SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Procyclidine 5 mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg procyclidine hydrochloride

Excipient with known effect:
Each tablet contains 137.0 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White, round 8.5 mm diameter biconvex tablets scored on one side debossed with “PDE” and “5” on each side of the score, and debossed with twin triangle logo on reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Symptomatic treatment of arteriosclerotic, idiopathic, and post-encephalitic parkinsonism.
2. Control of troublesome extra-pyramidal 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 physician.

Adult Dose
Initially 2.5mg three times daily after meals. Maybe increased by 2.5 – 5mg daily at intervals of two to three days, until optimum clinical response is reached. Usual maximum daily dose is 20 – 30mg but occasionally 60mg may be required.

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.

When used for the control of neuroleptic-induced extra-pyramidal symptoms the dose should not exceed 20mg daily. Treatment should be stopped after 3-4 months to see if these symptoms recur. Periodic cessation of treatment is to be recommended even in patients who appear to require longer term treatment.

Use in Children
Not recommended.

Use in the Elderly
A reduced dose may be required as elderly patients are more sensitive to anticholinergics.

Method of administration
For oral use. The tablets may be better tolerated if taken with a meal.

4.3 Contraindications

Procyclidine tablets are contra-indicated in untreated urinary retention, closed angle glaucoma, gastrointestinal obstruction, prostatic hypertrophy or in patients with known hypersensitivity to any of the ingredients.

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. 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.

Caution: procyclidine may be liable to abuse; it may produce a euphoric effect. Although the cases of abuse are rare, physicians should exercise caution in prescribing procyclidine to

patients with symptoms that may not be genuine. Transition to or from procyclidine therapy should be gradual otherwise symptoms may be aggravated.

Excipients
Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

A proportion of patients undergoing treatment with neuroleptics agents will develop tardive dyskinesia. If these patients are receiving concurrent treatment with procyclidine their susceptibility to tardive dyskinesia may be increased. Should this syndrome occur adjustment of the neuroleptic therapy is indicated.

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.

The anticholinergic action of procyclidine may be increased by agents having anticholinergic activity, e.g. tricyclic and related antidepressants (e.g. amitriptyline) and MAOI's, clozapine, phenothiazines (e.g. thioridazine), antihistamines, amantadine, memantine, disopyramide and nefopam.

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.

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

Procyclidine may potentiate the vagolytic effects of quinidine.

The absorption of ketoconazole may be reduced by the concomitant administration of procyclidine (anticholinergics).

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

Antimuscarinics antagonise the gastro-intestinal effects of cisapride, metoclopramide and domperidone and the effects of parasympathomimetics.

There may be reduced effect of sublingual nitrates due to failure to dissolve under the tongue because of a dry mouth.

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

Safety of use during pregnancy has not been established, but extensive clinical use has not shown any effect on 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 excretion in breast milk following administration of Procyclidine.

4.7 Effects on ability to drive and use machines

Drowsiness is not a problem but the occurrence of tardive dyskinesia in susceptible patients, and also of blurred vision, dizziness, mental confusion, impaired cognition and memory, disorientation, and hallucinations in patients on higher dosage, could affect their ability to drive or operate machinery. Therefore, if affected, patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

Frequencies displayed use the following convention:
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 form the available data).

Immune system disorders	Not known	hypersensitivity
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
Cardiac disorders	Not known	tachycardia
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

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, excitement, impaired cognition and memory, disorientation, anxiety, agitation, insomnia 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 mental confusion, restlessness and agitation, visual and auditory hallucinations, and sleeplessness lasting up to twenty four hours or more. Mood disturbance is likely. Most subjects are euphoric but the occasional patient may be anxious and aggressive. Most 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 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 procyclidine overdose.

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

Procyclidine is a synthetic anticholinergic agent which acts by blocking the excitatory effects of acetylcholine at the muscarinic receptor. The control of symptoms is exerted by its central action on the cell bodies of the corpus striatum.

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 68ml/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 twelve 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 40mg/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 100mg/kg/day on days 8 to 16 of pregnancy. Maternal bodyweight gain was reduced at doses of 30 or 100mg/kg/day, and a 10% reduction in foetal weight was seen at 100mg/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 monohydrate
Microcrystalline cellulose (Avicel pH 101) –Part A
Microcrystalline cellulose (Avicel pH 102) –Part B
Pregelatinised starch
Purified Water
Magnesium Stearate
Talc
Sodium Starch Glycolate

6.2 Incompatibilities

None known

6.3 Shelf life

3 years packed in blister packs

6.4 Special precautions for storage

Do not store above 25°C
Store in the original package

6.5 Nature and contents of container

PVdC coated PVC/Aluminium blisters (60gm/m^2 PVdC on 250µm PVC/20µm Al) in pack sizes of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120 tablets.

6.6 Special precautions for disposal

None

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point
Whistler Drive
Castleford
WF10 5HX
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1645

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08.10.1984 / 30/03/2004

10. DATE OF REVISION OF THE TEXT

11/01/2021