SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIVASTAL RETARD 50 mg, sustained-release coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Piribedil ..... 50.00 mg per sustained-release coated tablet.

For a full list of excipients, see section 6.1.

Excipients with known effects: sucrose, ponceau 4R (E124).

3. PHARMACEUTICAL FORM

Sustained-release coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of Parkinson's disease:
  - either as single-agent therapy (treatment of essential forms with tremor),
  - or in combination with levo-dopa, from the outset or secondarily, in particular in forms with tremor.

4.2. Posology and method of administration

Posology

Treatment of Parkinson's disease:

- Single-agent therapy: 150 to 250 mg, i.e. 3 to 5 tablets daily to be divided into 3 to 5 intakes daily.
- In combination with levo-dopa: 80 to 140 mg (about 20 mg of piribedil per 100 mg of levo-dopa).

Treatment discontinuation

A sudden withdrawal of dopaminergics exposes to a risk of neuroleptic malignant syndrome. To avoid this risk the dose of piribedil should be decreased gradually until full withdrawal.

Impulse control disorder

To avoid the risk of impulse control disorders the prescription of the lowest effective dose is recommended. Dose reduction/tapered discontinuation should be considered if such symptoms develop (see section 4.4).

Patients with hepatic and/or renal impairment

Piribedil has not been investigated in these patient groups. Caution is advised when treating patients with hepatic and/or renal impairment.

Paediatric population

The safety and efficacy of Piribedil in children and adolescents aged below 18 years have not been established. No data are available. There is no relevant use of Piribedil in the paediatric population for the indication.

Method of administration
Oral route.
The tablets are to be swallowed with half a glass of water, without chewing them, at the end of meals.
The dosage is to be built up gradually: increment by 1 tablet every 3 days.

4.3. Contraindications

This medicine is contra-indicated in the following situations:

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

4.4. Special warnings and special precautions for use

Sudden sleep onset

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.

Orthostatic hypotension
Dopamine agonists are known to impair the systemic regulation of the blood pressure resulting in postural orthostatic hypotension.
It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

Considering the age of the population treated with piribedil, the risk of falls whether due to sudden sleep onset, hypotension 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, hyper-sexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Piribedil. Dose reduction/tapered discontinuation should be considered if such symptoms develop.
Abnormal behavior
Abnormal behaviour has been reported and can be associated with manifestations including confusion, agitation, aggression.
Dose reduction/tapered discontinuation should be considered if such symptoms occur.

Psychotic disorders
Dopaminergic agonists can induce or aggravate psychotic disorders such as delusion, delirium and hallucinations (see section 4.5).

Dose reduction/tapered discontinuation should be considered if such symptoms occur.

Dyskinesia
In advanced Parkinson's disease, in combination with levodopa, dyskinesia can occur during the initial titration of piribedil. If they occur, the dose of piribedil should be decreased.

Neuroleptic malignant syndrome
Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

Peripheral oedema
Peripheral oedema has been observed with the use of dopamine agonists. This should be also considered when prescribing piribedil.

Due to the presence of saccharose, patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Due to the presence of the colorant Ponceau 4R (E124), risk of allergic reactions.

Level of sodium:
TRIVASTAL RETARD 50 mg contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium-free'.

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

+ The association with Neuroleptics (excluding clozapine) is contraindicated as there is a Reciprocal antagonism between dopaminergic antiparkinsonian drugs and neuroleptics (see section 4.3).

1. Subjects with extrapyramidal syndrome induced by neuroleptics should be treated with an anticholinergic drug and not with a dopaminergic antiparkinsonian drug (dopaminergic receptors blocked by neuroleptics).
2. The dopaminergic agonists can induce or aggravate psychotic disorders (see section 4.4). 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").
3. Concerning neuroleptic anti-emetics: an anti-emetic devoid of extrapyramidal effects should be used.

