EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Saroten and associated names

INN/active substance: amitriptyline

Procedure number: EMEA/H/A-30/1430

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product, the Greek National Competent Authority notified the CHMP/European Medicines 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 authorised product information and thus harmonise its divergent product information across the EU.

2. Scientific discussion

2.1. Introduction

Amitriptyline is a well-known tricyclic antidepressant (TCA) with an established mechanism of action and use (Brunton 2011). 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) by H. Lundbeck A/S group of companies and associated companies, Bayer Vital GmbH and PNG Gerolymatos Medical A.E. 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 and associated names are available for oral use in film-coated tablets and modified-release capsules and tablets with strengths including 10, 25, 50 and 75 mg. Saroten 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 State, Greece, identified the need to harmonise the product information for the originator Saroten across the EU. The current Summaries of Product Characteristics (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.

2.2. Critical Evaluation

Submitted supporting data consisted of published studies conducted with amitriptyline. These studies, reviews and meta-analyses have been assessed together with the current relevant guidelines.

The Product Information (PI) of amitriptyline-containing products currently approved in the EU countries and some additional published reviews on the use of the tricyclic antidepressants have also been taken into account.

The main points discussed for the harmonisation of the different sections of the PI are hereafter summarised.

2.2.1. Product information

Section 4.1 – Therapeutic Indications

Treatment of depression

Current Saroten indications in depression vary on national basis and include:

- Depression
- Depressive episodes
- Treatment of depression and other depressive disorders
- Endogenous depression and other depressive disorders
- Major depression
- Major depressive episodes in adults
- Major depressive disorder with melancholia, severe or long lasting
- Major depressive disorder without melancholia.
- Bipolar syndrome with major depressive disorder
- Depression, particularly endogenous. More appropriate in patients with anxiety and psychomotor restlessness.
- In-hospital treatment of depression

Amitriptyline is a well-established product with a long standing use as antidepressant. MAHs have provided the reference book Martindale (Martindale 2014) and the online reference resource Micromedex (Micromedex 2016) as the main sources supporting the indication on depression. Martindale was considered as a comprehensive and reliable reference resource on drugs and their use. In addition, the CHMP took into consideration recent publications and systematic reviews published in the literature (Leucht, Huhn, and Leucht 2012; Guaiana, Barbui, and Hotopf 2007, 2003) and the following current treatment guidelines:

- Practice guideline for the treatment of patients with major depressive disorder - American Psychiatric Association, 2010

- Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines

- Goodman Gilman: The Pharmacological Basis of Therapeutics, Chapter 15, 2017

- Harrison Principles of Internal Medicine, Chapter 466, 2017

- World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders

- What are the most effective diagnostic and therapeutic strategies for the management of depression in specialist care? WHO 2005

- A Systematic Review of Newer Pharmacotherapies for Depression in Adults: Evidence Report Summary (Williams et al. 2000)

Based on the available evidence the CHMP considered necessary a rewording of the indication to major depressive disorder in adults. The specific indications on depressive states in the context of other disorders such as bipolar syndrome are considered covered by the main indication in major depressive disorders.

Therefore the final endorsed wording for the treatment of depression was the following:

Oral use

- The treatment of major depressive disorder in adults.

Solution for injection

- In-hospital treatment of major depressive disorder in adults.

Treatment of pain

Current Saroten indications in chronic pain vary on national basis and include:

- Chronic pain
- In certain cases of chronic pain (e.g. with cancer patients, neuropathic pain) in order to reduce symptoms
- Chronic pain in line with the therapeutic concept

In order to justify a general indication for the treatment of chronic pain, compelling evidence in both neuropathic and nociceptive pain components was expected, a per draft guideline on the clinical development of medicinal products intended for the treatment of pain (EMA/CHMP/970057/2011, Corr. 1). Therefore, current clinical evidence in support of the use of amitriptyline in the treatment of chronic pain was reviewed addressing separately the different categories of chronic pain.

Neuropathic pain

The use of amitriptyline in the treatment of neuropathic pain is supported by recent systematic reviews and meta-analysis of pharmacological treatments of neuropathic pain in adults (Moore et al. 2015; Finnerup et al. 2015; Moore et al. 2012). Although the trial sizes within the clinical trials are modest, the number of trials can be considered substantial and the benefit of the use of amitriptyline is considered proven.

Amitriptyline has been studied in randomized double-blind placebo-controlled studies in the following neuropathic pain conditions: Central post stroke pain (Leijon and Boivie 1989), Spinal Cord Injury Pain (Baastrup and Finnerup 2008), Peripheral Nerve Injury Pain (PNI) (Max et al. 1987; Kalso, Tasmuth, and Neuvonen 1996), painful diabetic polyneuropathy (PDN) (Max et al. 1987; Vrethem et al. 1997), post-herpetic neuralgia (PHN) (Watson et al. 1982; Max et al. 1988), painful peripheral polyneuropathy (PPP) (Vrethem et al. 1997; Kieburtz et al. 1998) and multiple sclerosis (MS) pain (Osterberg A 2005) .

Amitriptyline has also been used as a standard-of-care comparator in head-to head comparisons in post-herpetic neuralgia (PHN) (Achar et al. 2012; Graff-Radford, Shaw, and Naliboff 2000; Max et al. 1988; Rowbotham et al. 2005; Watson et al. 1992; Watson et al. 1998; Watson and Evans 1985), Painful Peripheral Polyneuropathy (PPP) including Painful Diabetic Polyneuropathy (DPN) (Kieburtz et al. 1998; Vrethem et al. 1997; Kaur et al. 2011; Morello et al. 1999; Bansal et al. 2009; Boyle et al. 2012) deafferentation pain (Ventafridda et al. 1987; Ventafridda et al. 1988), Spinal Cord Injury (SCI) Pain (Rintala et al. 2007), where amitriptyline overall has been found to be superior to fluphenazine, zimelidine, maprotiline, and other antidepressants and not different from nortriptyline, tradozone, gabapentin, pregabalin, nortriptyline, imipramine and desipramine. In trials with patients with diabetic neuropathy, amitriptyline has overall been shown to be efficacious (Bansal et al. 2009; Boyle et al. 2012; Kaur et al. 2011; Jose et al. 2007; Morello et al. 1999; Max et al. 1992; Max et al. 1987).

In addition, amitriptyline is considered first line treatment in several international and national guidelines on the treatment of neuropathic pain including the European Federation of Neurological Societies (EFNS) and the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest group (NeuPSIG) (Attal et al. 2010).

There are few published studies on the use of amitriptyline in non-specific neuropathic conditions such as phantom pain, cancer neuropathy and HIV neuropathy, and although the use is recommended by clinical guidelines, it is not supported by randomised controlled clinical trial data mainly due to the difficulties of performing controlled trials in particular in cancer pain (Vadalouca et al. 2012). Overall the data provided cannot be considered as sufficient evidence to support a specific indication in these pain conditions; however, the CHMP was of the opinion that this fact should not limit a general indication in neuropathic pain.

