

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIVASTAL[®] 50 mg L.P, prolonged-release coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Piribedil 50.00 mg

For one sustained release coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sustained release coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of Parkinson's disease:

- either as monotherapy,
- or combined with dopathery from the onset, or secondarily.

4.2. Posology and method of administration

Oral route.

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 dopathery: 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.

4.3. Contra-indications

This medicine is contra-indicated in the following situations:

- hypersensitivity to piribedil, or to any of the excipients,
- cardiovascular shock,
- acute phase of myocardial infarction,
- in association with antiemetic neuroleptics (see section 4.5).

4.4. Warnings and special precautions for use

Piribedil has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease.

Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Piribedil. Patients who have experienced somnolence and/or an episode of

sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Considering the age of the population treated with piribedil, the risk of falls whether due to hypotension, sudden sleep onset or confusional state should be considered.

Impulse control disorders: Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including TRIVASTAL. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

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

4.5. Interactions with other medicines and other forms of interactions

Contra-indicated associations

+ Antiemetic neuroleptics

Reciprocal antagonism between dopaminergic agonist and neuroleptics.
Use an anti-emetic devoid of extrapyramidal effects.

Unadvisable associations

+ Antipsychotic neuroleptics (excluding clozapine)

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").

+ Tetrabenazine

Reciprocal antagonism between dopaminergic agonists and tetrabenazine.

+ Alcohol consumption

Increase of piribedil sedative effect by the alcohol.

The modification of vigilance could make driving and using machines dangerous.

Associations to be taken into account

+ Other sedatives

Increase in central depression.

The modification of vigilance could make driving and using machines dangerous.

4.6. 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.

4.7. 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 (see section 4.4).

4.8. Undesirable effects

The following undesirable effects have been observed during treatment with piribedil and ranked under the following frequency:

Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10000$), not known (cannot be estimated from the available data).

The following symptoms may occur:

Gastrointestinal disorders:

- Common: minor gastrointestinal disorders (nausea, vomiting, flatulence), which may disappear particularly if the individual dose is adjusted (gastro-intestinal symptoms can be greatly reduced by stepwise up-titration (50mg increase every 2 weeks);

Psychiatric disorders:

- Common: psychic disorders such as confusion, hallucinations or agitation have been observed, which disappear when treatment is stopped.
- Impulse control disorders: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including TRIVASTAL (see section 4.4. "Special warnings and precautions for use").

Nervous system disorders:

- Common: dizziness has been observed which disappears when treatment is stopped.
- Piribedil is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Vascular disorders:

Uncommon: hypotension, orthostatic hypotension with syncope or malaise or unstable blood pressure. Due to the presence of Cochineal red, risk of allergic reactions.

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

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

The signs of overdose are:

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

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

5. Pharmacological properties

5.1. 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).

5.2. 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Povidone, magnesium stearate, talc, sodium hydrogen carbonate, carmellose sodium, white beeswax, titanium dioxide (E171), cochineal red A aluminium lake (E124), polysorbate 80, sucrose, colloidal anhydrous silica.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

10, 20, 30, 40, 50, 60 or 100 tablets in blisters (PVC/Aluminium).

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER

8. DATE OF REVISION OF THE TEXT

August 2013
