Annex II

Scientific conclusions

Scientific conclusions

Amitriptyline is a well-known tricyclic antidepressant with an established mechanism of action and use (Brunton 2011)[1]. Amitriptyline is a tertiary amine that acts primarily as a serotonin-norepinephrine reuptake inhibitor. Its main metabolite, nortriptyline, is a more potent and selective norepinephrine reuptake inhibitor, although it still blocks serotonin uptake. Amitriptyline has potent anticholinergic, antihistaminergic, and sedative properties and it potentiates the effects of catecholamines.

Amitriptyline was first approved by the US in 1961. In the EU the originator product for amitriptyline is marketed as Saroten (and associated names including Saroten Retard, Saroten Tabs, Sarotex, Sarotex Retard, Redomex and Redomex Diffucaps). It is authorised in the following Member States: AT, BE, CY, DK, DE, EE, EL, LU, NL, NO and SE. Other amitriptyline containing products are also authorised under different brand names in the EU. Amitriptyline is authorised worldwide in more than 56 countries.

Saroten is available for oral use in film-coated tablets and modified-release capsules and tablets, with strengths including 10, 25, 50 and 75 mg. It is also available as solution for injection (2ml, 50 mg).

As part of the assessment of a previous PSUR procedure for amitriptyline (PSUSA/0000168/201501), the Lead Member, Greece, identified the need to harmonise the product information for the originator Saroten across the EU. The current SmPCs approved in the EU Member States differ significantly in the approved indications, posology and recommendations for use.

Therefore, due to the divergent national decisions taken by Member States concerning the authorisation of amitriptyline-containing products, Greece notified the Agency on 17 December 2015 of a referral under Article 30 of Directive 2001/83/EC for Saroten and associated names, in order to resolve divergences amongst the nationally authorized SmPCs for the above-mentioned product and thus to harmonise its divergent SmPCs across the EU.

Overall summary of the scientific evaluation by the CHMP

Therapeutic Indications

Amitriptyline is a well-established product with a long standing use as antidepressant. Taking into account current treatment guidelines and recent systematic reviews published in the literature, the CHMP endorsed an indication for amitriptyline in the treatment of major depressive disorder in adults.

Although the use of amitriptyline in a broad indication in chronic pain was not agreed by the CHMP, the use of amitriptyline in the treatment of neuropathic pain in adults was considered supported by recent systematic reviews and meta-analysis of pharmacological treatments of this condition. On the other hand, the evidence provided by the MAH on the use of amitriptyline in non-specific neuropathic conditions such as phantom pain, cancer neuropathy and HIV neuropathy was not considered adequate to support a specific indication in these pain categories. Moreover, the CHMP did not endorse a separate indication in nociceptive pain due to the insufficient evidence provided in relation to back pain and visceral pain.

In addition, the CHMP concluded that the totality of the data provided by the MAHs was supportive of a first line treatment for amitriptyline in the prophylactic treatment of chronic tension type headache (CTTH) and migrane in adults, although a specific indication in fibromyalgia was not agreed.

[1] Brunton, L. L.; Chabner, Bruce; Knollmann, Björn C. 2011. *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (McGraw-Hill: New York).

Finally, based on current recommendations by national and international treatment guidelines and available literature, the use of amitriptyline for enuresis nocturna in children was restricted to third line therapy in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products.

Posology

The MAHs proposed harmonised dosing recommendations based on the doses studied in clinical trials and in line with the reference book Martindale (Martindale 2014). The therapeutic effect is normally seen after 2-4 weeks of dosing.

On review of all available data the recommended doses for the treatment of depression in adults is of 50 mg daily. If necessary, the dose can be increased by 25 mg every other week. The maintenance dose is the lowest effective dose and doses above 150 mg daily are not recommended.

For the elderly patients over 65 years of age and patients with cardiovascular disease it is generally recommended to initiate treatment in the lower dose range as recommended for adult, as these populations are particularly susceptible to the known adverse reactions and in particular cardiac toxicity. A starting dose of 10-25 mg in the evening are recommended for this patient population and although the dose may be increased depending on individual patient response and tolerability, doses above 100 mg should be used with caution.

