STABLON®

Tianeptine

1. NAME OF THE MEDICINAL PRODUCT

STABLON 12.5 mg, coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tianeptine sodium salt..... 12.5 mg

For one coated tablet

Excipients with known effect: sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Major depressive episodes (i.e. characteristic).

4.2. Posology and method of administration

Posology

The recommended dosage is one tablet containing 12.5 mg, three times a day (morning, midday and evening) at the beginning of the main meals.

Special populations

Elderly subjects

The efficacy and safety of tianeptine have been established in elderly depressed patients (≥ 65 years) (see section 5.1). No dose adjustment is required in relation to age.

In frail elderly patients (<55 kg), posology should be restricted to 2 tablets/day (see section 5.2).

Renal failure

In patients with severe renal failure (ClCr < 19 ml/min), the posology should be restricted to 2 tablets per day (see section 5.2).

Hepatic impairment

In patients with severe cirrhosis (Class C, Child Pugh Score), the posology should be restricted to 2 tablets per day (see section 5.2).

In chronic alcoholic patients, irrespective of whether they have mild or moderate cirrhosis or no cirrhosis, the posology does not need to be adjusted (see section 5.2).

Paediatric population

The safety and efficacy of tianeptine in children and adolescents under 18 years of age have not been determined. There is no data available (see section 4.4).

Tianeptine is contraindicated in children and adolescents under 15 years old (see section 4.3).

Discontinuation of treatment

Abrupt discontinuation of the treatment should be avoided. The dosage should be gradually reduced over a period of 7 to 14 days in order to reduce the risk of withdrawal reactions (see sections 4.4).

Method of administration

Oral route.

4.3. Contraindications

- Hypersensitivity to the drug substance or to any of the excipients mentioned in section 6.1.
- Children and adolescents under 15 years old.

4.4. Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harming and suicide (suicidal behaviour). This risk persists until a significant remission has been obtained. Clinical improvement may not be obtained until after several weeks of treatment, therefore, patients must be closely monitored until this improvement has been achieved. Clinical experience shows that the risk of suicide can increase during the very early stages of recovery.

Patients with a history of suicidal type behaviour or those expressing significant suicidal thoughts before starting the treatment face a higher risk of the onset of suicidal thoughts or suicidal type behaviour, and must be closely monitored during treatment. A meta-analysis of placebo-controlled clinical trials of the use of antidepressants in adults displaying psychiatric disorders has revealed an increase in the risk of suicidal behaviour in patients under 25 years of age treated with antidepressants compared to those receiving a placebo. Careful monitoring of patients, and particularly of high-risk patients, must accompany the use of this drug treatment, particularly at the beginning of treatment and at times of dose changes.

The patients (and their family and friends) must be warned of the need to monitor the onset of clinical worsening, the appearance of suicidal-thoughts/behaviour and any abnormal change of behaviour, and to seek medical advice immediately if such symptoms arise.

In case of general anaesthesia, the anaesthetist should be informed of the treatment, and the treatment discontinued 24 or 48 hours prior to surgery.

In case of emergency, surgery may still be performed without prior discontinuation; under peroperative monitoring.

As with any psychotropic treatment, the administration of this medicinal product with alcoholic beverages or medicinal products containing alcohol is inadvisable.

Do not exceed the recommended doses.

Abuse/dependence and withdrawal syndrome

In case of a history of drug-dependence or alcohol-dependence, the patients must be very closely monitored in order to avoid any increase in dosage.

After discontinuation of treatment with tianeptine, withdrawal symptoms have been observed in some patients. The following events have been observed: anxiety, muscle pain, abdominal pain, insomnia, joint pain. When the treatment is started, the patient should be informed on the risk of withdrawal syndrome at discontinuation.

If the treatment is to be interrupted, the dosage should be gradually reduced over a period of 7 to 14 days in order to reduce the risk of withdrawal reactions (see section 4.2).

A combination with MAOI is inadvisable (see section 4.5). It is necessary to allow a free interval:

- of two weeks when tianeptine is used as a replacement of MAOI,
- of 24 hours when a MAOI is used as a replacement of tianeptine.

Hyponatraemia

Hyponatraemia, probably due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH), has been reported with the use of tianeptine. The majority of cases were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution should be exercised in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients or those treated with diuretics.

This medicinal product contains sucrose. Its use is inadvisable in patients with fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency (rare hereditary diseases).

Level of sodium

This medicine contains less than 1 mmol sodium (23 mg) per coated-tablet, i.e. is essentially 'sodium-free'.

