European Medicines Agency

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Questions and answers on the referral for Zoloft
Hard capsules and film coated tablets containing 25 mg, 50 mg or 100 mg sertraline
Concentrate for oral solution containing 20 mg/ml sertraline

The European Medicines Agency (EMEA) has completed a review of Zoloft. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that there is a need to harmonise the prescribing information for Zoloft in the European Union and the European Economic Area (EEA). The review was carried out under an 'Article 30' referral[1].

What is Zoloft?
Zoloft contains the active substance sertraline. Sertraline is a selective serotonin re-uptake inhibitor (SSRI), It works by preventing the neurotransmitter serotonin from being taken back up into nerve cells in the brain and spinal cord. Neurotransmitters are chemicals that transfer chemical signals from one nerve cell to another. Low levels of serotonin in the central nervous system may be associated with depression or anxiety.
Zoloft can be used in adults to treat depression and prevent recurrence of depression, social anxiety disorder, post traumatic stress disorder (PTSD), panic disorder; and to treat obsessive compulsive disorder (OCD) in adults and children and adolescents, aged 6-17 years old.

Zoloft can also be available in the EU and the EEA under other trade names: Tresleen, Serlain, Lustral, Tatig, Sertraline and Besitran.

Why was Zoloft reviewed?
Zoloft is authorised in the European Union (EU) via national procedures. This has led to divergences across member states on the way the medicine can be used, as seen in the differences observed in the Summaries of Product Characteristics (SPCs), labelling and package leaflets in the countries where the product is marketed. Zoloft has been identified as needing harmonisation by the Co-ordination Group on the Mutual and Decentralised Procedures – Human (CMD(h)).

On 18 October 2007, the European Commission referred the matter to the Committee for Medicinal Products for Human Use (CHMP) in order to harmonise the marketing authorisations for Zoloft in the EU and the EEA.

What are the conclusions of the CHMP?
The CHMP, in the light of the data submitted and the scientific discussion within the Committee, was of the opinion that the SPCs, labelling and package leaflets should be harmonised across the EU. The areas harmonised include:

<u>Therapeutic Indication</u>

Panic disorder with or without agoraphobia disorder. The CHMP discussed the results of the clinical programme that showed a significant improvement in reducing panic attacks.

[1] Article 30 of Directive 2001/83/EC as amended, referral on the grounds of divergent decisions adopted by member States

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The CHMP concluded that short-term efficacy has been demonstrated, but that concerns remain over the lack of evidence with respect to relapse. Although the safety profile of sertraline is acceptable, the CHMP implemented the section 'Posology and Method of Administration' of the SPC, to indicate that the need for continued treatment should be regularly evaluated.
The CHMP endorsed the harmonised indication: *"Panic disorder with or without agoraphobia"*.

Post-traumatic Stress Disorder:. The CHMP also discussed this indication.
Data from the clinical programme for the indication PTSD were submitted and the results showed that only two of the four studies demonstrated efficacy. Considering the incidence of adverse events in PTSD, the CHMP agreed that the safety of sertraline in the treatment of PTSD is similar to that of major depressive disorder and does not present any new issues.
The CHMP endorsed the harmonised indication:
"Sertraline is indicated for the treatment of post traumatic stress disorder (PTSD)",

The CHMP, considered the benefit/risk balance, approved the following indication:
"Sertraline is indicated for the treatment of social anxiety disorder".

Obsessive Compulsive Disorder in adults. The clinical programme for the indication OCD was submitted and sertraline demonstrated a modest short-term effect and no safety concerns. Therefore the CHMP endorsed the following indication:
"Sertraline is indicated for the treatment of obsessive compulsive disorder (OCD) in adults",

Obsessive Compulsive Disorder in paediatric patients .In order to support the paediatric indication, one single study was submitted including children and adolescents aged 6-17. Paediatric-onset OCD shares important similarities with the adult disorder but also shows important differences.
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 in order to adopt 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 the section 5.1 "Pharmacodynamic Properties" of the SPC:
"Long term safety and efficacy data are lacking for this paediatric population. No data is available for children under 6 years of age."

Depression. The CHMP considered acceptable the evidence in support of the depression indication. Prevention of relapse and recurrence was proposed during the assessment by the CHMP. Noting that major depression is considered to be a chronic or chronic intermittent condition, the CHMP considered it unnecessary to accept this separate indication.
The CHMP adopted the following:

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

<u>Posology and Method of Administration</u>

The CHMP considered the wordings proposed for this section to be acceptable.
Regarding the dosing of paediatric patients with OCD, the CHMP requested the insertion of the following wording in this section:

"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.

Contraindications

Pimozide. The CHMP endorsed the following: "*Concomitant intake of pimozide is contraindicated (see section 4.5)"*

Hepatic Impairment. The CHMP considered that patients with significant hepatic impairment are not strictly contraindicated with sertraline and that appropriate warnings are provided in the concerning section of the product information.

The European Commission issued a decision on 27 March 2009.

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