Therefore the final endorsed wording for the treatment of neuropathic pain was the following:

- The treatment of neuropathic pain in adults.

Nociceptive Pain

Two clinical trials have been published supporting the use of amitriptyline in chronic low back pain (Pheasant et al. 1983; Kalita et al. 2014). There are also some clinical trials published in two models of visceral pain, interstitial cystitis/painful bladder syndrome (IC/PBS) and irritable bowel syndrome (IBS)(van Ophoven et al. 2004; Foster et al. 2010; van Ophoven and Hertle 2005; Sohn et al. 2012), including two meta-analyses in IBS reviewing the use of tricyclics vs. placebo (Ford et al. 2009; Chao and Zhang 2013). One randomised head-to-head clinical trial has shown evidence supporting the use in amitriptyline in women with chronic pelvic pain (Sator-Katzenschlager et al. 2005).

In terms of current clinical practice, a recent guideline from the International Association for the Study of Pain recommends amitriptyline as first line treatment in functional abdominal pain (Farmer AD 2013). In addition, the current treatment guideline on IC/PBS by the American Urology Association considers amitriptyline as second line treatment of an evidence level B (Hanno et al. 2011; Hanno et al. 2015).

The data presented to support the use of amitriptyline in nociceptive pain was not considered sufficient to recommend a separate indication in this pain category. TCAs have shown to produce moderate symptom reductions for patients with chronic low back pain and visceral pain, however, this is based on a small number of studies, most of which were not randomised controlled clinical trial data. Based on the limited data available, the CHMP was not supportive of recommending an indication in nociceptive pain.

Headaches

i. *Chronic tension type headache* (CTTH)

The MAHs carried out a literature search for chronic tension type headache and amitriptyline. In total, 21 publications were identified (11 were randomised clinical trials) including 964 patients, out of which 552 having received amitriptyline. A total of 298 patients received amitriptyline as monotherapy. Six of these were placebo controlled in which amitriptyline was favoured due to significant reduction in headache frequency and/or headache duration compared to the comparator, placebo (see Table 1). Five studies compared amitriptyline to five different active treatments without a placebo control, pindolol, buspirone, citalopram, ritanserin, stress management therapy and spinal manipulation (See Table 2).

Table 1 Placebo controlled trials of Chronic Tension Type Headache (CTTH) with endpoints and whether they favour amitriptyline (AMI) or comparator.

Author	Comparator	AMI dose (mg)	Headache frequency	Headache duration	Headache index (frequency* duration)	Pain intensity	AUC (duration* intensity)	Responder rate	Rescue analgesics
Agius	Placebo	10	AMI			AMI		AMI	AMI
Bendtsen	Placebo	75		AMI			AMI		AMI
Couch	Placebo	75	AMI					AMI	
Göbel	Placebo	75					AMI		
Holroyd	Placebo	25-100	AMI		AMI			AMI	AMI
Pfaffenrath[1]	Placebo	50-75			No diff	AMI[1]		No diff	AMI

[1]confoundingly high number of rescue analgesics. Post hoc analysis in patients not taking rescue favours AMI.

Table references: (Agius, Jones, and Muscat 2013; Bendtsen, Jensen, and Olesen 1996; Couch and Amitriptyline Versus Placebo Study 2011; Gobel et al. 1994; Holroyd et al. 2001; Pfaffenrath et al. 1994)

Table 2 Comparator trials of Chronic Tension Type Headache (CTTH) with endpoints and whether they favour amitriptyline (AMI) or comparator

Author	Comparator	AMI dose (mg)	Headache frequency	Headache duration	Headache index (frequency* duration)	Pain intensity	AUC (duration* intensity)	Responder rate	Rescue analgesics
Bettucci	Tizanidine 4mg + AMI	20		Combination	No sign diff	Combina-tion			
Boline	Spinal manipulation	30	No diff				AMI		No diff
Mitsikostas	Buspirone	50			No diff				AMI
Nappi	Ritanserin 30mg	50					AMI		AMI
Rampello	Citalopram 20mg/ AMI+citalopram	50		No difference between mono, favours combo		No difference between mono, favours combo		No difference between mono, favours combo	

Table references: (Bettucci et al. 2006; Boline et al. 1995; Mitsikostas et al. 1997; Nappi et al. 1990; Rampello et al. 2004)

The scientific evidence discussed by the MAHs comprises studies with mostly adequate designs and outcome measures. Although some deficiencies in methodological design were identified including the absence of a specific posology recommendation, differences in the definition of endpoints, and in some studies the open-label nature (e.g. (Bettucci et al. 2006)) or small sample sizes (e.g. (Nappi et al. 1990)), the overall evidence presented supports the use of amitriptyline in the prophylactic treatment of CTTH.

It should also be noted that none of the active comparators namely pindolol, buspirone, citalopram and ritanserin has an approved indication the prevention of CCTH. In addition, results obtained from the trials are not statistically significant for all the evaluated outcomes.

In terms of clinical practice, current treatment guidelines widely accept and recommend the use of amitriptyline in chronic tension type headache. Most European and international guidelines recommend the use of amitriptyline in chronic tension type headache among other therapeutic approaches (see Table 3).

Table 3. National treatment guidelines for the management and treatment of CTTH and for migraine prophylaxis

Country / reference	CTTH		Migraine	
	1st line/ level of evidence (A/B/C/-)	2nd line/ level of evidence (A/B/C/-)	1st line/ level of evidence (A/B/C/-)	2nd line / level of evidence (A/B/C/-)
Denmark – same as EFNS	AMI (A)	mirtazapine (B), venlafaxine (B) 3rd choice: Clomipramine (B), maprotiline (B), mianser-in (B)	propranolol (A), metoprolol (A), fluranizine (A), valproate (A), topiramate (A)	AMI (B), venlafaxine (B), bisoprolol (B)
EFNS (CTTH 2010, migraine 2009)	AMI (A)	mirtazapine (B), venlafaxine (B) 3rd choice: Clomipramine (B), maprotiline (B), mianserin (B)	propranolol (A), metoprolol (A), fluranizine (A), valproate (A), topiramate (A)	AMI (B), venlafaxine (B), bisoprolol (B)
France (2014)	Refers back to ICH/ EFNS, no French recommendation for pharmacological treatment first line	AMI, valproate, GBP, fluoxetin	Beta blockers (A-B)	AMI (B), candesartan (B/C), flunarizine (B/C), valproate (A), topiramate (A)
Germany (2008)	Amitriptyline (A)	Mirtazapine (B), clomipramine (B),	Topiramate (B), valproate (B), amitriptyline (B), beta	Botulinum toxin (C), CBT (B), biofeedback

