutic effect may be seen within 7 days. However, longer periods are usually necessary to demonstrate therapeutic response, especially in OCD.

Maintenance

Dosage during long-term therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response.

Depression
Longer-term treatment may also be appropriate for prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during current episode. Patients with depression should be treated for a sufficient period of time of at least 6 months to ensure they are free from symptoms.

Panic disorder and OCD
Continued treatment in panic disorder and OCD should be evaluated regularly, as relapse prevention has not been shown for these disorders.

Paediatric patients

Children and adolescents with obsessive compulsive disorder
Age 13-17 years: Initially 50 mg once daily.
Age 6-12 years: Initially 25 mg once daily. The dosage may be increased to 50 mg once daily after one week.

Subsequent doses may be increased in case of less than desired response in 50 mg increments over a period of some weeks, as needed. The maximum dosage is 200 mg daily. However, the generally lower body weights of children compared to those of adults should be taken into consideration when increasing the dose from 50 mg. Dose changes should not occur at intervals of less than one week.

Efficacy is not shown in paediatric major depressive disorder.

No data is available for children under 6 years of age (see also section 4.4)

Use in elderly
Elderly should be dosed carefully, as elderly may be more at risk for hyponatraemia (see section 4.4).

Use in hepatic insufficiency
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 (see section 4.4). Sertraline should not be used in cases of severe hepatic impairment as no clinical data are available (see section 4.4).

Use in renal insufficiency
No dosage adjustment is necessary in patients with renal insufficiency (see section 4.4).

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 sections 4.4 and 4.8). 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

Hypersensitivity to the active substance or any of the excipients.
Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see section 4.5).

Concomitant intake of pimozide is contraindicated (see section 4.5).
Sertraline concentrate for oral solution is contraindicated with the use of disulfiram due to the alcohol content of the oral concentrate (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Switching from Selective Serotonin Reuptake Inhibitors (SSRIs), antidepressants or antiobsessional drugs
There is limited controlled experience regarding the optimal timing of switching from SSRIs, antidepressants or antiobsessional drugs to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents such as fluoxetine.

Other serotonergic drugs e.g. tryptophan, fenfluramine and 5-HT agonists
Co-administration of sertraline with other drugs which enhance the effects of serotonergic neurotransmission such as tryptophan or fenfluramine or 5-HT agonists, or the herbal medicine, St John's Wort (*hypericum perforatum*), should be undertaken with caution and avoided whenever possible due to the potential for a pharmacodynamic interaction.

Activation of hypomania or mania
Manic/hypomanic symptoms have been reported to emerge in a small proportion of patients treated with marketed antidepressant and antiobsessional drugs, including sertraline. Therefore sertraline should be used with caution in patients with a history of mania/hypomania. Close surveillance by the physician is required. Sertraline should be discontinued in any patient entering a manic phase.

Schizophrenia
Psychotic symptoms might become aggravated in schizophrenic patients.

Seizures
Seizures may occur with sertraline therapy: sertraline should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures.

Suicide/suicidal thoughts/suicide attempts or clinical worsening
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 suicide may increase in the early stages of recovery.

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 disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age
Sertraline should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with obsessive compulsive disorder aged 6-17 years old. 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 appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking. Physicians must monitor paediatric patients on long term treatment for abnormalities in these body systems.

Abnormal bleeding/Haemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura and other hemorrhagic events such as gastrointestinal or gynaecological bleeding, with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. anticoagulants, atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders (see section 4.5).

Hyponatraemia
Hyponatraemia may occur as a result of treatment with SSRIs or SNRIs including sertraline. In many cases, hyponatraemia appears to be the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium levels lower than 110 mmol/l have been reported. Elderly patients may be at greater risk of developing hyponatraemia with SSRIs and SNRIs. Also patients taking diuretics or who are otherwise volume-depleted may be at greater risk (see Use in elderly). Discontinuation of sertraline should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatraemia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Withdrawal symptoms seen on discontinuation of sertraline treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, among patients treated with sertraline, the incidence of reported withdrawal reactions was 23% in those discontinuing sertraline compared to 12% in those who continued to receive sertraline treatment.

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 section 4.2).

Akathisia/psychomotor restlessness
The use of sertraline has been associated with the development of 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.

Hepatic 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 Cmax in comparison to 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 must be approached with caution. If sertraline is administered to patients with hepatic impairment, a lower or less frequent dose should be considered. Sertraline should not be used in patients with severe hepatic impairment (see section 4.2).

Renal impairment
Sertraline is extensively metabolised, and excretion of unchanged drug in urine is a minor route of elimination. In studies of patients with mild to moderate renal impairment (creatinine clearance 30-60 ml/min) or moderate to severe renal impairment (creatinine clearance 10-29 ml/min), multiple-dose pharmacokinetic parameters (AUC_{0-24} or Cmax) were not significantly different compared with controls. Sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Use in elderly
Over 700 elderly patients (>65 years) have participated in clinical studies. The pattern and incidence of adverse reactions in the elderly was similar to that in younger patients.

SSRIs or SNRIs including sertraline have however been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse event (see Hyponatraemia in section 4.4).

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Glycaemic control should be carefully monitored in patients receiving sertraline and the dosage of insulin and/or concomitant oral hypoglycaemic medicinal products may be needed to be adjusted.

Electroconvulsive therapy
There are no clinical studies establishing the risks or benefits of the combined use of ECT and sertraline.

