SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Procyclidine hydrochloride 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg Procyclidine hydrochloride

Excipient(s) with known effect

Each tablet contains 187.0 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablets, one side with a break-line debossed ‘5’ above the break-line and ‘PC’ below the break-line and plain on other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Procyclidine is indicated:

- For the treatment and symptomatic relief of all forms of Parkinson's disease e.g. idiopathic (paralysis agitans), postencephalitic and arteriosclerotic disease.
- For the control of extrapyramidal symptoms induced by neuroleptic drugs including pseudo-parkinsonism, acute dystonic reactions and akathisia.

4.2 Posology and method of administration

Posology

The variation in optimum dosage from one patient to another should be taken into consideration by the prescriber.

Adults:

Parkinson's disease:

Treatment is usually started at 2.5 mg procyclidine three times per day, increasing by 2.5 to 5 mg per day at intervals of two or three days until the optimum clinical response is achieved.

The usual maintenance dose to achieve optimal response is 15 to 30 mg procyclidine per day.

Addition of a fourth dose before retiring has been seen to be beneficial in some patients. Doses up to 60 mg procyclidine have been well tolerated, and at the discretion of the attending physician dosing to this level may be appropriate.

In general younger patients or those with postencephalitic parkinsonism may require higher doses for a therapeutic response than older patients and those with arteriosclerotic parkinsonism.

Procyclidine may be combined with levodopa or amantadine in patients who are inadequately controlled on a single agent.

Neuroleptic-induced extra-pyramidal symptoms:

Treatment is usually initiated at 2.5 mg procyclidine three times per day increasing by 2.5 mg daily until symptoms are relieved.

The effective maintenance dose is usually 10 to 30mg procyclidine per day.

Withdrawal:

After a period of 3 to 4 months of therapy, Procyclidine should be withdrawn and the patient observed to see whether the neuroleptic-induced extra-pyramidal symptoms recur.

If this is the case Procyclidine should be reintroduced to avoid debilitating extra-pyramidal symptoms. Cessation of treatment periodically is to be recommended even in patients who appear to require the drug for longer periods.

Older people:

Elderly patients may be more susceptible than younger adults to the anticholinergic effects of Procyclidine and a reduced dosage may be required (see section 4.4).

Paediatric population:

The use of procyclidine in this age group is not recommended.

Method of administration:

Pharmacokinetic studies have indicated that the mean plasma elimination half-life of Procyclidine is sufficient to allow twice daily administration orally, if more convenient.

Oral administration may be better tolerated if associated with a meal.

Tablets can be divided into equal doses.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Procyclidine is contraindicated in individuals with untreated urinary retention, closed angle glaucoma and gastrointestinal obstruction.

4.4 Special warnings and precautions for use

As with all anticholinergics the benefit/risk ratio should be assessed when prescribing procyclidine in patients with existing angle-closure (narrow angle) glaucoma or those considered to be predisposed to glaucoma. Also use with caution in patients with obstructive disease of the gastrointestinal tract, cardiac disorders, cardiovascular disease, hepatic and renal impairment, and those with urinary symptoms associated with prostatic hypertrophy.

In a proportion of patients undergoing neuroleptic treatment, tardive dyskinesias will occur. While anticholinergic agents do not cause this syndrome, when given in combination with neuroleptics they may exacerbate the symptoms of tardive dyskinesia or reduce the threshold at which these symptoms appear in predisposed patients. In such individuals subsequent adjustment of neuroleptic therapy or reduction in anticholinergic treatment should be considered.

Patients with mental disorders occasionally experience a precipitation of a psychotic episode when procyclidine is administered for the treatment of the extrapyramidal side effects of neuroleptics.

Elderly patients, especially those on high doses of anticholinergics may be more susceptible to the adverse events associated with such therapy (see section 4.8). Specifically, the elderly patient may be vulnerable to Central Nervous System disturbances such as confusion, impairment of cognitive function and memory,

disorientation and hallucinations. These effects are usually reversible on reduction or discontinuation of anticholinergic therapy.

There is no specific information available concerning the use of procyclidine hydrochloride in patients with impaired renal or hepatic function. However, since procyclidine is metabolised in the liver and excreted via the urine, care should be exercised when administering procyclidine to patients with impairment of renal or hepatic function.

Procyclidine should not be withdrawn abruptly as rebound parkinsonian symptoms may occur.

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

Abuse:

Procyclidine, along with other anticholinergic drugs, has the potential to be abused. Although the cases of abuse are rare, physicians should exercise caution in prescribing Procyclidine to patients with symptoms that may not be genuine.

4.5 Interaction with other medicinal products and other forms of interaction

The use of drugs with cholinergic properties, such as tacrine, may reduce the therapeutic response to Procyclidine. Furthermore, drugs with anticholinergic properties may antagonise the effect of parasympathomimetic agents.

Monoamine oxidase inhibitors or drugs with anticholinergic properties, such as amantadine, memantine, antihistamines, phenothiazines, tricyclic and related antidepressants, clozapine, disopyramide and nefopam may increase the anticholinergic action of procyclidine.

Drugs with anticholinergic properties may decrease salivation causing dry mouth and, in theory, may reduce the absorption and therefore the therapeutic effect of sublingual or buccal nitrate tablets.

The concomitant use of procyclidine with some neuroleptics for the treatment of extrapyramidal symptoms has been associated with a reduction in neuroleptic plasma concentrations. However this reduction is unlikely to be associated with a significant reduction in clinical effect.

Anticholinergics, including procyclidine, may reduce the efficacy of levodopa by increasing gastric emptying time, resulting in enhanced gastric degradation.