Country / reference	CTTH		Migraine	
		doxepine (B), imipramin (B), tizanidin (B), valproate (B). Topiramate (C), sulpirid (C), physiotherapy/ manual therapy (C).	blocker (B), flunarizin (B)	(C)
Italy	AMI (A) Mirtazapine (A)	Clomipramine (B), flovoxamine (B), maprotiline (B), mianser-ine (A), venlafaxine (B), tizanidine (B), topiramate (C), diazepam (B),	Propranolol, metoprolol, atenolol, flunarizine, AMI, valproate, topiramate (without order of recommen-dation)	Other beta blockers, gabapentin, cinnarizine
Netherlands (2008)	AMI		Propranolol, metoprolol, atenolol, flunarizine, AMI, valproate, topiramate (without order of recommen-dation)	
Portugal 2009	AMI, (nortriptyline, imipramine, clorimi-pramine, doxepine, maprotiline, mianserine, dotiepin (All A)	Paroxetine, fluoxetine, venlafaxine, sertraline (all A)	Beta blockers (propranolol (A), timolol (A), metoprolol (B)Atenolol (B), nadolol (B), fluranizine (A), AMI (A) Valproate (A) topiramate (A)	Fluoxetine (B), verapamil (B), gabapentin (B),

Country / reference	CTTH		Migraine	
Spain (2011)	AMI (A) (nortriptyline if not tolerated)	Clomipramine (A), Mirtazapine (A), maprotiline (A), mianserine (A)	Propranolol, metoprolol, atenolol, flunarizine, AMI, valproate, topiramate (without order of recommendation)	Other beta blockers, gabapentin, Botulinum toxin A, fluvoxamine, candesartan
Sweden (2016) Läkemedelsboken	AMI, nortriptyline	None	Propranolol (A), metoprolol (A)	Pizotifen, Topiramate, dihydroergotamine (license drug), 3rd line (stated due to no MA): AMI, valproate, fluranizine but documented efficacy stated in reference).
Sweden (2016) www.internetmedicin.se (independent expert website)	AMI (A)	None	Propranolol, metoprolol, atenolol	Amitriptyline, fluranizine, topiramate, verapamil, candesartan
Switzerland	Antidepressants (not specified)		Without order of prioritization: Bisoprolol, candesartan, Lisinopril, metoprolol, propranolol, telmisartan. AMI, imipramine, nortriptyline, clomipramine, doxepin, trimiptramin, vanlafaxin, duloxetin, mirtazapine, topiramate, valproate	
UK (2008, 2016)	AMI	dothiepin, Nortriptyline, protriptyline (for tolerability)	Beta blockers without intrinsic activity AMI (or nortriptyline, desipramine, protriptyline for tolerability)	Topiramate, valproate
In summary, for prevention of CTTH, AMI is most often the first line recommendation across Europe, also in countries where Lundbeck does not have the indication approved. Evidence level graded A, when graded in recommendations. For migraine prophylaxis, AMI is recommended as the first line option in some countries, and as the second line in others. Evidence level graded A or B, when graded in recommendations.				

In conclusion, the totality of the data available is supportive of an indication for amitriptyline as a first line treatment in the prevention of chronic tension type headache. The CHMP considered that the published available data from randomised clinical trials on amitriptyline together with the recommendations in current therapeutic guidelines supported an indication for amitriptyline in the prevention of CTTH.

Therefore the final endorsed wording for the prevention of CTTH was the following:

- The prophylactic treatment of chronic tension type headache (CTTH) in adults.

ii. Migraine

The MAHs carried out a literature search for migraine prophylaxis and amitriptyline. In total 20 publications were identified describing randomised controlled trials, 11 of which were double-blind and

9 were open label. Six studies were placebo controlled trials (see Table 4) and 10 studies compare amitriptyline to one or two active treatments: botulinum toxin A, citalopram, dihydroergotamine ER, divalproate, fluvoxamine, fluoxetine, pizotifen, propranolol, topiramate and venlafaxine (see Table 5). At least 1400 patients were exposed to amitriptyline in small to medium size trials. All studies included at least one of the endpoints advised by the ICH guidelines for migraine trials.

The MAHs provided an extensive review of the existing literature on clinical trials investigating amitriptyline in migraine prophylaxis with most of the relevant studies listed. Despite some caveats including substantial drop-out rates, clinically meaningful effect was demonstrated in these trials in the prophylaxis of migraine. Most studies report adequate recommended endpoints, e.g. headache frequency and index and included at least one of the endpoints advised by the ICH guidelines for migraine trials (Tfelt-Hansen et al. 2012). Attack frequency and duration in migraine were clinically meaningful since both attacks and fear of an attack are equally disabling to migraine patients.

In addition, a recent Cochrane meta-analysis was evaluated (Jackson et al. 2015). The meta-analysis included a pooled analysis of 6 placebo controlled trials and showed a benefit of amitriptyline over placebo for the prophylaxis of migraine.

Table 4. Placebo controlled trials in migraine prophylaxis with endpoints and whether they favour amitriptyline (AMI) vs. placebo

Author	Compara-tor	AMI dose (mg)	Frequency	Duration	Headache index (frequen-cy* duration)	Pain intensity	Responder rate	Rescue analgesics
Couch 1976	Placebo	25-100			AMI			
Couch 1979	Placebo	25-100	AMI				AMI	
Couch 2011	Placebo	25-100		No Diff	AMI	No diff		
Gomersall 1973	Placebo	10-60	AMI	AMI				
Mathew 1981	Placebo	75			AMI			
Ziegler 1987	Placebo	40-150			AMI	AMI		

Table 5. Comparator trials in migraine prophylaxis with endpoints and whether they favour amitriptyline (AMI) vs. comparator

Author	Comparator, (dose, mg)	AMI dose (mg)	Frequency	Duration	Headache index	Days w headache	Pain intensity	Response rate	Rescue
Bánk 1994	Fluvoxamine (50)	25	No diff						
Bonuso 1983	Dihydroergotamine ER (10)	30		No diff			AMI	AMI	
Bulut 2004	Venlafaxine (37.5-75)	10-25	No diff	No diff			No diff		
Dodick 2009	Topiramate (50-100)	50-100	No diff	No diff		No diff		No diff	No diff
Israil 2013	Pizotifen (1.5) Propranolol (40)	25	No diff	No diff			No diff	No diff	No diff
Kalita 2013	Divalproate (500-1000)	25-50	3mo: DVA 6mo: no diff				3mo: DVA 6mo: no diff	3mo: DVA 6mo: no diff	No diff
Keskinbora 2008	Topiramate (25-100) Combo	25-100	Combo	Combo			Combo		
Krymchantowski 2002	Fluoxetine 40mg + AMI	40	No diff		No diff				
Lampl	AMI	25 vs. 50				No diff		No diff	