Medicinal products containing lactose
As the capsule contains the excipient lactose (see section 6.1), patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sertraline concentrate for oral solution
Sertraline concentrate for oral solution contains 12% ethanol (see sections 4.3 and 4.5), glycerol and butylhydroxytoluene.
Ethanol: The alcohol content has to be taken into consideration in patients with liver impairment, alcohol abuse, epilepsy, brain trauma or disease, pregnant women and children.
Butylhydroxytoluene: can cause irritation of eyes, skin and mucous membranes.
Glycerol: at high doses, can cause headache, abdominal pain and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated

Monoamine Oxidase Inhibitors
Irreversible (non-selective) MAOIs (selegiline)
Sertraline must not be used in combination with irreversible (non-selective) MAOIs such as selegiline. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible (non-selective) MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible (non-selective) MAOI (see section 4.3).

Reversible, selective MAO-A inhibitor (moclobemide)
Due to the risk of serotonin syndrome, the combination of sertraline with a reversible and selective MAOI, such as moclobemide, is not recommended. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of sertraline treatment. It is recommended that sertraline should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.3).

Reversible, non-selective MAOI (linezolid)
The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with sertraline (see section 4.3).

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on sertraline, or have recently had sertraline therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

Pimozide
Increased pimozide levels of approximately 35% have been demonstrated in a study of a single low dose pimozide (2 mg). These increased levels were not associated with any changes in EKG. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated (see section 4.3).

Co-administration with sertraline is not recommended

CNS depressants and alcohol
The co-administration of sertraline 200 mg daily did not potentiate the effects of alcohol, carbamazepine, haloperidol, or phenytoin on cognitive and psychomotor performance in healthy subjects; however, the concomitant use of sertraline and alcohol is not recommended.

Other serotonergic drugs
See section 4.4.

Special Precautions

Lithium
In a placebo-controlled trial in normal volunteers, the co-administration of sertraline with lithium did not significantly alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When co-administering sertraline with lithium, patients should be appropriately monitored.

Phenytoin
A placebo-controlled trial in normal volunteers suggests that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, as some case reports have emerged of high phenytoin exposure in patients using sertraline, it is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels.

Triptans
There have been rare post-marketing reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. Symptoms of serotonergic syndrome may also occur with other products of the same class (triptans). If concomitant treatment with sertraline and triptans is clinically warranted, appropriate observation of the patient is advised (see section 4.4).

Warfarin
Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time, which may in some rare cases unbalance the INR value. Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Other drug interactions, digoxin, atenolol, cimetidine
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 of sertraline 200 mg daily was observed with digoxin.

Drugs affecting platelet function
The risk of bleeding may be increased when medicines acting on platelet function (e.g. NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might increase bleeding risk are concomitantly administered with SSRIs, including sertraline (see section 4.4).

Drugs Metabolized by Cytochrome P450
Sertraline may act as a mild-moderate inhibitor of CYP 2D6. Chronic dosing with sertraline 50 mg daily showed moderate elevation (mean 23%-37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isozyme activity). Clinical relevant interactions may occur with other CYP 2D6 substrates with a narrow therapeutic index like class 1C antiarrhythmics such as propafenone and flecainide, TCAs and typical antipsychotics, especially at higher sertraline dose levels.

Sertraline does not act as an inhibitor of CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2 to a clinically significant degree. This has been confirmed by *in-vivo* interaction studies with CYP3A4 substrates (endogenous cortisol, carbamazepine, terfenadine, alprazolam), CYP2C19 substrate diazepam, and CYP2C9 substrates tolbutamide, glibenclamide and phenytoin. *In vitro* studies indicate that sertraline has little or no potential to inhibit CYP 1A2.

Sertraline Oral Concentrate and disulfiram
The oral concentrate formulation contains a small amount of alcohol. Ethanol ingestion will result in an adverse reaction with disulfiram as long as serum levels of disulfiram persist, or the activity of

acetaldehyde dehydrogenase is diminished. Depending on hepatic function, this effect may still be present for as long as two weeks after the last dose of disulfiram, although one week is the more typical duration of action with standard doses. Therefore, sertraline concentrate for oral solution should not be used in combination with disulfiram or within 14 days of discontinuing treatment with disulfiram (see sections 4.3 and 4.4).

4.6 Pregnancy and lactation

Pregnancy
There are no well controlled studies in pregnant women. However, a substantial amount of data did not reveal evidence of induction of congenital malformations by sertraline. Animal studies showed evidence for effects on reproduction probably due to maternal toxicity caused by the pharmacodynamic action of the compound and/or direct pharmacodynamic action of the compound on the foetus (see 5.3).

Use of sertraline during pregnancy has been reported to cause symptoms, compatible with withdrawal reactions, in some neonates, whose mothers had been on sertraline. This phenomenon has also been observed with other SSRI antidepressants. Sertraline is not recommended in pregnancy, unless the clinical condition of the woman is such that the benefit of the treatment is expected to outweigh the potential risk.

Neonates should be observed if maternal use of sertraline continues into the later stages of pregnancy, particularly the third trimester. The following symptoms may occur in the neonate after maternal sertraline use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty in sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances the complications begin immediately or soon (<24 hours*)* after delivery.

Lactation
Published data concerning sertraline levels in breast milk show that small quantities of sertraline and its metabolite N-desmethylsertraline are excreted in milk. Generally neglible to undetectable levels were found in infant serum, with one exception of an infant with serum levels about 50% of the maternal level (but without a noticeable health effect in this infant). To date, no adverse effects on the health of infants nursed by mothers using sertraline have been reported, but a risk cannot be excluded. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefit outweighs the risk.

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 psychotropic drugs may impair the mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly.

4.8 Undesirable effects

Nausea is the most common undesirable effect. In the treatment of social anxiety disorder, sexual dysfunction (ejaculation failure) in men occurred in 14% for sertraline vs 0% in placebo. These undesirable effects are dose dependent and are often transient in nature with continued treatment.

The undesirable effects profile commonly observed in double-blind, placebo-controlled studies in patients with OCD, panic disorder, PTSD and social anxiety disorder was similar to that observed in clinical trials in patients with depression.

