Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Almirid 20mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 20 mg of α-dihydroergocryptine mesylate.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet.

A white to off-white multiscored tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

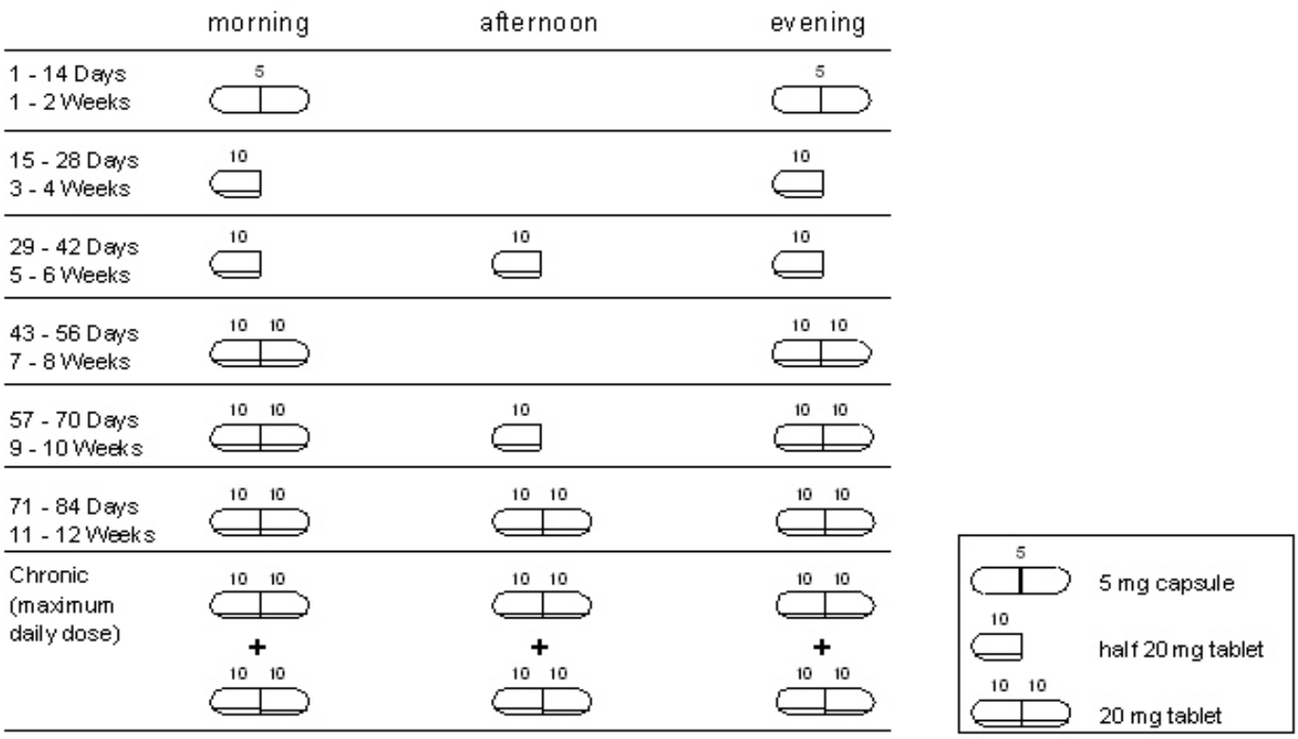
Treatment of advanced Parkinson's disease. Almirid® is to be administered by specialists with access to monitoring facilities.

4.2 Posology and method of administration

Dosage must be adjusted according to the patient's response. It is suggested that treatment should begin with Almirid® 5. The initial recommended dosage is 5 mg twice a day. The maintenance dosage is generally 60 mg/day, and may be increased to 120 mg/day, this dosage can be reached gradually with successive increases of 10 mg/day every two weeks.

If Almirid® is administered together with levodopa, with or without decarboxylase inhibitor, lower dosage should be sufficient. Reduction in levodopa dosage must be carried out gradually until the optimal therapeutic effect is reached.

There are no special dosage requirements for elderly patients



4.3 Contraindications

Documented individual hypersensitivity to the product.
Documented or presumed pregnancy and paediatric use.
Due to the high rate of liver metabolism, the drug is contraindicated in severe liver failure.
With regard to its inhibitory effect on lactation, the use of the drug is contraindicated during breast-feeding

4.4 Special warnings and precautions for use

In parkinsonian patients with galactorrhoea, prolactin dependent amenorrhoea, menstrual disturbances or acromegaly, treatment with Almirid® can eliminate the pre-existing sterility. Therefore, women at risk of pregnancy must adopt some type of non-hormonal contraceptive. Acromegalic patients with a positive history of peptic ulcer or with on-going peptic ulcer, in view of the absence of experimental and safety data, should preferably be given an alternative treatment.

Due to the structural similarity with ergot derivatives, care must be taken in the administration of high dosages of Almirid® to patients with medical history of psychotic disturbances, severe cardiovascular diseases, peptic ulcer or gastrointestinal bleeding.

α-dihydroergocryptine has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment. Patients who have experienced somnolence must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

Pleuritis and pleuropulmonary fibrosis are known effects of long-term treatment with related dopaminergic substances. Any connection between these clinical findings and α-Dihydroergocryptine mesylate is not proved. Patients with pleuropulmonary symptoms should be monitored and should be encouraged to contact their doctor in case of coughing and dyspnoea.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

α-dihydroergocryptine counteracts the activity of anti-dopaminergic agents, such as neuroleptics.

The possible interaction of α-dihydroergocryptine with hypotensive drugs cannot be excluded. Particular care must be given to patients being treated with other ergot alkaloids, or drugs active on arterial blood pressure, with regard to a possible enhancing effect. This is particularly important in elderly patients.