The effect of anticholinergics such as procyclidine may antagonise the gastrointestinal effects of cisapride, domperidone and metoclopramide.

Anticholinergics may reduce the absorption of ketoconazole.

Procyclidine may potentiate the vagolytic effects of quinidine.

Exposure to high environmental temperature and humidity in association with a phenothiazine/anticholinergic drug regimen has rarely resulted in hyperpyrexia.

Daily administration of paroxetine increases significantly the plasma levels of procyclidine. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of using procyclidine during pregnancy has not been established.

However, extensive clinical use has not given any evidence that it in any way compromises the normal course of pregnancy. Nevertheless, as with all drugs, use should be considered only when the expected clinical benefit of treatment for the mother outweighs any possible risk to the developing foetus.

Breast-feeding

No data are available on the excretion of this drug in breast milk.

4.7 Effects on ability to drive and use machines

Adverse events of a neurological character such as blurred vision, dizziness, confusion and disorientation have been reported with procyclidine. Therefore, if affected, patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

For this preparation of procyclidine, there is no modern clinical documentation which can be used as support for determining the frequency of adverse reactions.

Psychiatric disorders	Uncommon (≥ 1/1000 and <1/100)	Agitation, anxiety, nervousness, confusion, disorientation, hallucinations
	Rare (<1/1000)	Psychotic disorder
Nervous system disorders	Uncommon (≥1/1000 and <1/100)	Dizziness, memory impairment, impaired cognition
Gastrointestinal disorders	Common (≥ 1/100)	Dry mouth, constipation
	Uncommon (≥1/1000 and <1/100)	Nausea, vomiting, gingivitis
Eye disorders	Common (≥ 1/100)	Blurred vision
Renal and urinary disorders	Common (≥1/100)	Urinary retention
Skin and subcutaneous tissue disorder	Uncommon (≥1/1000 and <1/100)	Rash

The main undesirable effects are those to be expected from any anticholinergic agent – these are generally reversible on reducing the dosage.

With high doses of procyclidine dizziness, mental confusion, impaired cognition and memory, disorientation, anxiety, agitation and hallucinations may occur.

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and signs

Symptoms of overdosage include stimulant effects such as agitation, restlessness and confusion with severe sleeplessness lasting up to 24 hours or more. Visual and auditory hallucinations have been reported. Most subjects are euphoric but the occasional patient may be anxious and aggressive. The pupils are widely dilated and unreactive to light. In recorded cases, the disorientation has lasted 1 to 4 days and ended in a recuperative sleep. Signs of CNS depression include somnolence, reduced consciousness and occasionally coma have been reported usually following very large overdoses.

Tachycardia has also been reported in associated with cases of procyclidine overdose.

Treatment:

If procyclidine has been ingested within the previous hour or two (or possibly longer in view of its likely effects on gastric motility) then activated charcoal should be used to reduce absorption. Gastric lavage should only be considered if clinically appropriate. Other active measures such as the use of cholinergic agents or haemodialysis are extremely unlikely to be of clinical value although if convulsions occur they should be controlled by injections of diazepam.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticholinergic group

ATC code: N04A A04

Mechanism of action:

Procyclidine is a synthetic anticholinergic agent which blocks the excitatory effects of acetylcholine at the muscarinic receptor.

Idiopathic Parkinson's disease is thought to result from degeneration of neurones in the substantia nigra whose axons project and inhibit cells in the corpus striatum. Blockade by neuroleptic drugs of the dopamine released by these terminals produces a similar clinical picture. The cell bodies in the corpus striatum also receive cholinergic innervation which is excitatory.

Relief of the Parkinsonian syndrome can be achieved, either by potentiation of the dopaminergic system or blockade of the cholinergic input by anticholinergics. It is by a central action of this latter type by which procyclidine exerts its effect.

Procyclidine is particularly effective in the alleviation of rigidity. Tremor, akinesia, speech and writing difficulties, gait, sialorrhoea and drooling, sweating, oculogyric crises and depressed mood are also beneficially influenced.

5.2 Pharmacokinetic properties

Absorption

Procyclidine is adequately absorbed from the gastrointestinal tract with a bioavailability of 75% and disappears rapidly from the tissue.

Biotransformation

No detailed information is available on the metabolic fate of procyclidine but very little of the parent compound is excreted in the urine unchanged. When given orally about one fifth of the dose is known to be metabolised in the liver, principally by cytochrome P450 and then conjugated with glucuronic acid. This conjugate has been detected in the urine.

Elimination

The relatively low clearance of 68 ml/min represents a predominantly metabolic change with a small first pass effect. The mean plasma elimination half-life after oral administration of procyclidine is approximately12 hours.

5.3 Preclinical safety data

Fertility

A three generation study in rats dosed at 40 mg/kg/day via the diet before and during pregnancy showed only that the number of viable pups was slightly decreased from the second mating. No other parameters were affected.

Teratogenicity

No teratogenic effects were seen in rats dosed subcutaneously with 10, 30 or 100 mg/kg/day on days 8 to 16 of pregnancy. Maternal bodyweight gain was reduced at doses of 30 or 100 mg/kg/day, and a 10% reduction in foetal weight was seen at 100 mg/kg/day.

Carcinogenicity, mutagenicity

Procyclidine was not genotoxic in *in vitro* bacterial mutation or mouse lymphoma assays.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Sodium starch glycolate, Povidone K30, Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium blister packs of Opaque PVC (250μm) / aluminium (25μm) available in packs of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120 tablets.

HDPE bottles available in packs of 100 and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited
11 Boumpoulinas , Nicosia
1060 Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0256

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2024

10 DATE OF REVISION OF THE TEXT

29/11/2024