Table 1 displays adverse reactions observed from postmarketing experience (frequency not known) and placebo-controlled clinical trials (comprising a total of 2542 patients on sertraline and 2145 on placebo) in depression, OCD, panic disorder, PTSD and social anxiety disorder.
Some adverse drug reactions listed in Table 1 may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Table 1: Adverse Reactions

Frequency of adverse reactions observed from placebo-controlled clinical trials in depression, OCD, panic disorder, PTSD and social anxiety disorder. Pooled analysis and postmarketing experience (frequency not known).

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
Infections and Infestations					
	Pharyngitis	Upper Respiratory Tract Infection, Rhinitis	Diverticulitis, Gastroenteritis, Otitis Media		
Neoplasms benign, malignant (including cysts and polyps)					
			Neoplasm†		
Blood and lymphatic system disorders					
			Lymphadenopathy		Leucopaenia, Thrombocytopaenia
Immune system disorders					
					Anaphylactoid Reaction, Allergic Reaction, Allergy
Endocrine disorders					
					Hyperprolactinaemia, Hypothyroidism and syndrome of inappropriate ADH secretion
Metabolism and Nutrition Disorders					

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
	Anorexia, Increased Appetite*		Hypercholesterolaemia, Hypoglycaemia		Hyponatremia
Psychiatric Disorders					
Insomnia (19%)	Depression*, Depersonalisation, Nightmare, Anxiety*, Agitation*, Nervousness, Libido Decreased*, Bruxism	Hallucination*, Euphoric Mood*, Apathy, Thinking Abnormal	Conversion Disorder, Drug Dependence, Psychotic disorder*, Aggression*, Paranoia, Suicidal Ideation, Sleep Walking, Premature Ejaculation		Paroniria, Suicidal ideation/behaviour***
Nervous System Disorders					
Dizziness (11%), Somnolence (13%), Headache (21%)*	Paraesthesia*, Tremor, Hypertonia, Dysgeusia, Disturbance in Attention,	Convulsion*, Muscle Contractions Involuntary*, Coordination Abnormal, Hyperkinesia, Amnesia, Hypoaesthesia*, Speech Disorder, Dizziness Postural, Migraine*	Coma*, Choreoathetosis, Dyskinesia, Hyperaesthesia, Sensory Disturbance		Movement Disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, teeth grinding or gait abnormalities), Syncope. Also reported were signs and symptoms associated with serotonin syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia. Akathesia and

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
					pyschomotor restlessness (see section 4.4).
Eye Disorders					
	Visual Disturbance		Glaucoma, Lacrimal Disorder, Scotoma, Diplopia, Photophobia, Hyphaema, Mydriasis*		Vision Abnormal
Ear and Labyrinth Disorders					
	Tinnitus*	Ear Pain			
Cardiac Disorders					
	Palpitations*	Tachycardia	Myocardial Infarction, Bradycardia, Cardiac Disorder		
Vascular Disorders					
	Hot flush*	Hypertension*, Flushing	Peripheral Ischaemia		Abnormal Bleeding (such as epistaxis, gastrointestinal bleeding or haematuria)
Respiratory, Thoracic, and Mediastinal Disorders					
	Yawning*	Bronchospasm*, Dyspnoea, Epistaxis	Laryngospasm, Hyperventilation, Hypoventilation, Stridor, Dysphonia, Hiccups		
Gastrointestinal Disorders					
Diarrhoea (18%), Nausea (24%), Dry Mouth (14%)	Abdominal Pain* Vomiting*, Constipation* Dyspepsia, Flatulence	Oesophagitis, Dysphagia, Haemorrhoids, Salivary Hypersecretion, Tongue Disorder, Eructation	Melaena, Haematochezia, Stomatitis, Tongue ulceration, Tooth Disorder, Glossitis, Mouth Ulceration		Pancreatitis
Hepatobiliary Disorders					

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
			Hepatic Function Abnormal		Serious liver events (including hepatitis, jaundice and liver failure)
Skin and Subcutaneous Tissue Disorders					
	Rash*, Hyperhidrosis	Periorbital Oedema*, Purpura*, Alopecia*, Cold Sweat, Dry skin, Urticuria*	Dermatitis, Dermatitis Bullous, Rash Follicular, Hair Texture Abnormal, Skin Odour Abnormal		Rare reports of severe cutaneous adverse reactions (SCAR): e.g. Stevens-Johnson syndrome and epidermal necrolysis, Angioedema, Face Oedema, Photosensitivity, Skin Reaction, Pruritus
Musculoskeletal and Connective Tissue Disorders					
	Myalgia	Osteoarthritis, Muscular Weakness, Back Pain, Muscle Twitching	Bone Disorder		Arthralgia, Muscle Cramps
Renal and Urinary Disorders					
		Nocturia, Urinary Retention*, Polyuria, Pollakiura, Micturition disorder	Oliguria, Urinary Incontinence*, Urinary Hesitation		
*Reproductive System and Breast Disorders***					
Ejaculation Failure (14%)	Sexual Dysfunction, Erectile Dysfunction	Vaginal Haemorrhage, Female Sexual Dysfunction	Menorrhagia, Atrophic Vulvuvaginitis, Balanoposthitis, Genital Discharge, Priapism*, Galactorrhoea*		Gynaecomastia, Menstrual Irregularities

Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)	**Rare** (≥1/10000 to <1/1000)	**Very. rare** (<1/10000)	**Frequency not Known**
General Disorders and Administration Site Conditions					
Fatigue (10%)*	Chest Pain*	Malaise*, Chills, Pyrexia*, Asthenia*,Thirst	Hernia, Injection Site Fibrosis, Drug Tolerance Decreased, Gait Disturbance, Unevaluable Event		Oedema Peripheral
Investigations					
		Weight Decreased*, Weight Increased*	Alanine Aminotransferarase Increased*, Aspartate Aminotransferase Increased*, Semen Abnormal		Abnormal Clinical Laboratory Results, Altered Platelet Function, Increased Serum Cholesterol
Injury and poisoning					
			Injury		
Surgical and medical procedures					
			Vasodilation Procedure		