+ The association with tetrabenazine is not advisable as there is a reciprocal antagonism between dopaminergic antiparkinsonian drugs and tetrabenazine.

+ The combination of piribedil and alcohol is not advisable.

+ Caution should be exercised when prescribing piribedil with other sedative drugs.

4.6. Pregnancy and lactation

Fertility:

Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal development, parturition or postnatal development.

Pregnancy:

Piribedil has been shown to cross the placental barrier in the pregnant mouse and is distributed in fetal organs.

In the absence of relevant data, piribedil is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding:

In the absence of relevant data, the use of this drug during breast-feeding is not recommended.

4.7. Effects on ability to drive and use machines

Patients being treated with Piribedil and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g.operating machines) until such recurrent episodes and somnolence have resolved (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 (≥1/1000, <1/1000; very rare (<1/10000); not known (cannot be estimated from the available data).

***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 (50 mg increase every 2 weeks).

***Psychiatric disorders*:**

Common: psychic disorders such as confusion, agitation, hallucinations (visual, auditory, mixed), have been observed, which disappear when treatment is stopped.
Frequency not known: aggression, psychotic disorders (delusion, delirium).

***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 (see section 4.4).

Frequency not known: dyskinesia.

Cardiovascular disorders:

Uncommon: hypotension, orthostatic hypotension with syncopes or malaise or unstable blood pressure.

Impulse control disorders

Pathological gambling, increased libido, hyper-sexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including piribedil (see section 4.4).

General disorders and administration site conditions
Frequency not known: Peripheral oedemas have been observed with the use of dopamine agonists.

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 ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9. Overdose

Symptoms

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

Management

However, in the case of accidental ingestion of a supra-therapeutic dose, the following signs and symptoms may be observed:
- 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 cerebral dopaminergic pathways).

In man, the mechanism of action has been demonstrated by clinical pharmacology studies:
- stimulation of cortical electrogenesis of "dopaminergic" type during both wakefulness and sleep,
- clinical activity on the various functions controlled by dopamine. This activity has been shown using behavioural and psychometric scales.

In addition, Piribedil induces an increase in femoral blood flow rate (the existence of dopaminergic receptors in the femoral vasculature may explain the action of Piribedil on the peripheral circulation).

5.2. Pharmacokinetic properties

Piribedil is rapidly absorbed.

The peak concentration is obtained 1 hour after oral dosing. Plasma elimination is biphasic: it consists of an initial phase characterised by a half-life of 1.7 hours and a second, slower, phase characterised by a half-life of 6.9 hours.
Piribedil is intensely metabolised, yielding two main metabolites (a hydroxyl and a dihydroxyl derivative).

Piribedil is mainly eliminated by the urinary route: 68% of the Piribedil absorbed is excreted by the renal route in the form of metabolites, and 25% via the bile.

The Piribedil 50 mg sustained-release tablet enables sustained release and absorption of the active substance in vivo.

Kinetic studies conducted in man have shown the extension of therapeutic coverage, which exceeds 24 hours.

Urinary elimination is about 50% at hour 24 and total at hour 48.

5.3. Preclinical safety data

Piribedil, administered sub-chronically or chronically, was well tolerated in animals.
Piribedil did not demonstrate any teratogenic potential in mice, rats and rabbits.
The drug did not show any evidence of genotoxic potential in a series of in vitro and in vivo tests.
No carcinogenicity studies were performed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

TABLET:
Magnesium stearate, povidone, talc.

COATING:
Carmellose sodium, polysorbate 80, ponceau 4R (E124) aluminium lake, povidone, silica colloidal anhydrous, sodium hydrogen carbonate, sucrose, talc, titanium dioxide (E171), beeswax white.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 25°C.

6.5. Nature and contents of container

30 tablets in heat-sealed blister packs (PVC/aluminium).

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER

MA 066/01101

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

23rd September 2005.

10. DATE OF REVISION OF THE TEXT

05-07-2021
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