SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Procyclidine Hydrochloride 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg procyclidine hydrochloride

Excipient with known effect:
Each tablet contains 147 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

A white normal convex tablet marked “PE”; B/L; “5” on one side and the generic “G” on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Procyclidine is indicated in all forms of Parkinson’s disease: idiopathic (paralysis agitans), post encephalitic and arteriosclerotic. Symptoms often responding well to procyclidine include: rigidity, akinesia, tremor, speech and writing difficulties, gait, sialorrhoea and drooling, sweating, oculogyric crises and depressed mood.

Tardive dyskinesia is not improved by procyclidine and may be made worse (see section 4.4).

Procyclidine is also used to control troublesome 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.

Avoid abrupt discontinuation of treatment (see section 4.4).

When changing from one drug to another, withdraw the one in small amounts whilst gradually increasing the dose of the other.

Adults
All forms of Parkinsonism
Treatment is usually started at 2.5 mg three times a day, increasing by 2.5 to 5 mg 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 mg 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 have been well tolerated, and at the discretion of the attending prescriber 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 tablets may be given with other drugs employed for the relief of Parkinsonism e.g. other antimuscarinic drugs, levodopa and amantadine in patients who are inadequately controlled on a single agent. Dose reduction may be required.

Neuroleptic-induced extra-pyramidal symptoms
Treatment is usually started at 2.5 mg three times per day, increasing by 2.5 mg daily until symptoms are relieved.

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

Withdrawal
After a period of 3 to 4 months of therapy, procyclidine should be withdrawn and the patient observed to see if the neuroleptic-induced extrapyramidal 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
Older people may be more sensitive to the anticholinergic effects of procyclidine, and a reduced dose may be required (see section 4.4).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Individuals with untreated urinary retention, closed angle glaucoma and gastrointestinal obstruction.

### 4.4 Special warnings and precautions for use

Since treatment is to be continued for an indefinite period, the patient should be carefully supervised over the long term.

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.

Cautious prescribing is also indicated in patients predisposed to obstructive disease of the gastrointestinal tract, those with urinary symptoms associated with prostatic hypertrophy and those with hypertension and cardiac disorders.

**Tardive dyskinesia**

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 dyskinesias appear in patients predisposed to this abnormality. In such individuals subsequent adjustment of neuroleptic therapy or reduction in anticholinergic treatment should be considered.

**Patients with mental health conditions**

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

**Older people**

Older people, especially those on high doses of anticholinergics may be more susceptible to the adverse events associated with such therapy (see section 4.8). Specifically, older people 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.

**Impaired renal and hepatic function**

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.

**Abrupt withdrawal**

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 procyclidine to patients with symptoms that may not be genuine.
**Lactose intolerance**

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, 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.
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.

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon (≥ 1/1,000 to &lt;1/100) Agitation, anxiety, nervousness, confusion, disorientation, hallucinations</td>
</tr>
<tr>
<td></td>
<td>Rare (≥1/10,000 to &lt;1/1,000) Psychotic disorder</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon (≥ 1/1,000 to &lt;1/100) Dizziness, memory impairment, impaired cognition</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Common (≥ 1/100 to &lt;1/10) Blurred vision</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Not known (cannot be estimated from the available data) Tachycardia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common (≥ 1/100 to &lt;1/10) Dry mouth, constipation</td>
</tr>
<tr>
<td></td>
<td>Uncommon (≥ 1/1,000 to &lt;1/100) Nausea, vomiting, gingivitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon (≥ 1/1,000 to &lt;1/100) Rash</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common (≥ 1/100 to &lt;1/10) Urinary retention</td>
</tr>
</tbody>
</table>

The main side 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.

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

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.

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 agents; tertiary amines, ATC Code: N04AA04

*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.

Symptoms often responding well to procyclidine include: rigidity, akinesia, tremor, speech and writing difficulties, gait, sialorrhoea and drooling, sweating, oculogyric crises and depressed mood.
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 approximately 12 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.

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

 Carcinogenicity
 There are no data on the carcinogenic potential of procyclidine hydrochloride.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

 Lactose anhydrous
 Cellulose, microcrystalline
 Magnesium stearate
6.2. Incompatibilities

None known.

6.3. Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

Blisters: Store in the original package in order to protect from light and moisture.
Bottles: Keep the bottle tightly closed in order to protect from light and moisture.

6.5. Nature and contents of container

Polypropylene containers with polypropylene caps and optional polyethylene ullage filler, or high density polyethylene containers (HDPE) with polyethylene snap closures, or PVC/aluminium foil blister packs, in packs of 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250 and 500 tablets.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan Station Close Potters Bar Herts EN6 1TL

8. MARKETING AUTHORISATION NUMBER(S)
9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

   Date of last renewal : 22/04/99

10 **DATE OF REVISION OF THE TEXT**

   12/06/2014