If adverse experience occurred in depression, OCD, panic disorder, PTSD and social anxiety disorder, body term reclassified by depression studies body term.
† One case of neoplasm was reported in one patient receiving sertraline compared with no cases in the placebo arm.
** these adverse reactions also occurred in postmarketing experience*
*** the denominator uses the number of patients in that sex group-combined: sertraline (1118 males, 1424 females) placebo (926 males, 1219 females)*
For OCD, short term, 1-12 week studies only
**** Cases of suicidal ideation and suicidal behaviours have been reported during sertraline therapy or early after treatment discontinuation (see section 4.4).*

Withdrawal symptoms seen on discontinuation of sertraline 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 or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported. 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 sections 4.2 and 4.4).

Elderly population
SSRIs or SNRIs including sertraline have been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse event (see section 4.4).

Paediatric population
In over 600 paediatric patients treated with sertraline, the overall profile of adverse reactions was generally similar to that seen in adult studies. The following adverse reactions were reported from controlled trials (n=281 patients treated with sertraline):
Very common (≥1/10): Headache (22%), insomnia (21%), diarrhoea (11%) and nausea (15%).
Common (≥1/100 to <1/10): Chest pain, mania, pyrexia, vomiting, anorexia, affect lability, aggression, agitation, nervousness, disturbance in attention, dizziness, hyperkinesia, migraine, somnolence, tremor, visual disturbance, dry mouth, dyspepsia, nightmare, fatigue, urinary incontinence, rash, acne, epistaxis, flatulence.
Uncommon (≥1/1000 to <1/100): ECG QT prolonged, suicide attempt, convulsion, extrapyramidal disorder, paraesthesia, depression, hallucination, purpura, hyperventilation, anaemia, hepatic function abnormal, alanine aminotransferase increased, cystitis, herpes simplex, otitis externa, ear pain, eye pain, mydriasis, malaise, haematuria, rash pustular, rhinitis, injury, weight decreased, muscle twitching, abnormal dreams, apathy, albuminuria, pollakiuria, polyuria, breast pain, menstrual disorder, alopecia, dermatitis, skin disorder, skin odour abnormal, urticaria, bruxism, flushing.

4.9 Overdose

Toxicity
On the evidence available, sertraline has a wide margin of safety in overdose. Overdoses of sertraline alone of up to 13.5 g have been reported. Deaths have been reported involving overdoses of sertraline, primarily in combination with other drugs and/or alcohol. Therefore, any overdosage should be medically treated aggressively.

Symptoms
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.

Treatment
There are no specific antidotes to sertraline. Establish and maintain an airway and ensure adequate oxygenation and ventilation, if necessary. Activated charcoal, which may be used with a cathartic, may be as or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended. Cardiac and other vital sign 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

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors (SSRI), ATC code: N06 AB06
Sertraline is a potent and specific inhibitor of neuronal serotonin (5 HT) uptake in vitro, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of brain norepinephrine receptors as observed with other clinically effective antidepressants and antiobsessional drugs.

Sertraline has not demonstrated potential for abuse. In a placebo-controlled, double-blind randomized study of the comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria and abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforcer in rhesus monkeys trained to self administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

Clinical Trials

Major Depressive Disorder
A study was conducted which involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50-200 mg/day. These patients (n=295) were randomized to continuation for 44 weeks on double-blind sertraline 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo. The mean dose for completers was 70 mg/day. The % of responders (defined as those patients that did not relapse) for sertraline and placebo arms were 83.4% and 60.8%, respectively.

Post traumatic stress disorder (PTSD)
Combined data from the 3 studies of PTSD in the general population found a lower response rate in males compared to females. In the two positive general population trials, the male and female sertraline vs. placebo responder rates were similar (females: 57.2% vs 34.5%; males: 53.9% vs 38.2%). The number of male and female patients in the pooled general population trials was 184 and 430, respectively and hence the results in females are more robust and males were associated with other baseline variables (more substance abuse, longer duration, source of trauma etc) which are correlated with decreased effect.

Paediatric OCD
The safety and efficacy of sertraline (50-200 mg/day) was examined in the treatment of non-depressed children (6-12 years old) and adolescent (13-17 years old) outpatients with obsessive compulsive disorder (OCD). After a one week single blind placebo lead-in, patients were randomly assigned to twelve weeks of flexible dose treatment with either sertraline or placebo. Children (6-12 years old) were initially started on a 25 mg dose. Patients randomized to sertraline showed significantly greater improvement than those randomised to placebo on the Children's Yale-Brown Obsessive Compulsive Scale CY-BOCS (p =0.005) the NIMH Global Obsessive Compulsive Scale (p=0.019), and the CGI Improvement (p =0.002) scales. In addition, a trend toward greater improvement in the sertraline group than the placebo group was also observed on the CGI Severity scale (p=0.089). For CY-BOCs the mean baseline and change from baseline scores for the placebo group was 22.25 ± 6.15 and -3.4 ± 0.82, respectively, while for the sertraline group, the mean baseline and change from baseline scores were 23.36 ± 4.56 and -6.8 ± 0.87, respectively. In a post-hoc analysis, responders, defined as patients with a 25% or greater decrease in the CY-BOCs (the primary efficacy measure) from baseline to endpoint, were 53% of sertraline-treated patients compared to 37% of placebo-treated patients (p=0.03).

Long term safety and efficacy data are lacking for this paediatric population.