Author	Compar-ator, (dose, mg)	AMI dose (mg)	Frequen-cy	Duration	Head-ache index	Days w headache	Pain intensity	Response rate	Rescue
2009									
Magalhães 2010	BTX A (250U)	25-50	No diff				No diff	No diff	No diff
Nelson 1998	Spinal manipu-lation/ combo	25-100			No diff				
Oguzhan o-glu 1999	Fluoxe-tine (20)	50	No diff	No diff			No diff		
Rampello 2004	Cital-opram (20) Combo	50	Mono: AMI Combo: no diff	No diff			No diff	No diff	
Santiago 2014	AMI+aer obics	25	No diff	Combo			Combo		No diff

Table references: (Bank 1994; Bonuso et al. 1983; Bulut et al. 2004; Dodick et al. 2009; Israil et al. 2013; Kalita, Bhoi, and Misra 2013; Keskinbora and Aydinli 2008; Krymchantowski et al. 2002; Lampl et al. 2009; Magalhaes et al. 2004; Nelson et al. 1998; Oguzhanoglu et al. 1999; Rampello et al. 2004; Santiago et al. 2014)

Furthermore, current clinical practise, as reflected in guidance documents issued by the International Headache Society, European national neurological societies, or other types of expert national treatment recommendations recommend amitriptyline as first or second line treatment for migraine prophylaxis, see Table 4. Six out of nine referenced published national guidelines also include amitriptyline in their list of first line treatments, while others recommend amitriptyline as second line for migraine prophylaxis.

In conclusion, the totality of the data available is supportive of a first line treatment for amitriptyline in the prophylactic treatment of migraine. The CHMP considered that the published available data from randomised clinical trials on amitriptyline together with the recommendations in current therapeutic guidelines supported an indication for amitriptyline in migraine prophylaxis.

Therefore the final endorsed wording for migraine prophylaxis is the following:

- The prophylactic treatment of migraine in adults.

iii. Fibromyalgia

Several publications including three systematic reviews and meta-analyses support the use of in the treatment of fibromyalgia pain. Amitriptyline, though studied in smaller studies than newer drugs is

considered efficacious for the treatment of fibromyalgia (Calandre, Rico-Villademoros, and Slim 2015; Moore et al. 2012; Uceyler, Hauser, and Sommer 2008). In some European as well as US treatment guidelines amitriptyline is recommended as first line pharmacological treatment (Mercier et al. 2013; Hauser et al. 2014; Hauser et al. 2009).

Based on the limited data available, the current evidence supporting the use of amitriptyline in the treatment of fibromyalgia was questionable, therefore, CHMP was not supportive of recommending a specific indication in this pain category.

In conclusion, due to the lack of compelling evidence for all pain types, the CHMP did not recommend a global indication for amitriptyline in chronic pain.

Treatment of enuresis nocturna

Current Saroten indications in enuresis nocturna vary on national basis and include:

- Tentatively enuresis nocturna

The use of tricyclic antidepressants in the treatment of enuresis nocturna in children and adolescents is supported by literature references (Burke et al. 1995; Poussaint, Ditman, and Greenfield 1966; Glazener, Evans, and Peto 2003; Meadow 1974; Glazener, Peto, and Evans 2003) and the reference book Martindale (Martindale 2014).

Amitriptyline use in third line treatment for enuresis nocturna (where organic pathology is excluded may be considered if the patient is resistant to desmopressin and/or alarm therapy) has been supported by a recent systematic review showing evidence that tricyclics are effective at reducing the number of wet nights during treatment, but do not have a sustained effect after treatment stops, with most children relapsing. In contrast, there was evidence that alarm therapy has better short- and long-term outcomes (Caldwell, Sureshkumar, and Wong 2016).

Current recommendations by national and international groups as UK National Institute for Clinical Excellence (NICE) and the International Children's Continence Society (ICCS) limit the use of tricyclic antidepressants for enuresis nocturna in children to third line therapy.

In addition, a recently finalised paediatric worksharing procedure (UK/W/054/pdWS/001) for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006 (EPAR 2015) concluded on the need to restrict amitriptyline to third line treatment for enuresis nocturna in children aged 6 years and above.

Therefore, the evidence available does not support a broad indication for the use of amitriptyline in treatment of enuresis nocturna in children. The CHMP considered necessary to restrict the indication as follows:

- The treatment of nocturnal enuresis 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. This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.2 – Posology and method of administration

Posology

Due to the different therapeutic indications and their specific posology, a general sentence has been added at the beginning of this section to highlight the need to select the appropriate formulation/strength for each patient population and dosage scheme, as they cannot be achieved with all pharmaceutical forms/strengths.

Importantly, in clinical practice over several decades a slowly increasing dosing of amitriptyline has proven to increase tolerability and attenuate severity of side effects, especially sedation, dry mouth, vertigo and others.

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 (Martindale 2014). The dose may be increased depending on individual patient response and tolerability, but the maintenance dose should be adjusted to the lowest effective dose.

Amitriptyline should not be used in children and adolescents aged less than 18 years for the treatment of depression or pain, as safety and efficacy have not been established in this patient population. It is recommended to use in children above 6 years of age for the treatment of nocturnal enuresis.

The general recommendation is that the initial treatment or treatment for a short period of time should be done with the immediate release formulations (available at lower strengths 10 mg, 25 mg and 50 mg) and after the patient is stabilised a switch to the retard formulations (available at higher strengths 25 mg, 50 mg and 75 mg) can be performed.

The revised posology recommended per therapeutic indication is summarised below:

- Major depressive disorder

The publication by (Coppen et al. 1978) has been the main reference provided by the MAHs for the posology in depression. It refers to a clinical study in 32 patients with primary depressive illness. In this study patients received 150 mg daily with duration of treatment up to 1 year. In addition the doses used in clinical trials and recommended in treatment guidelines for the treatment of depression have been taken into account (please see references in section 4.1, under treatment of depression).

Immediate release formulations

Based on the available evidence, the recommended doses in adults for immediate release formulations is 25 mg two times a day (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.

The recommended dose in elderly patients over 65 years of age and patients with cardiovascular disease is a starting dose of 10-25 mg in the evening. In this patient population doses above 100 mg should be used with caution.

Prolonged release formulations

From several clinical investigations it has been concluded that a single dose at bedtime is therapeutically as effective as a 3 times daily dosing (Snowdon 1976; Forrest and Hokanson 1975; James and Dean 1985). The tolerability of amitriptyline after single dosing at night has been described as more favourable than daily dosing, especially as also the sedative effects improve sleep quality and

thus add to improved mood. There was no evidence of an increase rate of cardiac complication despite dosages of up to 150 mg amitriptyline when given at night. Only in a very few patients a dose reduction to 75 mg was necessary due to hypotension in the morning.

