ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIVASTAL 50 mg LP, prolonged-release coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Piribedil ..... 50.00 mg

For one prolonged-release coated tablet

Excipients with known effects: sucrose, cochineal red A (E124)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of Parkinson's disease:

- either as monotherapy,
- or combined with dopatherapy from the outset, or secondarily.

4.2. Posology and method of administration

Posology

Treatment of Parkinson's disease

- as monotherapy: 150 mg to 250 mg, i.e. 3 to 5 tablets daily, to be divided into 3 to 5 administrations per day.
- as a supplement to dopatherapy: 100 to 150 mg, i.e. 2 to 3 tablets daily, to be divided into 2 to 3 administrations per day.

These doses must be attained gradually: by increasing the dose one tablet at a time, with an interval between dose increases that may vary from three days to 2 weeks depending on the patient's condition and acceptability of the drug. The interval between dose increases should not be less than 3 days.

Discontinuation of treatment

Sudden discontinuation of dopamine agents may result in neuroleptic malignant syndrome. To avoid this risk the dose of piribedil must be reduced gradually until complete discontinuation of treatment.

Impulse control disorders

To avoid the risk of impulse control disorders, prescription of the minimum effective dose is recommended. Dose reduction or gradual discontinuation of treatment should be considered if such symptoms occur (see section 4.4).

Kidney or liver failure

Piribedil has not been studied in these groups of patients. It is recommended to treat these patients with caution.

Paediatric population

The safety and efficacy of piribedil in children under the age of 18 years have not been established. There is no available data. There is no justified use of piribedil in the paediatric population for this indication.

Method of administration
Oral route.
The tablets should be swallowed, without chewing, with half a glass of water at the end of the meal.

4.3. Contraindications

This medicine is contraindicated in the following situations:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- cardiovascular collapse,
- acute phase of myocardial infarction,
- in association with anti-emetic neuroleptics (see section 4.5).

4.4. Special warnings and precautions for use

Dyskinesia
In advanced stage Parkinson's disease, in conjunction with levodopa, dyskinesia may occur at the start of treatment with piribedil. In this case, the dose of piribedil should be reduced.

Orthostatic hypotension
Dopamine agonists are known to alter systemic blood pressure regulation resulting in postural orthostatic hypotension.
Monitoring of blood pressure is recommended, particularly at the start of treatment, given the risk of orthostatic hypotension associated with dopaminergic treatment.

Abnormal behaviour
Abnormal behaviour has been reported and may be associated with manifestations of confusion, agitation, aggressiveness. Dose reduction or gradual discontinuation of treatment should be considered if such symptoms occur.

Sleep disorders
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 dose reduction or termination of therapy may be considered.
Given the age of the population treated, the risk of falls, whether related to hypotension, sudden sleep onset or confusional state, should be taken into account.

Impulse control disorders
The onset of impulse control disorders should be regularly monitored in these patients. The patients and those close to them must be informed of the behavioural symptoms of impulse control disorders such as: pathological gambling (compulsive gambling), hypersexuality, increased libido, compulsive spending or shopping, excessive consumption of food and compulsive food disorders, which may appear in patients treated with Dopamine agonists including TRIVASTAL. A decrease of the doses or progressive discontinuation of the treatment should be envisaged if such symptoms appear.

Psychotic disorders
Dopamine agonists may cause or worsen psychotic disorders such as delusion, delirium, hallucinations (see section 4.5). Dose reduction or gradual discontinuation of treatment should be considered if such symptoms occur.

Peripheral oedema
Peripheral oedema has been observed during the use of dopamine agonists. This should be taken into

account when prescribing piribedil.

Neuroleptic malignant syndrome
Characteristic symptoms of neuroleptic malignant syndrome have been reported following sudden discontinuation of dopaminergic treatment (see section 4.2).

Excipients
Due to the presence of sucrose, patients with fructose intolerance, glucose-galactose malabsorption syndrome or sucrase-isomaltase insufficiency (rare hereditary diseases) should not take this medicine.
Due to the presence of cochineal red A (E124), there is a risk of allergic reactions (see section 4.8).
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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

Concomitant use contraindicated
+ Antiemetic neuroleptics
Reciprocal antagonism between the dopaminergic agent and the neuroleptic.
Use an anti-emetic without extrapyramidal effects.

