

SUMMARY OF PRODUCT CHARACTERISTICS

TRIVASTAL Retard 50

INN : Piribedil

NAME OF THE MEDICINAL PRODUCT

TRIVASTAL Retard 50, sustained release coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Piribedil 50 mg

Excipients : q.s.f. one tablet

PHARMACEUTICAL FORM

Sustained release coated tablets.

THERAPEUTIC INDICATIONS

Adjunctive symptomatic treatment of chronic pathological cognitive and neurosensorial deficit in elderly subjects (excluding Alzheimer's disease and other dementia).

Adjunctive treatment of intermittent claudication in chronic obliterating arteriopathies of the lower limbs (in stage 2).

NB : this indication is based on studies in favour of improvement of the distance able to be walked.

Proposed in ischaemic symptoms in ophthalmology.

Treatment of Parkinson's disease :

- either as monotherapy (treatment of forms with predominant tremor),
- or in association with dopatherapy from the outset, or secondarily, particularly in forms with tremor.

POSOLOGY AND METHOD OF ADMINISTRATION

Oral route

For all indications, except for treatment of Parkinson's disease : 1 tablet per day to be taken at the end of the main meal, or even 2 tablets per day in more severe cases in 2 administrations at the end of the 2 main meals.

The tablets are to be swallowed with a half-glass of water, without chewing, at the end of meals.

Treatment of Parkinson's disease :

- as monotherapy : 150 mg to 250 mg, i.e. 3 to 5 tablets per day, to be divided into 3 to 5 administrations per day.
- as a supplement to dopatherapy: 80 to 140 mg (approximately 20 mg of piribedil per 100 mg of L. Dopa). Given the dose division, the tablet containing 20 mg of piribedil is more suitable.

The tablets are to be swallowed with a half-glass of water, without chewing, at the end of meals. These doses must be attained gradually : increase by one tablet every three days.

CONTRA-INDICATIONS

This medicine is contra-indicated in the following situations :

- hypersensitivity to piribedil,
- cardiovascular shock,
- acute phase of myocardial infarction,
- in association with:
 - antiemetic neuroleptics (cf. Interactions with other medicines and other forms of interactions).
 - antipsychotic neuroleptics (excluding clozapine) (except in the case of parkinsonian patient) (cf. Interactions with other medicines and other forms of interactions).

WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Somnolence and sudden sleeping fits have been reported during treatment with piribedil especially in patients with Parkinson's disease.

Suddenly falling asleep during daily activities, in certain cases without prodroma, has been very rarely reported. Patients must be informed of the possibility of occurrence of these effects and must be warned to be careful if driving a car or using machines during piribedil treatment. Patients who have presented somnolence or sudden sleeping fits must not drive vehicles or use machines. A reduction in the doses or treatment withdrawal may be envisaged.

Due to the presence of sucrose, this medicine is contra-indicated in case of fructose intolerance, glucose or galactose malabsorption or sucrase-isomaltase deficiency.

Cases of pathological gambling (compulsive gambling), hypersexuality and increased libido have been reported in patients with Parkinson's disease treated with dopamine agonists, and with Trivastal in particular. These cases have been seen mainly in patients receiving high doses and were generally reversible following dosage reduction or discontinuation of the treatment with dopamine agonists (see section 4.8).

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Contra-indicated associations :

- + **Antipsychotic neuroleptics (excluding clozapine) (in non- parkinsonian patients)**
Reciprocal antagonism between dopaminergic agonist and neuroleptics. In case of extrapyramidal syndrome induced by neuroleptics, patients should not be treated with a dopaminergic agonist but with an anticholinergic drug.
- + **Antiemetic neuroleptics**
Reciprocal antagonism between dopaminergic agonist and neuroleptics. Use an anti-emetic devoid of extrapyramidal effects.

Unadvisable association :**+ Antipsychotic neuroleptics (excluding clozapine) (in parkinsonian patients)**

Reciprocal antagonism between dopaminergic agonist and neuroleptics. The dopaminergic agonist can induce or aggravate psychotic disorders. If a neuroleptic treatment is required in patients with Parkinson's disease treated with dopaminergic agonists, the latter must be decreased progressively until full withdrawal (a sudden withdrawal of dopaminergics exposes to a risk of "malignant neuroleptic syndrome").

PREGNANCY AND LACTATION

This medicine is restricted to elderly subjects, for whom the risk of pregnancy does not exist.

In the absence of relevant data, the use of this drug during pregnancy or breastfeeding is not recommended.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Patients treated with piribedil presenting somnolence and/or sudden sleeping fits, must be told not to drive vehicles or perform an activity in which an alteration of alertness could expose them or other persons to a risk of serious accident or death (for example the use of machinery) until the disappearance of such effects (cf. Warnings and special precautions for use)

UNDESIRABLE EFFECTS

The following symptoms may occur :

- Minor digestive disturbances (nausea, vomiting, flatulence), which may disappear particularly by adjusting the individual dosage.
- Somnolence has been reported with piribedil treatment. In very rare cases, excessive diurnal somnolence and sudden appearance of sleeping fits have been reported.
- More rarely, psychological disturbances such as confusion or agitation have been observed, which disappear when treatment is discontinued.
- Exceptionally, disturbances in blood pressure (orthostatic hypotension), or blood pressure instability.
- Due to the presence of Cochineal red, risk of allergic reactions.

Cases of pathological gambling (compulsive gambling), hypersexuality and increased libido have been reported since the introduction of piribedil (see section 4.4).

OVERDOSE

Given the emetic effect of piribedil at very high doses, overdosage is unlikely with the tablet form.

The signs of overdosage are:

- blood pressure instability (arterial hypertension or hypotension),
- digestive symptoms (nausea, vomiting).

These symptoms disappear on discontinuation of administration and with symptomatic treatment.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic class: DOPAMINERGIC AGONISTS, ATC code: N04BC08

Piribedil: dopaminergic agonist (stimulates dopamine receptors and the cerebral dopaminergic pathways).

In humans, the mechanism of action is demonstrated by the clinical pharmacology studies :

- stimulation of cortical electrogenesis of the "dopaminergic" type both while awake and during sleep,
- clinical activity on the different functions controlled by dopamine, with this activity being demonstrated via the use of behavioural or psychometric scales.

In addition, piribedil results in an increase in femoral blood flow (the existence of dopaminergic receptors in the femoral vascular bed explains the action of piribedil on peripheral circulation).

Pharmacokinetic properties

Piribedil is absorbed rapidly.

The maximum concentration is reached one hour after oral administration of piribedil.

Plasma elimination is biphasic and is composed of a first phase characterised by a half-life of 1.7 hours and a second, slower phase characterised by a half-life of 6.9 hours.

Metabolism of piribedil is intense, with two main metabolites: (a hydroxylated derivative and a dihydroxylated derivative).

Piribedil is excreted essentially in the urine: 68 % of the piribedil absorbed is excreted by the renal route in the form of metabolites and 25 % is excreted in bile.

The tablet containing 50 mg of sustained-release piribedil allows in vivo gradual absorption and release of the active ingredient.

The kinetic studies conducted in humans show extension of the therapeutic coverage which exceeds each 24 hour period.

Urinary excretion is approximately 50 % at the 24th hour and is total at the 48th hour.