# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Kemadrin 5mg/ml Solution for injection
Procyclidine Hydrochloride 5mg/ml, Solution for Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Procyclidine Hydrochloride BP 5mg per ml (10mg in each 2m1 ampoule)

## 3 PHARMACEUTICAL FORM

Solution for injection

## 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.

Procyclidine is also 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.

Dosage in adults:-

Parkinson's disease:-

Treatment is usually started at 2.5mg three times per day, increasing by 2.5 to 5mg
daily 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 30mg procyclidine per day.

Addition of a fourth dose before retiring has been seen to be beneficial in some patients. Doses up to 60mg 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 extrapyramidal symptoms:-

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

The effective maintenance dose is usually 10 to 30 mg procyclidine per day. After a period of 3 to 4 months of therapy, Procyclidine should be withdrawn and the patient observed to see whether the neuroleptic-induced extra-pyramidal symptoms recur.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.

Procyclidine Injection may be given intramuscularly in doses of 5 to 10mg, repeated after 20 minutes if necessary, up to a daily maximum of 20mg procylidine.

In acute torsion dystonia and paroxysmal dyskinesias, doses of 5 to 10mg procyclidine intravenously are frequently effective within 5 to 10 minutes. Occasionally, patients may need more than 10 mg procyclidine, and may require up to half an hour to obtain relief.

Dosage in children:-

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

Dosage in Elderly:-

Elderly patients may be more susceptible than younger adults to the anticholinergic effects of Procyclidine and a reduced dosage may be required (See Special Warnings and Special Precautions for Use).

Administration:-

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

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

## 4.3 Contraindications

Procyclidine is contra-indicated in individuals with known hypersensitivity to any component of the preparation, untreated urinary retention, closed angle glaucoma and gastro-intestinal obstruction.

## 4.4 Special warnings and precautions for use

As with all anticholinergics the benefit/risk ratio should be assessed when prescribing in Procyclidine patients with existing angle-closure (narrow angle) glaucoma or those considered to be predisposed to glaucoma. Cautious prescribing is also indicated in patients predisposed to obstructive disease of the gastro-intestinal tract and those with urinary symptoms associated with prostatic hypertrophy.

In a proportion of patients undergoing neuroleptic treatment, tardive dysknesias 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 ADVERSE EVENTS). Specifically, the elderly patient may be particularly 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.

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 to Procyclidine patients with symptoms that may not be genuine.

**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, tricyclic and related 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 Procyclidine. Furthermore, drugs with anticholinergic properties may antagonise the effect of parasympathomimetic agents.

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.

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.

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

**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.

**Lactation:-**

No information is available on the passage of procyclidine into human breast milk following administration of Procyclidine.

## 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 there is no modern clinical documentation which can be used as support for determining the frequency of adverse reactions.

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.

| | | |
|---|---|---|
| **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 |

| | | |
|---|---|---|
| **Eye disorders** | Common (> 1/100) | Blurred vision |
| **Gastrointestinal disorders** | Common (> 1/100) | Dry mouth, constipation |
| | Uncommon ( >1/1000 and <1/100) | Nausea, vomiting, gingivitis |
| **Skin and subcutaneous tissue Disorder** | Uncommon ( >1/1000 and <1/100) | Rash |
| **Renal and urinary disorders** | Common (> 1/100) | Urinary retention |

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 (Website: www.mhra.gov.uk/yellowcard).

### 4.9 Overdose

**Symptoms & Signs:**

Reports of overdosage are relatively rare and no fatalities are known. Symptoms of overdosage are 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. Tachycardia has also been reported in association 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 gastric lavage is probably indicated. 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

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

Procyclidine is adequately absorbed from the gastro-intestinal tract with a bioavailability of 75% and disappears rapidly from the tissues. 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 both oral and intravenous administration is approximately 12 hours.

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.

## 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

**Mutagenicity:-**

No data is available regarding the mutagenic potential of procyclidine hydrochloride.

**Carcinogenicity:-**

There is no data on the carcinogenic potential of procyclidine hydrochloride.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Lactic acid 10µg
Lactic acid for pH 3.9 to 4.5 (quantity not fixed)
Water for Injections to 2ml

## 6.2 Incompatibilities

None known.

## 6.3 Shelf life

5 years.

## 6.4 Special precautions for storage

Store below 25°C

## 6.5 Nature and contents of container

2ml Neutral glass ampoules

## 6.6 Special precautions for disposal

No special instructions

# 7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow

Middlesex
HA1 4HF
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0706

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 April 2003

## 10 DATE OF REVISION OF THE TEXT

16/05/2018