Paediatric population

STABLON is contraindicated in children and adolescents under 15 years old (see section 4.3) and should not be used in adolescents aged 15 to 18 years. Suicidal type behaviours (suicide attempts and suicidal thoughts) and hostile type behaviour (mainly aggressiveness, opposition behaviour and anger) have been observed more frequently during clinical studies in children and adolescents treated with antidepressants compared to those treated with placebo. If the decision to treat is nonetheless taken, in case of clinical need, the patient must be closely monitored to detect the appearance of suicidal symptoms. Furthermore, there is no long-term safety data in children and adolescents, concerning growth, sexual maturation and cognitive and behavioural development.

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

- **Irreversible MAOIs (iproniazide):** due to risk of cardiovascular collapse or paroxysmal hypertension, hyperthermia, convulsions, death.

4.6. Fertility, pregnancy and lactation

Pregnancy

An increase in post-implantation and post-natal losses were observed in a peri- and post-natal study in rats at maternal toxic doses (see section 5.3).

There is no data or limited data (less than 300 pregnancies) on the use of tianeptine in pregnant women.

It is therefore preferable to avoid the use of tianeptine during pregnancy, irrespective of the term.

It is preferable to maintain a balanced maternal psychic equilibrium throughout pregnancy. If a drug treatment with tianeptine is required to maintain this equilibrium, the treatment must be started or continued at the effective dose throughout the pregnancy and if possible in monotherapy and the pharmacological profile of the molecule must be taken into account when monitoring the newborn baby.

Lactation

Lactic secretion dysfunction has been observed in rats at materno-toxic doses (see section 5.3).

Tricyclic antidepressants are excreted into breast milk, therefore, breast-feeding is not recommended for the duration of the treatment.

Fertility

In rats, a study showed a decrease in the reproductory performance (increase of pre-implantation losses), at materno-toxic doses. (see section 5.3).
The clinical impact is unknown.

4.7. Effects on ability to drive and use machines

Diminished alertness could appear in some patients. Therefore, the attention of drivers and users of machines should be drawn to the risks of drowsiness attached to the use of this medicinal product.

4.8. Undesirable effects

Summary of the safety profile:

The undesirable effects observed with tianeptine during clinical trials are moderate in intensity. They consist primarily of nausea, constipation, abdominal pain, drowsiness, headaches, dry mouth and vertigo.

Table of undesirable effects

The following undesirable effects have been observed during clinical trials and/or post-MA use of tianeptine and are classified as a function of their frequency:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), and not known (cannot be estimated from the available data).

System Organ-Class (SOC)	Frequency	Undesirable effects
Metabolism and nutrition disorders	Common	Anorexia
	Not known*	Hyponatraemia
Psychiatric disorders	Common	Nightmares
	Uncommon	Abuse, dependence, in particular in subjects under 50 years of age with a history of drug-dependence or alcohol-dependence
	Not known*	Cases of suicidal thoughts and behaviour have been reported during treatment with tianeptine or shortly after its discontinuation (see section 4.4.)
		Confusional state, hallucinations
Nervous system disorders	Common	Insomnia
		Somnolence
		Dizziness
		Headaches
		Pre-syncope
		Tremors
	Not known*	Extrapyramidal disorders
		Dyskinaesia
Cardiac disorders	Common	Tachycardia
		Extrasystoles
		Chest pain
Vascular disorders	Common	Hot flushes
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Gastralgia
		Abdominal pain
		Dry mouth
		Nausea
		Vomiting
		Constipation
		Flatulence
Skin and subcutaneous tissue disorders	Uncommon	Maculopapular or erythematous rash
		Pruritus
		Urticaria
	Not known*	Acne
		Exceptional bullous reactions

System Organ-Class (SOC)	Frequency	Undesirable effects
Musculoskeletal and systemic disorders	Common	Myalgia
		Lumbar pain
General disorders and administration site anomalies	Common	Asthenia
		Discomfort sensation in the throat
Hepato-biliary disorders	Not known*	Increased hepatic enzymes
		Hepatitis that may be exceptionally severe

*Post-marketing data**

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

Symptoms

The experience concerning cases of acute tianeptine intoxication (maximum quantity: 2250 mg, ingested in a single dose) primarily reveals alertness disorders which can lead to coma, especially in case of multiple intoxications.

Recommended procedure

Tianeptine has no known specific antidote. In case of acute intoxication, a symptomatic treatment and routine monitoring must be started. Medical monitoring in a specialised setting is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: OTHER ANTIDEPRESSANTS, ATC code: N06AX14.

Mechanism of action

Tianeptine is an antidepressant:

Tianeptine has the following characteristics in animals:

- tianeptine increases the spontaneous activity of pyramidal cells in the hippocampus and accelerates their recovery after functional inhibition,
- tianeptine increases the rate of serotonin re-uptake by neurons in the cortex and hippocampus.