No data is available for children under 6 years of age.

5.2 Pharmacokinetic properties

Absorption
Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg. In man, following an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of

sertraline occur at 4.5 to 8.4 hours after the daily administration of the drug. Food does not significantly change the bioavailability of sertraline tablets.

Since the bioavailability of sertraline capsules is increased in the presence of food, it is recommended that sertraline capsules be administered with meals.

Food does not significantly change the bioavailability of sertraline concentrate for oral solution.

Distribution
Approximately 98% of the circulating drug is bound to plasma proteins.

Biotransformation
Sertraline undergoes extensive first-pass hepatic metabolism.

Elimination
The mean half-life of sertraline is approximately 26 hours (range 22-36 hours). Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation up to steady state concentrations, which are achieved after one week of once-daily dosing. The half-life of N-desmethylsertraline is in the range of 62 to 104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized 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.

Pharmacokinetics in specific patient groups

Paediatric patients with OCD
Pharmacokinetics of sertraline was studied in 29 paediatric patients aged 6-12 years old, and 32 adolescent patients aged 13-17 years old. Patients were gradual uptitrated to a 200 mg daily dose within 32 days, either with 25 mg starting dose and increment steps, or with 50 mg starting dose or increments. The 25 mg regimen and the 50 mg regimen were equally tolerated. In steady state for the 200 mg dose, the sertraline plasma levels in the 6-12 year old group were approximately 35% higher compared to the 13-17 year old group, and 21% higher compared to adult reference group. There were no significant differences between boys and girls regarding clearance. A low starting dose and titration steps of 25 mg are therefore recommended for children, especially with low bodyweight. Adolescents could be dosed like adults.

Adolescents and elderly
The pharmacokinetic profile in adolescents or elderly is not significantly different from that in adults between 18 and 65 years.

Liver function impairment
In patients with liver damage, the half life of sertraline is prolonged and AUC is increased three fold (see sections 4.2 and 4.4).

Renal impairment
In patients with moderate-severe renal impairment, there was no significant accumulation of sertraline.

5.3 Preclinical safety data

Preclinical data does not indicate any special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenesis. Reproduction toxicity studies in animals showed no evidence of teratogenicity or adverse effects on male fertility. Observed foetotoxicity was probably related to maternal toxicity. Postnatal pup survival and body weight were decreased only during the first days after birth. Evidence was found that the early postnatal mortality was due to in-utero exposure after day 15 of pregnancy. Postnatal developmental delays found in pups from treated dams were probably due to effects on the dams and therefore not relevant for human risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

No special requirements

Sertraline concentrate for oral solution contains 20 mg/ml of sertraline. It must be diluted before use. Use the dropper provided to remove the required amount of sertraline oral concentrate and dilute with approximately 120 ml (*one glass*) of water, ginger ale, lemon/lime soda, lemonade or orange juice. Do not mix sertraline oral concentrate with anything other than the liquids listed. The dose should be taken immediately after dilution. Do not prepare in advance. At times, a slight haze may appear in the solution after mixing; this is normal.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON/BOX

1. NAME OF THE MEDICINAL PRODUCT

Zoloft and associated names (see Annex I) 25 mg film coated tablets
Zoloft and associated names (see Annex I) 50 mg film coated tablets
Zoloft and associated names (see Annex I) 100 mg film coated tablets

Zoloft and associated names (see Annex I) 25 mg hard capsules
Zoloft and associated names (see Annex I) 50 mg hard capsules
Zoloft and associated names (see Annex I) 100 mg hard capsules

Zoloft and associated names (see Annex I) 20 mg/ml concentrate for oral solution

[See Annex I - To be completed nationally]

Sertraline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zoloft and associated names (see Annex I) 25 mg film coated tablets
Zoloft and associated names (see Annex I) 50 mg film coated tablets
Zoloft and associated names (see Annex I) 100 mg film coated tablets

Zoloft and associated names (see Annex I) 25 mg hard capsules
Zoloft and associated names (see Annex I) 50 mg hard capsules
Zoloft and associated names (see Annex I) 100 mg hard capsules

[See Annex I - To be completed nationally]

Sertraline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POLYETHYLENE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zoloft and associated names (see Annex I) 25 mg film coated tablets
Zoloft and associated names (see Annex I) 50 mg film coated tablets
Zoloft and associated names (see Annex I) 100 mg film coated tablets

Zoloft and associated names (see Annex I) 25 mg hard capsules
Zoloft and associated names (see Annex I) 50 mg hard capsules
Zoloft and associated names (see Annex I) 100 mg hard capsules

[See Annex I - To be completed nationally]

Sertraline

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BROWN BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zoloft and associated names (see Annex I) 20 mg/ml concentrate for oral solution

[See Annex I - To be completed nationally]

Sertraline

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zoloft and associated names (see Annex I) 25 mg film coated tablets
Zoloft and associated names (see Annex I) 50 mg film coated tablets
Zoloft and associated names (see Annex I) 100 mg film coated tablets

Zoloft and associated names (see Annex I) 25 mg hard capsules
Zoloft and associated names (see Annex I) 50 mg hard capsules
Zoloft and associated names (see Annex I) 100 mg hard capsules

Zoloft and associated names (see Annex I) 20 mg/ml concentrate for oral solution

[See Annex I - To be completed nationally]
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 Zoloft is and what it is used for.
2. Before you take Zoloft.
3. How to take Zoloft.
4. Possible side effects.
5. How to store Zoloft.
6. Further information.

1. WHAT ZOLOFT IS AND WHAT IT IS USED FOR

Zoloft contains the active ingredient sertraline. Sertraline is one of a group of medicines called Selective Serotonin Re-uptake Inhibitors (SSRIs); these medicines are used to treat depression and or anxiety disorders.