After administration of amitriptyline in a slow release formulation (e. g. Saroten 75 mg tabs) maximal plasma concentrations are reached after 4-12 hrs (vs 1-6 hrs after administration of immediate release tablets), and are only half as high as after non-retarded tablets (Jorgensen 1977). As the risk for occurrence of cardiac side effects increases at plasma concentrations of amitriptyline >200-300 ng/ml (Burrows et al. 1976) and as these concentrations are far higher than those reached after administration of even 150 mg slow release amitriptyline formulations the maintenance dose may be given at once preferably at bedtime.

Based on the available evidence, the recommended doses in adults for prolonged release formulations is 50 mg daily in the evening. If necessary, the dose can be increased by 25 mg or 50 mg after one week. The maintenance dose is the lowest effective dose and doses above 150 mg daily are not recommended.

The recommended dose in elderly patients over 65 years of age and patients with cardiovascular disease is a starting dose of 25 mg in the evening. The maintenance dose is the lowest effective dose and doses above 100 mg should be used with caution in this patient population.

For both immediate release and prolonged release the antidepressant effect sets in after 2 to 4 weeks. The duration of treatment is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after recovery in order to prevent relapse.

The efficacy and safety of amitriptyline in preventing recurrence of new depressive episodes has not been supported with adequate clinical data and/or references, therefore the CHMP did not agree on the inclusion of the following statement*: "In patients with recurrent depression (unipolar) maintenance therapy may need to be continued for a number of years to prevent new episodes."*

Solution for injection

Based on the available clinical data of parenteral amitriptyline administration to depressed patients as well as on pharmacokinetic parameters (Breyer-Pfaff 1985) the recommended dosage is 50 – 150 mg/day (amitriptyline hydrochloride, equivalent to 44.2-132.6 mg amitriptyline), given in 1 to 3 ampoules daily. No sufficient data have been submitted to allow that the injectable formulation can be administered in doses exceeding 150 mg daily, therefore the SmPC now recommends that a maximum daily dosage of 150 mg amitriptyline given by injection/infusion should not be exceeded.

The solution for injection is used for acute treatment in the hospital setting. Parenteral administration of amitriptyline can achieve more rapidly higher plasma concentrations. These may lead to a rapid sleep-inducing which is desired for severely depressed and often suicidal patients (Laux 1985; Kirino and Gitoh 2011). From clinical practice with a parenteral administration of amitriptyline a dose range of 50 to 150 mg/day has proved to be most favourable in terms of efficacy, onset of action and tolerability (Laux 1985; Deisenhammer et al. 2000).

Elderly often require a considerably lower dose and often show at half the daily dose a satisfying success of treatment. Doses above 100 mg should be used with caution.

The solution for injection should mainly be used for acute treatment. After 1-2 weeks the oral formulations should be used for further treatment. The antidepressant effect usually sets in after 2-4 weeks; the sedative action is not delayed.

Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after recovery in order to prevent relapse.

- Neuropathic pain, prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine in adults

The recommended posology for neuropathic pain, tension type headache and migraine prophylaxis in adults has been supported by the doses used in clinical trials and recommended in treatment guidelines for the endorsed pain indications (please see references in section 4.1, under treatment of pain).

For the treatment of pain doses are in general lower than in depression, with doses rarely exceeding 100 mg (Finnerup et al. 2015; Holroyd et al. 2001; Ziegler et al. 1987). 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. In all cases the lowest effective dose should be used for the shortest duration required to treat the symptoms. The therapeutic effect is normally seen after 2-4 weeks of dosing. Amitriptyline is normally dosed 1-2 hours before bedtime. The immediate release formulation may need to be dosed twice daily, in order to reduce excessive sleepiness in the morning and ensure therapeutic coverage over 24 hours.

Immediate release formulations

The recommended doses in adults are 25 mg to 75 mg daily in the evening. The dose can be taken once daily, or be divided into two doses. The initial dose should be 10 mg to 25 mg in the evening. Doses can be increased with 10 mg to 25 mg every 3 to 7 days as tolerated. A single dose above 75 mg is not recommended.

Prolonged release formulations

The recommended doses in adults are 25 mg to 75 mg in the evening. The initial dose should be 10 mg to 25 mg in the evening. Daily doses above 100 mg should be used with caution.

In both immediate and prolonged release formulations, the recommended starting dose for 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 general it is recommended to initiate treatment in elderly and patients with cardiovascular disease in the lower dose range as recommended for adult. The dose may be increased depending on individual patient response and tolerability.

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.

- Nocturnal enuresis in children

Based on the drug reference Martindale (Martindale 2014) the recommended dose 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 and importantly to increase the dose gradually. The treatment should be administered 1-1½ hours before bedtime. These recommendations are in accordance with the recently finalised paediatric work-sharing procedure UK/H/054/pdWS/001 (EPAR 2015).

The correct dosing in this particularly vulnerable patient population was considered a key message to be highlighted in the product information; therefore, specific sentences have been included that stress

the need to choose a suitable dosage form. In addition, treatment duration should not to exceed a period of 3-months and when stopping treatment, amitriptyline should be withdrawn gradually.

Additional recommendations for the use of tricyclic antidepressants include the need to perform an ECG prior to initiating therapy with amitriptyline to exclude long QT syndrome (Gutgesell et al. 1999).

Divisibility of 50 mg immediate release tablet and 75 prolonged-release tablets

The MAH Bayer submitted data that adequately supported the dosing accuracy of the score lines for the 50 mg film-coated tablet and 75 mg modified release tablet for breaking into equal parts, in accordance with the current Ph. Eur. Monograph for tablets and the stability of the broken tablets until the next administration.

In addition, for the 75 mg modified release tablet a correlation in vitro/in vivo has been demonstrated. Comparison dissolution studies of broken tablets (75mg) with an entire 75 mg retard 8h tablet have shown a slight faster release of amitriptyline of the broken tablets (similar to an entire 6h retard tablet); this is due to the higher surface area of the broken tablets. Therefore, the data provided has confirmed that the subdivision does not affect the modified release characteristics.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.3 – Contraindications

The following contraindications were discussed by the MAHs and the rationale provided for keeping them in the SmPC was agreed by the CHMP:

- *Hypersensitivity to the active substance or to any of the excipient*

Hypersensitivity is included according to the Guideline on Summary of Product Characteristics (SmPC). The wording has been updated according to the latest version of the QRD template.

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

The cardiovascular toxicity of older generation of tricyclic antidepressants including amitriptyline has been described as well established. These drugs inhibit cardiovascular Na+, Ca2+ and K+ channels often leading to life-threatening arrhythmia (Pacher and Kecskemeti 2004). The degree of cardiotoxicity depends on the concentration of the drug and the pre-existing cardiac disease of the patient.