Concomitant use not recommended
+ Antipsychotic neuroleptics (except clozapine)
Reciprocal antagonism between the dopaminergic agent and the neuroleptics.
The dopaminergic agent can provoke or worsen psychotic disorders. If a neuroleptic treatment is required in parkinsonian patients treated with dopaminergic agents, the latter must be gradually reduced until withdrawal (the sudden withdrawal of dopaminergic agents can expose to a "neuroleptic malignant syndrome" risk).

+ Tetrabenazine
Reciprocal antagonism between the dopaminergic agent and tetrabenazine.

+ Alcohol consumption
Alcohol increases the sedative effect of piribedil.
Impaired vigilance may make driving vehicles and the use of machinery dangerous.

Concomitant use to be taken into consideration
+ Other sedatives
Increase in central depression.
The impairment of alertness could make driving and using machines dangerous.

4.6. Fertility, pregnancy and lactation

Pregnancy
The available data in mice shows piribedil passes through the placental barrier, and is distributed in fœtal organs.
In the absence of relevant data, the use of this drug during pregnancy and in women of childbearing age not using contraception is not recommended.

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

Fertility
Studies conducted in animals have not shown any direct or indirect harmful effects on embryonic/fœtal development, parturition or post-natal development.

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 effects 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 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

The following signs may appear:

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 uptitration: 50 mg increase every 2 weeks).

Psychiatric disorders

- Common: psychic disorders such as confusion, agitation or hallucinations (visual, auditory, mixed) have been observed, which disappear when treatment is stopped.
- Unknown frequency: aggression, psychotic disorders (delusion, delirium).

Impulse control disorders

- Symptoms such as: pathological gambling (compulsive gambling), hypersexuality, increased libido, compulsive spending or shopping, excessive consumption of food and compulsive food disorders may appear in patients treated with dopamine agonists including TRIVASTAL (see sections 4.2 and 4.4).

Nervous system disorders

- Common: dizziness has been observed, which disappears when treatment is stopped.
- Unknown frequency: dyskinesia
- 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, unstable blood pressure causing syncope or malaise.

General disorders and anomalies at the administration site

- Unknown frequency: peripheral oedema
- Risk of allergic reactions due to the presence of cochineal red A (E124).

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 - National agency for the safety of medicines and health products (ANSM) and network of Regional Pharmacovigilance Centres, website: www.signalement.social-sante.gouv.fr.

4.9. Overdose

Given the emetic effect of piribedil at very high doses, overdose 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 group: DOPAMINE AGONISTS, ATC Code: N04BC08

Mechanism of action

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

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

- stimulation of "dopaminergic" type cortical electrogenesis 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

Absorption

Piribedil is absorbed rapidly.

Distribution

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.

Biotransformation

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

Elimination

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.

Pharmacokinetic/pharmacodynamic relationships

The prolonged-release tablet containing 50 mg of 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 24 hours.
Urinary excretion is approximately 50% at the 24th hour and is total at the 48th hour.

5.3. Preclinical safety data

Subchronic or chronic administration of piribedil has been well-tolerated in animals. No teratogenic potential has been demonstrated for piribedil in animals. In vitro and in vivo tests have shown no genotoxic potential. No carcinogenicity studies have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

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

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

10, 20, 30, 40, 50, 60 or 100 tablets in blisters (PVC/Aluminium).
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER
50, RUE CARNOT
92284 SURESNES CEDEX
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- CIP 34009 318 904 4 7 or 318.904.4: 10 tablets in blisters (PVC/Aluminium).
- CIP 34009 318 905 0 8 or 318.905.0: 20 tablets in blisters (PVC/Aluminium).
- CIP 34009 318 906 7 6 or 318.906.7: 30 tablets in blisters (PVC/Aluminium).
- CIP 34009 318 907 3 7 or 318.907.3: 40 tablets in blisters (PVC/Aluminium).
- CIP 34009 318 909 6 6 or 318.909.6: 50 tablets in blisters (PVC/Aluminium).
- CIP 34009 318 910 4 8 or 318.910.4: 60 tablets in blisters (PVC/Aluminium).
- CIP 34009 318 911 0 9 or 318.911.0: 100 tablets in blisters (PVC/Aluminium).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

to be further completed by the marketing authorisation holder

10. DATE OF REVISION OF THE TEXT

to be further completed by the marketing authorisation holder

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List II. Medicinal product subject to medical prescription.