Zoloft can be used to treat:
- Depression and prevention of recurrence of depression (in adults).
- Social anxiety disorder (in adults).
- Post traumatic stress disorder (PTSD) (in adults).
- Panic disorder (in adults).
- Obsessive compulsive disorder (OCD) (in adults and children and adolescents aged 6-17 years old).

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

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

PTSD is a condition that can occur after a very emotionally traumatic experience, and has some symptoms that are similar to depression and anxiety. Social anxiety disorder (social phobia) is an illness linked to anxiety. It is characterised by feelings of intense anxiety or distress in social

situations (for example: talking to strangers, speaking in front of groups of people, eating or drinking in front of others or worrying that you might behave in an embarrassing manner).

Your doctor has decided that this medicine is suitable for treating your illness.

You should ask your doctor if you are unsure why you have been given Zoloft.

2. BEFORE YOU TAKE ZOLOFT

Do not take Zoloft:

- If you are allergic (hypersensitive) to sertraline or any of the other ingredients of Zoloft.
- If you are taking or have taken medicines called monoamine oxidase inhibitors (MAOIs such as selegiline, moclobemide) or MAOI like drugs (such as linezolid). If you stop treatment with sertraline, you must wait until at least one week before you start treatment with a MAOI. After stopping treatment with a MAOI, you must wait at least 2 weeks before you can start treatment with sertraline.
- If you are taking another medicine called Pimozide (an antipsychotic medicine).
- If you are taking or have taken disulfiram with the last 2 weeks. Sertraline concentrate for oral solution should not be used in combination with disulfiram or within 2 weeks of discontinuing treatement with disulfiram.

Take special care with Zoloft:
Medicines are not always suitable for everyone. Tell your doctor before you take Zoloft, if you suffer from or have suffered in the past from any of the following conditions:

- Serotonin Syndrome. In rare cases this syndrome may occur when you are taking certain medicines at the same time as sertraline. (For symptoms, see section 4. Possible Side Effects). Your doctor will have told you whether you have suffered from this in the past.
- If you have low sodium level in your blood, since this can occur as a result of treatment with Zoloft. You should also tell your doctor if you are taking certain medicines for hypertension, since these medicines may also alter the sodium level in your blood.
- Take special care if you are elderly as you may be more at risk of having low sodium level in your blood (see above).
- Liver disease; your doctor may decide that you should have a lower dose of Zoloft.
- Diabetes; your blood glucose levels may be altered due to Zoloft and your diabetes medicines may need to be adjusted.
- Epilepsy or a history of seizures. If you have a fit (seizure), contact your doctor immediately.
- If you have suffered from manic depressive illness (bipolar disorder) or schizophrenia. If you have a manic episode, contact your doctor immediately.
- If you have or have previously had suicidal thoughts (see below-thoughts of suicide and worsening of your depression or anxiety disorder).
- If you have suffered from bleeding disorders or have been taking medicines which thin the blood (eg acetylsalicyclic acid (aspirin), or warfarin) or may increase the risk of bleeding.
- If you are a child or adolescent under 18 years old. Zoloft should only be used to treat children and adolescents aged 6-17 years old, suffering from obsessive compulsive disorder. If you are being treated for this disorder, your doctor will want to monitor you closely (see Use in children and adolescents below).
- If you are having electro-convulsive therapy (ECT).

Restlessness/Akathisia:
The use of sertraline has been linked to akathisia (a distressing restlessness and need to move, often being unable to sit or stand still). This is most likely to occur during the first few weeks of treatment. Increasing the dose may be harmful to patients who develop such symptoms.

Withdrawal reactions:
Withdrawal reactions when treatment is stopped are common, particularly if the treatment is stopped suddenly (see section 4 Possible side effects). The risk of withdrawal symptoms depends on the length of treatment, dosage, and the rate at which the dose is reduced. Generally, such symptoms are mild to moderate. However, they can be serious in some patients. They normally occur within the first few days after stopping treatment. In general, such symptoms disappear on their own and wear off within 2 weeks. In some patients they may last longer (2-3 months or more). When stopping treatment with Sertraline it is recommended to reduce the dose gradually over a period of several weeks or months, depending on the patient's needs.

Thoughts of suicide and worsening of your depression or anxiety disorder:
If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:
- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Use in children and adolescents:
Sertraline should not usually be used in children and adolescents less than 18 years old, except for patients with Obsessive Compulsive Disorder. Patients under 18 have an increased risk of undesirable effects, such as suicide attempt, suicidal thoughts and hostility (mainly aggressiveness, oppositional behaviour and anger) when they are treated with this class of medicines. Nevertheless, it is possible that your doctor decides to prescribe Zoloft to a patient under 18 if it is in the patient's interest. If your doctor has prescribed Zoloft to a patient less than 18 years old and you want to discuss this, please contact him/her. Furthermore, if any of the symptoms listed above appear or worsen when a patient under 18 is taking Zoloft, you should inform your doctor. Also, the long-term safety of Zoloft in regard to growth, maturation and cognitive and behavioural development in this age group has not yet been demonstrated.

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

Some medicines can affect the way Zoloft works, or Zoloft itself can reduce the effectiveness of other medicines taken at the same time.

Taking Zoloft together with the following medicines may cause serious side effects:
- Medicines called monoamine oxidase inhibitors (MAOIs), like moclobemid (to treat depression) and selegiline (to treat Parkinson's disease) and the antibiotic linezolid. Do not use Zoloft together with MAOIs.
- Medicines to treat mental disorders (pimozide). Do not use Zoloft together with pimozide.
- Do not use Zoloft together with disulfiram.