In vitro, tianeptine has no affinity for monoaminergic receptors and does not inhibit serotonin (5-HT), noradrenaline (NA) or dopamine (DA) re-uptake. Tianeptine can modulate synaptic glutamatergic neuro-transmission.

The specific contribution of each effect to the antidepressant activity is unknown.

Clinical efficacy and safety

Four double-blind, placebo-controlled trials were performed to evaluate the short-term efficacy of tianeptine in the treatment of major depressive episodes in adults: one at fixed doses (37.5 mg, 75 mg), two with possibility to adjust the dosage to a higher or lower dose (initial dose 37.5 mg, then 25, 37.5 or 50 mg) and one in elderly patients (311 patients aged 65 years and above; ~100 patients by treatment group, including ~20 patients above 75 years in each group) with a potential dose increase according to patient improvement after 2 weeks of treatment (25 mg then 25 mg or 50 mg). In the adult studies, the primary endpoint was the change in MADRS total score from baseline for the fixed dose and flexible dose trials.

At the end of treatment (6 weeks), the efficacy of tianeptine was significant in the two flexible dose trials but not in the fixed dose trial. In a trial, imipramine, used as an active control, demonstrated the sensitivity of the trial.

In the elderly study (potential dose increase trial), after 8 weeks of treatment, significant efficacy of tianeptine was demonstrated on the primary endpoint (HAMD total score change from baseline). The active control, escitalopram, used in this trial demonstrated the sensitivity of the trial.

The maintenance of the antidepressant efficacy was evaluated in a relapse and recurrence prevention trial. Patients considered as responding to treatment by the investigator (6 weeks of "open" treatment with tianeptine at a daily dosage of 2 to 4 tablets, i.e. 25 to 50 mg daily) were randomised to tianeptine or placebo for an additional duration of 16.5 months. Tianeptine showed a statistically significant efficacy superiority with respect to placebo ($p < 0.001$) on the main criterion of the trial: prevention of relapse or recurrence measured by the time to their onset. The incidence of relapse after 6 months of double-blind follow-up was 6% for tianeptine and 22% for placebo. The incidence of relapse or recurrence after 18 months of double-blind follow-up was 16% for tianeptine and 36% for placebo.

5.2. Pharmacokinetic properties

Absorption

Gastrointestinal absorption is rapid and complete.

Distribution

Distribution is rapid and is associated with protein binding of nearly 94 %, primarily to albumin.

Biotransformation

Tianeptine is extensively metabolised by the liver, primarily by beta-oxidation, without CYP450 involvement. Its main metabolite, pentanoic acid (MC5), is active and less potent than tianeptine.

Elimination

The elimination of tianeptine is characterised by a short terminal half-life of 3 h, most of the metabolites are excreted in the urine.

Elderly, very elderly and fragile patients

In elderly patients, tianeptine plasma concentrations increased by 30% and those of MC5 were nearly doubled after single or repeated administration, compared to that of younger patients (see section 4.2).

In very elderly (87 ± 5 years) or fragile (45 ± 9 kg), a significant increase of Cmax and exposure (area under the curve, AUC) to tianeptine and MC5 were observed after a single administration (see section 4.2).

Patients with severe renal failure (ClCr < 19 ml/min)

The pharmacokinetics of tianeptine remain unchanged but the exposure to MC5 is nearly doubled after single and repeated administration (see section 4.2).

Patients with severe liver cirrhosis (Class C, Child-Pugh Score)

Exposure to tianeptine and MC5, after the administration of a 12.5 mg dose, are increased compared to that of adult depressive patients (see section 4.2).

In case of milder cirrhosis, such as chronic alcoholics, the effects on the pharmacokinetic parameters are negligible (see section 4.2).

5.3. Preclinical safety data

Non-clinical data from conventional genotoxicity and carcinogenesis studies have not revealed any specific risk for humans.

In the fertility study, an increase in pre-implantation losses was observed at the maternotoxic dose of 45 mg/kg/day (i.e. 12 times the human dose determined with respect to the body surface).

Tianeptine is not teratogenic in rats and rabbits.

In the peri- and post-natal study, a lactic secretion dysfunction and an increase in post-implantation and post-natal losses have been observed in rats at the maternotoxic dose of 45 mg/kg/day (i.e. 12 times the human dose determined with respect to the body surface).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol, maize starch, talc, magnesium stearate.

Coating: ethylcellulose, glycerol monooleate, SEPIFILM SE 700 White (polyvidone, carmellose sodium, anhydrous colloidal silica, talc, sucrose, polysorbate 80, titanium dioxide, sodium bicarbonate), white beeswax.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at a temperature below 30°C (climate zones III and IV).

6.5. Nature and contents of container

Box of 30 coated tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER AND LOCAL CONTACT

Manufacturer :
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