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.

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.

1. NAME OF THE MEDICINAL PRODUCT
TRIVASTAL® RETARD 50, sustained 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*
• 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 walking distance.
• 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 onset, or secondarily, particularly in forms with tremor.

*In Egypt, in Saudi Arabia and in Jordan the therapeutic indication is “Treatment of certain forms of Parkinson’s disease”.

4.2. 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.
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 agonists and neuroleptics.
Use an anti-emetic devoid of extrapyramidal effects.

Unadvisable associations

Antipsychotic neuroleptics (excluding clozapine)
Reciprocal antagonism between dopaminergic agonists 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 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 (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥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.
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

30 tablets in blisters (PVC/Aluminium).

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
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France
For any updates please refer to www.servier.com. As the SmPC may vary from country to country please also refer to SERVIER’s local agents and/or distributors.