Talk to your doctor if you are taking the following medicine:

- Herbal medicine containing St. John's Wort (*Hypericum perforatum*). The effects of St. John's Wort may last for 1-2 weeks. Talk to your doctor.
- Products containing the amino acid tryptophan.
- Medicines to treat severe pain (e.g. tramadol).
- Medicines to treat migraines (e.g. sumatriptan).
- Blood thinning medicine (warfarin).
- Medicines to treat pain/arthritis (Non steroidal antiinflammatory drug (NSAID) such as ibuprofen, acetylsalicylic acid (aspirin).
- Sedatives (diazepam).
- Diueretics.
- Medicines to treat epilepsy (phenytoin).
- Medicines to treat diabetes (tolbutamide).
- Medicines to treat excessive stomach acid and ulcers (cimetidine).
- Medicines to treat mania and depression (lithium).
- Other medicines to treat depression (such as amitriptyline, nortriptyline).
- Medicines to treat schizophrenia and other mental disorders (such as perphenazine, levomepromazine and olanzapine).

Taking Zoloft with food and drink:
Zoloft tablets can be taken with or without food.
Zoloft capsules should be taken with food.
Zoloft concentrate for oral solution can be taken with or without food.

Alcohol should be avoided whilst taking Zoloft.

Pregnancy and breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine.

The safety of sertraline has not fully been established in pregnant women. Sertraline should only be given to pregnant women if the doctor considers that the benefit for the mother exceeds any possible risk to the foetus. Women of childbearing potential should employ an adequate method of contraception if taking sertraline.

There is evidence that sertraline is excreted in human breast milk. Sertraline should only be used in women during lactation, if the doctor considers that the benefit for the mother exceeds any possible risk to the baby.

Driving and using machines:
Psychotropic drugs such as sertraline may influence your ability to drive or use machines. You should therefore not drive or operate machinery, until you know how this medication affects your ability to perform these activities.

Important information about some of the ingredients of Zoloft:
If you have been told by your doctor that you have intolerance to some sugars contact your doctor before taking this medicinal product.

This medicinal product contains 12 % ethanol (alcohol) and must be diluted before use. Each ml of oral liquid contains 150.7 mg of alcohol. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

This medicinal product contains butylhydroxytoluene which can cause irritation of eyes, skin and mucous membranes. It also contains glycerol which at high doses can cause headache, abdominal pain and diarrhea.

3. HOW TO TAKE ZOLOFT

Always take Zoloft exactly as your doctor has told you.
Zoloft tablets may be taken with or without food.
Zoloft capsules should be taken with food.
Zoloft concentrate for oral solution may be taken with or without food.

Take your medication once daily either in the morning or evening.

You should check with your doctor or pharmacist if you are not sure.

The usual dose is:
Adults:

Depression and Obssessive Compulsive Disorder
For depression and OCD, the usual effective dose is (2.5 ml) 50 mg/day. The daily dose may be increased in (2.5 ml) 50 mg increments and at intervals of at least one week over a period of weeks. The maximum recommended dose is (10 ml) 200 mg/day.

Panic disorder, Social anxiety disorder and Post Traumatic Stress Disorder:
For panic disorder, social anxiety disorder and post traumatic stress disorder, treatment should be started at (1.25 ml) 25 mg/day, and increased to (2.5 ml) 50 mg/day after one week.
The daily dose then may be increased in (2.5 ml) 50 mg increments over a period of weeks. The maximum recommended dose is (10 ml) 200 mg/day.

Children and adolescents:
Zoloft must only be used to treat children and adolescents suffering from OCD aged 6-17 years old.

Obsessive Compulsive Disorder:
Children aged 6 to 12: the recommended starting dose is (1.25 ml) 25 mg daily.
After one week, your doctor may increase this to (2.5 ml) 50 mg daily. The maximum dose is (10 ml) 200 mg daily.
Adolescents aged 13 to 17: the recommended starting dose is (2.5 ml) 50 mg daily.
The maximum dose is (10 ml) 200 mg daily.

If you have liver or kidney problems, please tell your doctor and follow the doctor's instructions.

Your doctor will advise you on how long to take this medication for. This will depend on the nature of your illness and how well you are responding to the treatment. It may take several weeks before your symptoms begin to improve

Instructions to take Zoloft properly:
The concentrate for oral solution must always be diluted before use. Never drink the concentrate undiluted.

The first time you open the bottle of oral concentrate, you should put the pipette on the bottle as follows:

1. Unscrew the cap on the bottle by pushing down hard on the cap while turning the cap to the left (counter clockwise). Dispose of the cap.
2. Put the dropper on the bottle and tighten well. The dropper is found in the carton.
3. When you later open the bottle, push down hard on the dropper while turning the dropper to the left (counter clockwise).
4. Put the dropper back on the bottle after use.

Measuring the dose:
Use the dropper to measure the dose, as prescribed by the doctor.
Mix the measured dose with 120 ml (one glass) of liquid. This may be water, ginger ale, lemon/lime soda, lemonade or orange juice.
Do not mix the concentrate with anything other than the liquids listed. The mixture should be taken immediately after mixing. The mixture may be a little cloudy, but this is normal.

If you take more Zoloft than you should:
If you accidentally take too much Zoloft contact your doctor at once or go to the nearest hospital casualty department. Always take the labelled medicine package with you, whether there is any medication left or not.

Symptoms of overdose may include drowsiness, nausea and vomiting, rapid heartrate, shaking, agitation, dizziness and in rare cases unconsciousness.

If you forget to take Zoloft:
If you forget to take a dose, do not take the missed dose. Just take the next dose at the right time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zoloft:
Do not stop taking Zoloft unless your doctor tells you to. Your doctor will want to gradually reduce your dose of Zoloft over several weeks, before you finally stop taking this medicine. If you suddenly stop taking this medicine you may experience side effects such as dizziness, numbness, sleep disturbances, agitation or anxiety, headaches, feeling sick, being sick and shaking. If you experience any of these side effects, or any other side effects whilst stopping taking Zoloft, please speak to 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, Zoloft can cause side effects, although not everybody gets them.