A recent and comprehensive review concluded that cardiotoxicity in overdose, potentially resulting in death, is a described class effect of tricyclic antidepressants, and symptoms include arrhythmia, conduction effects and hypotension. Furthermore it was concluded, that the only significant or serious cardiovascular adverse effects seen in patients with no history of cardiovascular disease given therapeutic doses of TCAs are orthostatic hypotension and tachycardia, but in patients with overt heart disease it was considered that increased risk was likely in those with conduction abnormalities. In patients with history of myocardial infarction but free of conduction defects, the use of TCAs appeared to be mainly limited by how often they developed orthostatic hypotension and to what degree (Martindale 2014).

- *Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (see section 4.5).*

  Simultaneous administration of amitriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

  Treatment with amitriptyline may be instituted 14 days after discontinuation of irreversible nonselective MAOIs and minimum one day after discontinuation of the reversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of amitriptyline.

As a potentially life-threatening pharmacodynamics interaction, serotonin syndrome predominantly occurs with a combination of serotonergic drugs, especially with concurrent use of MAOIs, SSRIs or TCAs (Fiedorowicz and Swartz 2004; Schellander and Donnerer 2010).

This contraindication is supported also by recent reviews of the literature on clinically relevant drug interactions. These are showing that TCAs, tetracyclics, and MAOIs show the highest potential for pharmacodynamics interactions due to their influence on multiple receptors and transporter systems, thus providing an overall advice that TCAs should not generally be given to patients receiving MAOIs (Martindale 2014; Schellander and Donnerer 2010).

In addition, the addition of the following contraindications was requested by the CHMP:

- *Children under 6 years of age*

In line with the outcome of the paediatric work-sharing procedure UK/W/054/pdWS/001 (EPAR 2015), a contraindication in children under 6 years of age was considered necessary.

- *Severe liver disease*

Because tricyclic antidepressants are metabolised and inactivated in the liver they should be used with caution in patients with hepatic impairment and avoided in severe liver disease (Martindale 2014).

The following contraindications, present in current national SmPCs, were also discussed and it was agreed that its inclusion in the product information for amitriptyline was not justified:

Mania

In the SmPC for amitriptyline mania is addressed in section 4.4 Special Warnings and precaution for use: “In manic-depressives, a shift towards the manic phase may occur; should the patient enter a manic phase amitriptyline should be discontinued.” This is considered in line with recent recommendations in the literature; therefore the current precaution and warning allows the prescriber to make his/her decision based on available knowledge on the individual patient for the best treatment was considered adequate. A contraindication was not considered warranted.

Porphyria

From the post-marketing experience, with an estimated cumulative exposure of 8,774,081 patients, no cases were reported concerning porphyria. Furthermore, literature does not support that treatment with amitriptyline triggers attacks of porphyria.

Hence, the CHMP was of the opinion that there was no evidence that amitriptyline triggers an attack of porphyria and the addition of porphyria to section 4.3 of the product information is therefore not considered warranted.

Lactation

No data was available to suggest that lactation should be contraindicated in treatment with amitriptyline.

Known risk of angle-closure glaucoma

The background for potential occurrence of glaucoma is that the antimuscarinic actions play a role, and that there have been some reports of glaucoma associated with other tricyclics (Martindale 2014). However, in the MAHs Global Safety Database, there are no cases including angle-closure glaucoma in amitriptyline treated patients.

The current SmPC includes in section 4.8, in the SOC of Eye disorders, Mydriasis, visual disturbance as uncommon events, and in section 4.4 Special Warnings and precaution for use, the following: "In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked."

The existing warning and precaution was considered appropriate advice for the prescriber, who should make the benefit risk assessment based on all available information for the individual patient when making decisions on treatment of that patient. This is also in line with the recent review in the drug reference Martindale (Martindale 2014).

Risk of urinary retention due to urethral prostatic disorders

In the harmonised SmPC, a warning/precaution exist the section 4.4: "should be used with caution in patients with convulsive disorders, urinary retention, prostatic hypertrophy, hyperthyroidism, paranoid symptomatology and advanced hepatic or cardiovascular disease." Furthermore, in section 4.8, under Renal and urinary disorders "Urinary retention" is listed as adverse reaction with frequency Uncommon.

This information was considered adequate as guidance and will allow the investigator to make the decision on treatment of an individual patient based on all available knowledge and a benefit risk assessment before treating the patient.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.4 – Special warnings and precautions for use

The current information covered in the existing SmPC was considered adequate; with the addition of a warning on the risk of QT prolongation in line with the recommendation from PRAC following the PSUR single assessment PSUSA/0000168/201501 (PSUR 2015).

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.5 – Interaction with other medicinal products and other forms of interaction

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

Two new sections have been added to add warnings on co-administration with Cytochrome P450 inhibitors of CYP2D6 and administration of amitriptyline to known poor metabolisers of CYP2D6 or CYP2C19, respectively. This is based on the article by Hicks (Hicks et al. 2013), representing the dosing recommendations by the Clinical Pharmacogenetics Implementation Consortium (CPIC). The

potential interaction with CYP1A2, CYP2C9 or CYP3A4 inhibitors has also been included in the SmPC based on in vitro studies by Venkatakrishnan (Venkatakrishnan et al. 1998).

In addition, the CHMP supported the addition of the following interactions:

- Diuretics inducing hypokalaemia: due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

- Tramadol: due to an increased risk of seizures and serotonin syndrome, and potentially causing opioid toxicity.

- St. John's Wort (Hypericum perforatum): due to a lowered plasma levels of amitriptyline and therefore a reduced antidepressant response.

- Thioridazine: due to increase of cardiac side effects.

- Alcohol: due to an increase of amitriptyline free plasma concentrations and nortriptyline.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.6 – Fertility, pregnancy and lactation

The MAHs have reviewed and analysed the available data including literature, and post marketing data from the MAHs Global Safety database.

The MAHs Global Safety Database has been searched up to the latest PSUR Data Lock Point (10-Jan-2016) using search terms within the SOC Congenital, familial and genetic disorders. The number of events is tabulated by year in Panel 1. The search yielded a total of 18 cases with a total of 32 events.

Panel 1; No. of events by year

Year	<2003	2008	2009	2010	2012	2013	2014	2015	**Total**
No. of events	4	2	7	3	1	3	1	11	**32**

In addition, in Panel 2 the type of events by preferred term is listed and tabulated by year.