Based on the available clinical data of parenteral amitriptyline administration to depressed patients as well as on pharmacokinetic parameters the recommended dosage is 50 – 150 mg/day, given in 1 to 3 ampoules daily. A maximum daily dosage of 150 mg amitriptyline given by injection/infusion should not be exceeded.

For the treatment of pain (neuropathic pain, prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine) in adults doses are in general lower than in depression, with doses rarely exceeding 100 mg. Dosing should start with 10mg at bedtime and then titrated in 10-25mg increments every 3-7 days. Generally, patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions and in all cases the lowest effective dose should be used for the shortest duration required to treat the symptoms.

The recommended starting dose for the treatment of pain in the elderly and patients with cardiovascular disease is 10 mg to 25 mg in the evening. In this patient population doses above 75 mg should be used with caution. In addition, as treatment is symptomatic it should be continued for an appropriate length of time. In many patients, therapy for neuropathic pain may be needed for several years. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

Based on the drug reference Martindale (Martindale 2014) the recommended dose for nocturnal enuresis is 10 mg to 20 mg for children aged 6 to 10 years and 25 mg to 50 mg for children aged 11 years to 17 years. It is most important to increase the dose gradually. The posology schemes cannot be achieved with every available formulation/strength and a suitable formulation/strength should be sought for a specific dose. In addition, treatment duration should not to exceed a period of 3-months and ECG should be performed prior to initiating therapy to exclude long QT syndrome.

Other sections of the SmPC

The data supporting contraindications included in section 4.3 of the SmPC was discussed by the MAHs and the rationale provided for keeping them in the SmPC was agreed by the CHMP for the following ones:

- Hypersensitivity to the active substance or to any of the excipients.

- Recent myocardial infarction. Any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency.

- Concomitant treatment with MAOIs (monoamine oxidase inhibitors)

- Severe liver disease.

- In children under 6 years of age.

A warning was added in section 4.4 of the SmPC on the risk of QT prolongation.

Section 4.5 of the SmPC on drug interactions was revised based on a review of the latest literature available.

With regards to fertility, pregnancy and lactation, section 4.6 of the SmPC was updated based on the review and analysis of all the available data provided by MAHs including literature, and post marketing data from the MAH Global Safety database. Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

The MAHs have performed an analysis of their databases and considered all available information in the literature including classical textbooks such as Martindale (Martindale 2014), in order to justify the inclusion of adverse drug reactions, for which a causal relationship is at least a reasonable possibility. In addition, section 4.9 of the SmPC focusing on the management of overdose has been streamlined.

Section 5.1 was revised to include a short factual description of the mechanism of action and Section 5.2 was updated to include data supporting the pharmacokinetic properties, especially of the parenteral formulation have been presented and discussed.

Finally, section 5.3 on preclinical safety data has been modified according to the most recent and relevant information from literature to reflect current knowledge with regards to cardiac toxicity, genotoxic potential, embryotoxicity and effect on fertility.

Labelling

Changes introduced in the SmPC were consistently reflected in the labelling where relevant, however most sections were left to be completed nationally.

Package Leaflet

The package leaflet was amended in accordance with the changes made to the SmPC.

Grounds for the CHMP opinion

Whereas

- the scope of the referral was the harmonisation of the product information,
- the product information proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,
- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the divergences identified in the notification for Saroten and associated names, as well as the remaining sections of the product information.

- The committee reviewed the totality of the data submitted by the MAHs as well as relevant available literature in support of the proposed harmonisation of the product information,

the CHMP recommended the variation to the terms of the marketing authorisations for which the product information is set out in Annex III for Saroten and associated names (see Annex I).

The CHMP as a consequence, concluded that the benefit-risk balance of Saroten and associated names remains favourable, subject to the agreed changes to the product information.