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.

Nausea is the most common side effect. The side effects depend on the dose and are often transient with continued treatment.

Tell your doctor immediately:
If you experience any of the following symptoms after taking this medicine, these symptoms can be serious.

- If you develop a severe skin rash that causes blistering (erythema multiforme), (this can affect the mouth and tongue). These may be signs of a condition known as Stevens Johnson Syndrome, or Toxic Epidermal Necrolysis (TEN). Your doctor will stop your treatment in these cases.

- Allergic reaction or allergy, which may include symptoms such as an itchy skin rash, breathing problems, wheezing, swollen eyelids, face or lips.
- If you experience agitation, confusion, diarrhoea, high temperature and blood pressure, excessive sweating and rapid heartbeat. These are symptoms of Serotonin Syndrome. In rare cases this syndrome may occur when you are taking certain medicines at the same time as sertraline. Your doctor may wish to stop your treatment.
- If you develop yellow skin and eyes which may mean liver damage.
- If you experience depressive symptoms with suicidal ideas.
- If you start to get feelings of restlessness and not be able to sit or stand still after you start to take Zoloft. You should tell your doctor if you start to feel restless.

The following side effects were seen in clinical trials in adults.

Very common side effects (occurs in more than 1 out of 10 patients):
Insomnia, dizziness, sleepiness, headache, diarrhoea, feeling sick, dry mouth, ejaculation failure, fatigue.

Common side effects (occurs in between 1 and 10 out of 100 patients):
Sore throat, anorexia, increased appetite, depression, feeling strange, nightmare, anxiety, agitation, nervousness, decreased sexual interest, teeth grinding, numbness and tingling, shaking, muscle tense, abnormal taste, lack of attention, visual disturbance, ringing in ears, palpitations, hot flush, yawning, abdominal pain, vomiting, constipation, upset stomach, gas, rash, increased sweating, muscle pain, sexual dysfunction, erectile dysfunction, chest pain.

Uncommon side effects (occurs in between 1 and 10 out of 1.000 patients):
Chest cold, runny nose, hallucination, feeling too happy, lack of caring, thinking abnormal, convulsion, involuntary muscle contractions, abnormal coordination, moving a lot, amnesia, decreased feeling, speech disorder, dizziness while standing up, migraine, ear pain, fast heartbeat, high blood pressure, flushing, breathing difficulty, possible wheezing, shortness of breath, nose bleed, oesophageal problem, difficulty swallowing, haemorrhoids, increased saliva, tongue disorder, burping, eye swelling, purple spots on skin, hair loss, cold sweat, dry skin, hives, osteoarthritis, muscular weakness, back pain, muscle twitching, nighttime urination, unable to urinate, increase in urination, increase in frequency of urination, problem urinating, vaginal haemorrhage, female sexual dysfunction, malaise, chills, fever, weakness, thirst, weight decreased, weight increased.

Rare side effects (occurs in between 1 and 10 out of 10.000 patients):
Intestine problem, ear infection, cancer, swollen glands, high cholesterol, low blood sugar, physical symptoms due to stress or emotions, drug dependence, psychotic disorder, aggression, paranoia, suicidal thoughts, sleep walking, premature ejaculation, coma, abnormal movements, difficulty moving, increased sensation, sensory disturbance, glaucoma, tear problem, spots in front of eyes, double vision, light hurts eye, blood in the eye, enlarged pupils, heart attack, slow heart beat, heart problem, poor circulation of arms and legs, closing up of throat, breathing fast, breathing slow, difficulty talking, hiccups, blood in stool, sore mouth, tongue ulceration, tooth disorder, tongue problem, mouth ulceration, problems with liver function, skin problem with blisters, hair rash, hair texture abnormal, skin odour abnormal, bone disorder, decreased urination, urinary incontinence, urinary hesitation, excessive vaginal bleeding, dry vaginal area, red painful penis and foreskin, genital discharge, prolonged erection, breast discharge, hernia, injection site scarring, drug tolerance decreased, difficulty walking, abnormal laboratory tests, semen abnormal, injury, relaxation of blood vessels procedure**.**

After marketing sertraline, the following side effects have been reported:
Decrease in white blood cells, decrease in clotting cells, low thyroid hormones, endocrine problem, low blood salt, terrifying abnormal dreams, suicidal behaviour, muscular movement problems (such as moving a lot, tense muscles and difficulty walking), passing out, vision abnormal, bleeding problems (such as nose bleed, stomach bleeding, or blood in urine), pancreatitis, serious liver function

problems, yellow jaundice, skin oedema, skin reaction to sun, itching, joint pain, muscle cramps, breast enlargement, menstrual irregularities, swelling in legs, problems with clotting, and severe allergic reaction.

Side effects in children and adolescents
In clinical trials with children and adolescents, the side effects were generally similar to adults (see above). The most common side effects in children and adolescents were headache, insomnia, diarrhoea and feeling sick.

5. HOW TO STORE ZOLOFT

Keep out of the reach and sight of children.

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

[To be completed nationally]

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Zoloft contains

[To be completed nationally]

What Zoloft looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer
[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<This medicinal product is authorised in the Member States of the EEA under the following names:>

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

[See Annex I - To be completed nationally]
This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

“The Marketing Authorisation Holder has committed:

To provide the relevant non-clinical data on juvenile animal toxicity available in the public domain, in order to justify why no further data needs to be generated in this field,

To undertake a long-term safety study looking at aspects of growth, sexual maturation, cognitive and emotional development to support the paediatric OCD indication in paediatric patients aged 6-17 years old. This study includes a comparison group consisting of paediatric patients receiving psychotherapy alone.”