Panel 2; No. of events by PT and year

SOC Congenital, familial and genetic disorders / PT	**Year**	**Total**
Accessory auricle	2013	1
Adactyly	2015	1
Atrial septal defect	2015	1
Cleft lip	2015	1
Congenital anomaly	1980, 1993	2
Congenital aural fistula	2013	1
Congenital bladder anomaly	2009	1
Congenital central nervous system anomaly	2015	1
Congenital choroid plexus cyst	2012	1
Congenital eye disorder	2009	1

Congenital nail disorder	2009	1
Ear malformation	1980	1
Gastroschisis	2008	1
Hemihypertrophy	2008	1
Hypertelorism of orbit	2009	1
Limb reduction defect	2015	1
Microgenia	2013	1
Polydactyly	2015	1
Prominent epicanthal folds	2009	1
Pulmonary artery stenosis congenital	2014	1
Pulmonary malformation	2009, 2010	2
Renal aplasia	2010	1
Skull malformation	2009, 2010	2
Talipes	2015, 2015, 2015, 1994	4
Ventricular septal defect	2015, 2015	2

The rate of exposure to an antidepressant during pregnancy increased from 0.2% in 1997 to 3.2% in 2010. The increasing exposure to antidepressant during pregnancy until 2010 was mainly due to redemption of SSRIs, and the use of TCAs and other antidepressants increased at a more moderate rate between 1997 and 2010 (Jimenez-Solem et al. 2013).

Overall the level of evidence for pharmacological treatment during pregnancy is generally poor. For ethical reasons, randomized controlled clinical trials of safety and efficacy cannot be performed in pregnant women. In the population of pregnant women, information therefore primarily stems from registry studies, prospective non-randomized trials, case reports and data gathered from spontaneous reports. A large review of antidepressants concluded that the majority of studies examining the full range of antidepressants (SSRIs, TCAs, SNRIs, MAOIs, tetracyclics, moclobemide) did not show related adverse reactions. However it was acknowledged, that interpreting the various results from studies of different methodology is difficult (Udechuku et al. 2010). Based on reviews in the literature, there is no evidence of an increased risk of any specific congenital malformations/malformative risks.

In conclusion, amitriptyline is a mature product, and although there have been isolated reports attributing congenital malformation to the use of tricyclics during pregnancy, large scale studies and case control data have failed to substantiate any association. Available evidence do not justify adding a general warning for women of childbearing potential not using contraception. Moreover, in line with overall considerations for precaution for all treatments in pregnant women, the treating physician should make a thorough evaluation of each individual patient considering need for treatment together with risk of not treating, before deciding on treatment of the patient.

Therefore, taking into consideration the information provided by the MAHs and the reproductive toxicity described in animals (see discussion on SmPC section 5.3 below), the CHMP agreed with the inclusion of the following statement:

“For amitriptyline only limited clinical data are available regarding exposed pregnancies.

Animal studies have shown reproductive toxicity (see section 5.3). Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit."

In addition, the risks for the neonate have been mentioned by organ class to increase the readability of the risks.

Breast-feeding

Amitriptyline and its active metabolite, nortriptyline, are excreted into breast milk. Some earlier case reports indicate that amitriptyline is present in milk in concentrations similar to those in maternal blood; it was found in lower concentration in two babies, who showed no clinical signs which could be drug related (Bader and Newman 1980; Brixen-Rasmussen, Halgrener, and Jorgensen 1982).

A recent study has measured the amount of a second active metabolite, E-10 hydroxynortriptyline, in milk. Serum and milk concentrations of amitriptyline in one patient were 0.14 and 0.15 µg/mL, respectively, and milk:plasma ratio of 1.0. No drug was detected in the infant's serum. In another patient, it was estimated that the baby received about 1% of the mother's dose. No clinical signs of drug activity were observed in the infant. In another study, the mother was treated with 175 mg/day of amitriptyline. Milk and maternal serum samples were analyzed for active drug and active metabolites on postpartum days 1–26. Amitriptyline serum levels ranged from 24 ng/mL (day 1) to 71 ng/mL (days 3–26), while those in the milk ranged from 24 ng/mL (day 1) to only 54% of the serum levels on days 2–26. Nortriptyline serum levels ranged from 17 ng/mL (day 1) to 87 ng/mL (day 26) with milk levels 74% of those in the serum. Mean concentration of the second metabolite, E-10-hydroxynortriptyline, was 127 ng/mL (days 1–26) in the serum and 70% of that in the milk. The total dose (parent drug plus metabolites) consumed by the male infant on day 26 was estimated to be 35 µg/kg (80 times lower than the mother's dose). None of the compounds were detected in the nursing infant's serum on day 26 and no adverse effects were observed in the infant. Although levels of amitriptyline and its metabolite have not been detected in infant serum, the effects of exposure to small amounts in the milk are not known. The American Academy of Pediatrics (AAP) classifies amitriptyline as a drug whose effect on the nursing infant is unknown but may be of concern (GG Briggs 2011).

As per the Hale's LRC, Briggs category, and the AAP rating, the considerations for use of amitriptyline is: "Amitriptyline: Drug concentrations of tricyclic antidepressants in breast milk are similar to plasma levels, but these drugs and their metabolites do not appear to accumulate in infants. Effect on nursing infants is unknown but may be of concern by the AAP. No pediatric adverse effects in several studies. LRC L2. Briggs category: potential toxicity" (Hutchinson et al. 2013).

A review and treatment guidance mentions that amitriptyline can be used during pregnancy, with RID (Relative Infant Dose) considered low, 1-3%, and adverse reactions rarely "convincingly described" (Nielsen and Damkier 2012). However, the recent guideline describes the consideration to be made before breastfeeding by a mother treated with medications; "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breastfed child from (name of drug) or from the underlying maternal condition." (FDA, 2014).

A more recent review summarises that, in general, only a small amounts of tricyclic antidepressants are distributed into breast milk; nevertheless, the American Academy of Paediatrics considered that the effect of all antidepressants, including tricyclics, on nursing infants is unknown but may be of concern, and that most manufacturers advice that tricyclics should be avoided by women during breast feeding (Martindale 2014).

In line with the fact that amitriptyline is excreted into breast milk, and in line with treatment guidelines, the following new wording was agreed:

"Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from the therapy of this medicinal product taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman."

Fertility

No data on the effects of amitriptyline on human fertility are available. In pre-clinical studies however, amitriptyline has shown to reduce the pregnancy rate in rats (see discussion on SmPC section 5.3 below).

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.7 – Effects on ability to drive and use machines

The current information covered in the existing SmPC was considered adequate.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.8 – Undesirable effects

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 all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.