α-dihydroergocryptine is subject to first-pass metabolism by the isoenzyme CYP3A4 of Cytochrome P450. A pharmacokinetic study in healthy subjects showed that, with concomitant administration of erythromycin, serum levels of α-dihydroergocryptine and its metabolites are significantly increased. Due to this fact there is potentially an increased risk of side effects. Therefore, during concomitant administration with drugs that inhibit CYP3A4, the dose of α-dihydroergocryptine must be adjusted. This must be considered each time concomitant treatment is proposed. Macrolide antibiotics (for example erythromycin) should not be administered together with α- dihydroergocryptine since the effects of α-dihydroergocryptine may be substantially increased.

4.6 Pregnancy and lactation

Almirid® is contraindicated in documented or presumed pregnancy. Since it inhibits lactation, its use is contraindicated during breast-feeding.

4.7 Effects on ability to drive and use machines

In the event of hypotensive reactions shown by certain patients especially during the early days of treatment, particular care must be taken during driving and operating machines.
Patients being treated with α-dihydroergocryptine and presenting with somnolence 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) unless patients have overcome such experiences of somnolence (*see also section 4.4, Special warnings and precautions for use*)

4.8 Undesirable effects

α-dihydroergocryptine is associated with somnolence.

During clinical trials some patients complained of nausea, vomiting, gastralgia, gastric burning, dyspepsia, constipation, dizziness, hypotension, postural hypotension, faintness, asthenia, sleepiness, anxiety, headache and tachycardia.

Side effects generally occur during the early days of therapy, and they are short-lasting. Some effects are dose-related and may be eliminated through a reduction of the dosage.

Rarely, skin rash was observed. In such a case it is suggested to withdraw the treatment and consult a physician.

In case of combined treatment with levodopa, the frequency of side effects such as gastralgia, pyrosis, faintness, and headache was increased. Appearance of oedema and hallucinations has been reported.

4.9 Overdose

Accidental overdose can cause hypotension, nausea and vomiting; in this case, intramuscular metoclopramide should be used as an antidote. The patient should be kept supine with arterial blood pressure monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The tremor, bradykinesia and stiffness observed in Parkinson's disease are due to the progressive degeneration of the dopaminergic neurons of the Substantia Nigra and the nigrostriatal fibres. This leads to a lack of inhibition of the cholinergic neurons of the striatum and thus to the extra-pyramidal symptoms. α-dihydroergocryptine binds strongly to dopamine receptors resulting in stimulation of D_2 dopaminergic receptors in the Substantia Nigra and Corpus Striatum. In addition, α-dihydroergocryptine possesses a partial agonist activity on D_1 receptors. Stimulation of dopaminergic neurons by α-dihydroergocryptine attenuates the extra-pyramidal motor symptoms characteristic of Parkinson's disease.

Animal studies have demonstrated that treatment with α-dihydroergocryptine leads to recovery from Parkinson-like symptoms induced by the toxin MPTP and prevents neuronal cell degeneration induced by oxidizing agents.

This neuroprotective activity is a direct action of dihydroergocryptine on the intracerebral content of reduced glutathione, which is an important endogenous factor (scavenger) against the cytotoxicity of highly reactive oxygen free radicals. Free radical formation in the brain is enhanced by ageing, by excito-toxic stimulation, and in certain degenerative diseases like Parkinson's and Alzheimer's. The treatment with dihydroergocryptine induces a significant increase in brain reduced glutathione, through activation of antioxidant enzymes. Through the above mechanism, the drug prevents the neuronal degeneration of the Substantia Nigra induced by MPTP in experimental Parkinson's disease.

5.2 Pharmacokinetic properties

The pharmacokinetics of α-dihydroergocryptine are probably best described by reference to a three component model. There is a linear relationship between dose, concentration, and effect.

α-dihydroergocryptine is rapidly absorbed following oral administration. Peak plasma levels are observed after 30 to 120 minutes. Protein binding is approximately 50%. Approximately 97% of α-dihydroergocryptine is metabolised by the liver. The absolute oral bioavailability of the drug is approximately 2.4% of the dose. The mean biological half life is approximately 12 hours. α-dihydroergocryptine is excreted in the faeces.

Steady state is rapidly achieved following administration of the drug two to three times per day. No accumulation phenomena have been observed in patients receiving chronic therapy.

5.3 Preclinical safety data

Oral LD_{50} was 4384.6 and > 5000 mg/kg in mice and rats, respectively. Intravenous LD_{50} was 192.3 and 50.7 mg/kg in the same species. In the long term oral toxicity tests performed in rats and monkeys, α-dihydroergocryptine was well tolerated particularly in monkeys, even at doses much higher than the daily therapeutic doses administered in man. The drug impairs fertility in rats, and reproductive toxicity at doses starting from 18 mg/kg/day, has been observed. This occurs as a result of the prolactin-lowering activity. Reproductive toxicity has also been observed in rabbits with doses of 18mg/kg/day. However, this dose is well in excess of the maximum daily dose for use in man. Mutagenicity tests gave negative results.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Povidone

6.2 Incompatibilities

No incompatibility is reported, however it is inadvisable to mix with other drugs.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

Aluminium blisters, coupled with white opaque PVC containing 10 tablets/blister strip.Cartons containing 2, 3 or 6 blister strips.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Polichem S.A.,
50, Val Fleuri,
L-1526,
Luxembourg.

8 MARKETING AUTHORISATION NUMBER

PA1005/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 February 2000
Date of last renewal: 04 February 2005

10 DATE OF REVISION OF THE TEXT

November 2005