Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kemadrin 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Procyclidine Hydrochloride 5 mg

Excipients with known effect:

Lactose Monohydrate 174.0 mg and Sodium 0.5 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets
White, round, biconvex tablets, one face with a break-line and coded KT above the breakline and 05 below the break-line, with a score line on the other face.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Kemadrin is indicated for the treatment of all forms of Parkinson's disease: idiopathic (paralysis agitans), postencephalitic and arteriosclerotic.

Symptoms often responding well to Kemadrin include: rigidity, akinesia, tremor, speech and writing difficulties, gait, sialorrhoea and drooling, sweating, oculogyric crises and depressed mood.

Kemadrin is used to control troublesome extra-pyramidal symptoms induced by neuroleptic drugs including pseudo-Parkinsonism, acute dystonic reactions and akathisia.

4.2 Posology and method of administration

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

Posology

Parkinson's disease

Treatment is usually started at 2.5 mg three times a day, increasing by 2.5 mg daily until the level of optimal control is reached. Addition of a fourth dose before retiring has been seen to be beneficial in some patients.

The usual maximum total daily dose is 30 mg. However, at the discretion of the attending physician where appropriate this total may be as high as 60 mg.

In general, young and postencephalitic patients may require a somewhat higher dosage than older patients and those with arteriosclerosis.

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

Neuroleptic-induced extrapyramidal symptoms

Treatment is usually started at 2.5 mg three times a day, increasing by 2.5 mg daily until the level of optimal control is reached. The daily dose used in the control of neuroleptic-induced extrapyramidal symptoms is usually not more than 20 mg daily.

After a period of three to four months, Kemadrin should be stopped and the patient observed to see if the neuroleptic-induced extrapyramidal symptoms recur. If this is the case Kemadrin 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.

Paediatric population

Safety and efficacy have not been established in the paediatric age group; therefore, the use of procyclidine in this age group requires that the potential benefits be weighed against the possible risk to the child.

Elderly patients

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

Method of administration

For oral use.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

As with all anticholinergics such as Kemadrin, cautious prescribing is indicated in the elderly, in patients either predisposed to glaucoma or with existing angle-closure (narrow angle) glaucoma, obstructive disease of the gastro-intestinal tract including pyloric stenosis and paralytic ileus, with urinary symptoms associated with prostatic hypertrophy and in patients with disorders characterised by tachycardia, e.g. thyrotoxicosis.

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

In rare instances, Kemadrin administered for the treatment of neuroleptic induced symptoms was associated with an apparent worsening of the patient’s state.

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 patients may be particularly vulnerable to Central Nervous System (CNS) 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 Kemadrin in patients with impaired renal or hepatic function. However, since procyclidine is metabolised in the liver and excreted via urine care should be exercised when administering Kemadrin to patients with impaired kidney or liver function.

Dosage should only be introduced gradually. Sudden withdrawal of the product should be avoided, as rebound of parkinsonian symptoms may occur.
High dosage may induce dizziness, mental confusion and hallucinations.

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

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

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

The use of drugs with cholinergic properties, such as tacrine, may reduce the therapeutic response to Kemadrin.

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.

Procyclidine may potentiate the vagolytic effects of quinidine.

Anticholinergics may reduce the absorption of ketoconazole.

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

Fertility
See section 5.3.

Pregnancy
The safety of using Kemadrin 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 information is available on the passage of procyclidine into human breast milk following administration of Kemadrin.

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 affected patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

Undesirable effects are listed below by system organ class and frequency. For this preparation there is no modern clinical documentation which can be used as support for determining the frequency of adverse reactions.
The frequency was determined based on literature data and defined as follows:
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).

System Organ Class	Frequency	Side effects
Psychiatric disorders	Uncommon	Agitation, anxiety, nervousness, confusion, disorientation, hallucinations
	Rare	Psychotic disorder
Nervous system disorders	Uncommon	Dizziness, memory impairment, impaired cognition
Eye disorders	Common	Blurred vision
Gastrointestinal disorders	Common	Dry mouth, constipation
	Uncommon	Nausea, vomiting, gingivitis
Skin and subcutaneous tissue disorders	Uncommon	Rash
Renal and urinary disorders	Common	Urinary retention

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: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

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 one to four days and ended in a recuperative sleep.

Signs of CNS depression including somnolence, reduced consciousness, and occasionally coma have been reported usually following very large overdoses.

Tachycardia has also been reported in association with cases of Kemadrin overdose.

Treatment
If procyclidine has been ingested within the previous hour or two (or possibly longer in view of its effects on gastric motility), activated charcoal should be used to reduce absorption. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticholinergic agents, 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 release 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.

5.2 Pharmacokinetic properties

Absorption
Procyclidine is adequately absorbed from the gastro-intestinal tract with a bioavailability of 75%

Distribution
Procyclidine disappears rapidly from the tissues.

Biotransformation
The relatively low clearance of 68 ml/min represents a predominantly metabolic change with a small first pass effect.

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 P_{450} and then conjugated with glucuronic acid. This conjugate has been detected in the urine.

Elimination
The mean plasma elimination half-life after both oral and intravenous administration is approximately 12 hours.

5.3 Preclinical safety data

Fertility
In studies in rats, procyclidine did not affect fertility or cause foetal abnormalities.

Mutagenicity, Carcinogenicity
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 Glycollate, Type A
Povidone K30
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottles with polyethylene snap-fit closure containing either 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979

Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

April 2016