The following adverse reactions were not consistently mentioned across products and Member States and have now been included in a harmonised way in the product information:

Metabolism and nutrition disorders

Not known: anorexia, elevation or lowering of blood sugar levels

Psychiatric disorders

Very common: aggression

Common: agitation

Not known: paranoia

Nervous system disorders

Very common: drowsiness, speech disorder (dysarthria)

Very rare: akathisia, polyneuropathy

Not known: extrapyramidal disorder

Eye disorders

Very rare: acute glaucoma

Cardiac disorders:

Uncommon: collapse conditions, worsening of cardiac failure

Very rare: cardiomyopathies, torsades de pointes

Not known: hypersensitivity myocarditis

Vascular disorders

Not known: hyperthermia

Respiratory, thoracic, and mediastinal disorders

Very common: congested nose

Very rare: allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively

(alveolitis, Löffler's syndrome)

Hepatobiliary disorders

Uncommon: hepatic impairment (e.g. cholestatic liver disease)

Not known: hepatitis

Renal and urinary disorders

Common: micturition disorders

Reproductive system and breast disorders:

Uncommon: galactorrhea

General disorders and administration site disorders

Common: feeling thirst

Investigations

Common: hyponatremia

In addition, the following adverse reactions were removed from section 4.8 due to the lack of causal relationship:

Endocrine disorders

Not known: syndrome of inappropriate ADH (antidiuretic hormone) secretion

Nervous system disorders

Not known: aphasia

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.9 – Overdose

The section on management of overdose has been streamlined in order to be helpful for the practitioners. In particular the severe toxicity with ingestions of 750 mg or more of amitriptyline has been highlighted and the text related to treatment has been simplified.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.1 – Pharmacodynamic properties

The section has been revised to include a short factual description of the mechanism of action.

Mechanism of action of amitriptyline has been attributed to several mechanisms, including the SERT and NERT mechanisms, but also includes ion-channel blocking effects on sodium (Dick et al. 2007; Hur et al. 2008), potassium (Galeotti, Ghelardini, and Bartolini 2001) and NMDA channels (Sawynok and Reid 2003; Kiefer, Fischer, and Feuerstein 1999; Eisenach and Gebhart 1995) at both central and spinal cord level (Eide, Stubhaug, and Stenehjem 1995; Willert et al. 2004).

Out of these mechanisms the NERT, and sodium and NMDA channel effects are well known to be involved in the maintenance of all types of chronic pain. It has been clearly demonstrated in several clinical trials that the pain-reducing effect of amitriptyline is not linked to its anti-depressive properties (Max et al. 1987; Watson et al. 1982).

In addition available data on the clinical efficacy has been worded based on the available evidence.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.2 – Pharmacokinetic properties

Data supporting the pharmacokinetic properties, especially of the parenteral formulation have been presented and discussed.

Oral formulations

The information on bioavailability of the oral formulations has been supported by studies performed by the MAHs, testing different oral formulations and coming to a bioavailability of round about 50% for the oral formulations compared to intravenous application. Other references are found via Martindale/Micromedex (Martindale 2014; Micromedex 2016).

In addition the section on pharmacokinetic/pharmacodynamic relationship has been updated using information from a recent publication on therapeutic drug monitoring in psychiatry (Hiemke et al. 2011).

Solution for injection

The pharmacokinetic properties of amitriptyline, its adsorption, metabolism and elimination characteristics, in particular after oral administration, have been investigated in a number of studies . For the amitriptyline solution for infusion after intravenous application only a few small pharmacokinetic investigations have been published. Due to avoiding the first-pass metabolism in the liver after iv-administration the drug reaches maximal plasma concentrations very rapidly and completely with a rapid consequent decline of the plasma levels, which reflects generation of the distribution equilibrium between tissue, peripheral and central compartments.

- Absorption:

The pharmacokinetic properties of amitriptyline, its adsorption, metabolism and elimination characteristics, in particular after oral administration, have been investigated in a number of studies (Breyer-Pfaff 2004). For the amitriptyline solution for infusion after intravenous application only a few small pharmacokinetic investigations have been published. Due to avoiding the first-pass metabolism in the liver after iv-administration the drug reaches maximal plasma concentrations very rapidly and completely with a rapid consequent decline of the plasma levels, which reflects generation of the distribution equilibrium between tissue, peripheral and central compartments (Jorgensen and Hansen 1976; Fridrich et al. 2007).

- Distribution:

The distribution data currently included in Saroten solution for injection are based on the studies performed by the MAHs, showing a mean $(Vd)_{\beta}$ value estimated after intravenous administration of 1221, 280 l (range 769-1702 l).

- Biotransformation:

The biotransformation of amitriptyline is well known (Breyer-Pfaff 2004). The metabolism of amitriptyline is independent of the route of administration.

- Elimination:

The elimination half-life after i.v. administration currently included in Saroten solution for injection are based on studies by Jorgensen et al (Jorgensen and Hansen 1976): intravenous infusion of 15 mg amitriptyline, half-life ranged from 15.5-19.5 hrs and Schulz et al (Schulz et al. 1983): intravenous infusion of 40-60 mg, half-live from 10.1-27.8 hrs. In elderly subjects the half-life is prolonged (Eschenhof and Rieder 1969; Schulz et al. 1983). To have a comparable value after i.v. administration and oral administration, the systemic clearance has been updated and calculated from the data by Schulz et al (Schulz et al. 1983). The systemic clearance from Schulz in “mL/min” was converted into “L/h” to use similar units as for the oral administration. No difference in plasma clearance between younger and elderly people was determined; therefore, both values were combined for calculation of systemic clearance.

The following values were obtained from Schulz et al (Schulz et al. 1983):

	Systemic CL (mL/min)	Systemic CL (L/h)
Mean	859.0	51.5
SD	230.2	13.8
Min	427.3	25.6
Max	1197.3	71.8

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.3 – Preclinical safety data

The section 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.

Amitriptyline inhibits ion channels, which are responsible for cardiac repolarization (hERG channels), in the upper micromolar range of therapeutic plasma concentrations. Therefore, amitriptyline may increase the risk for cardiac arrhythmia and a corresponding warning has been added as well in section 4.4 of the SmPC.

The genotoxic potential of amitriptyline has been investigated in various in vitro and in vivo studies. Although these investigations revealed partially contradictory results, particularly a potential to induce chromosome aberrations cannot be excluded. Long-term carcinogenicity studies have not been performed.

Teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2-40 mg/kg/day (up to 13 times the maximum recommended human amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50-kg patient). Studies in literature have shown amitriptyline to be teratogenic in mice and hamsters when given by various routes of administration at doses of 28-100 mg/kg/day (9-33 times the maximum recommended human dose), producing multiple malformations. Another study in the rat reported that an oral dose of 25 mg/kg/day (8 times the maximum recommended human dose) produced delays in ossification of foetal vertebral bodies without other signs of embryotoxicity. In rabbits, an oral dose of 60 mg/kg/day (20 times the maximum recommended human dose) was reported to cause incomplete ossification of the cranial bones.

There was a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for the effect on fertility is unknown (Di Carlo, Pagnini, and Pelagalli 1971; Beyer, Guram, and Geber 1984).

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Package Leaflet (PL)

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

2.3. Risk Management Plan

The CHMP did not require the MAHs to submit a risk management plan.

3. Recommendation

Based on the review of all available data the CHMP recommended the revision and harmonisation of the product information for Saroten and associated names. The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

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 MAHs 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 migraine in adults, although a specific indication in fibromyalgia was not agreed.

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:

- 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 MAHs 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.

4. Grounds for 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.

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