Summary Product Characteristics (SPC)

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1. NAME OF THE MEDICINAL PRODUCT

DE-SPAS Tablets (Dicyclomine Hydrochloride and Paracetamol Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Dicyclomine Hydrochloride USP 20 mg

Paracetamol BP 500 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A white circular beveled edged uncoated tablet, with one side is plain and on the other side is bisected.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

DE-SPAS is indicated for the relief of pain, inflammation and smooth muscle spasm associated with intestinal colic, acute renal colic, biliary colic, ureteric colic and dysmenorrhoea.

4.2 Posology and Method of Administration

Adults

DE-SPAS tablets are to be taken 2- 3 times daily or as directed by the Physician. The duration of treatment depends on the indication and the response obtained.

Children

Safety and effectiveness in Paediatric patients have not been established. Should be used with caution.

4.3 Contraindication

DE-SPAS tablets are contraindicated in those individuals with known hypersensitivity to any of the ingredients of the product. DE-SPAS tablets should not be given to patients with active gastro intestinal lesions or with a history of recurrent gastrointestinal lesions except under circumstances where patients can be monitored very closely.

DE-SPAS Tablets

DE-SPAS tablets should be used with caution in elderly people as well as those with those with - history of GI disease, urinary retention, prostate enlargement, tachycardia, cardiac insufficiency, paralytic ileus, pyloric stenosis or impairment of hepatic or renal function.

Avoid in patients with glaucoma, inflammatory bowel disease and jaundice, myasthenia gravis.

DE-SPAS is contraindicated in infants less than 6 months of age.

4.4 Special Warning and Precautions for Use

Precautions

Psychosis has been reported in sensitive individuals given anticholinergic drugs. CNS signs and symptoms include confusion, disorientation, short-term memory loss, hallucinations, dysarthria, ataxia, coma, euphoria, decreased anxiety, fatigue, insomnia, agitation and mannerisms, and inappropriate affect. These CNS signs and symptoms usually resolve within 12-24 hours after discontinuation of the drug. Caution should be taken while prescribing DE-SPAS tablets to the following category of patients

- Autonomic neuropathy
- Hepatic or renal disease
- Ulcerative colitis: large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon - Hyperthyroidism.
- Hypertension
- Coronary heart disease. - Congestive heart failure - Cardiac tachyarrhythmia.
- Hiatal hernia
- Known or suspected prostatic hypertrophy.

Warnings

In hot weather, renal, cardiovascular and urinary outflow disorders (elderly males with BHP) neuromuscular disorders. Dicyclomine HCl may produce drowsiness or

blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. Do not abruptly stop this medicine.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

The following agents may increase certain actions or side effects of anticholinergic drugs - Amantadine, antiarrhythmic agents of class (e.g. quinidine), antihistamines antipsychotic agents (e.g. phenothiazines), benzodiazepines. MAO inhibitors, narcotic analgesics (e.g., meperidine), nitrates and nitrites, sympathomimetic agents, tricyclic antidepressants, and other drugs having anticholinergic activity.

Anticholinergics antagonize the effects of antiglaucoma agents. Anticholinergic drugs in the presence of increased intraocular pressure may be hazardous when taken concurrently with agents such as corticosteroids.

Anticholinergic agents may affect gastrointestinal absorption of various drugs, such as slowly dissolving dosage forms of digoxin; increased serum digoxin concentrations may result.

Anticholinergic drugs may antagonize the effects of the drugs that alter gastrointestinal motility, such as metoclopramide. Because antacids may interfere with the absorption of anticholinergic agents, simultaneous use of these drugs should be avoided.

The inhibiting effects of anticholinergic drugs on gastric hydrochloric acid secretion are antagonized by agents used to treat achlorhydria and those used to test gastric secretion.

Paracetamol should be given with care to patients taking other drugs that affect the liver. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone. Concurrent use need not be avoided. The absorption of paracetamol may possibly be reduced if cholestyramine is given at the same time, but the reduction in absorption is small if given an hour later. The anticoagulatory effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding.

4.6 Pregnancy and Lactation

Reproduction studies performed in rats and rabbits at doses up to 33 times the maximum recommended human dose based on 160 mg/day (3 mg/kg) and have revealed no evidence of impaired fertility or harm to the fetus due to Dicyclomine. Epidemiologic studies in pregnant women with products containing Dicyclomine HCl (at doses up to 40 mg/day) have not shown that Dicyclomine increases the risk of fetal abnormalities if administered during the first trimester of pregnancy.

There are, however, no adequate and well-controlled studies in pregnant women at the recommended doses (80-160 mg per day). Because animal reproduction studies are not always predictive of human response, Dicyclomine HCl as indicated for functional bowel/irritable bowel syndrome should be used during pregnancy only if clearly needed.

4.7 Effects on Ability to Drive and Use Machines

None reported.

4.8 Undesirable Effects

Both Dicyclomine and Paracetamol in DE-SPAS are well tolerated. Not all of the following adverse reactions have been reported with Dicyclomine hydrochloride. Adverse reactions are included here that have been reported for pharmacologically similar drugs with anticholinergic/antispasmodic action.

Gastrointestinal: dry mouth nausea, vomiting, constipation. bloated feeling, abdominal pain, taste loss, anorexia.

Central Nervous System: dizziness, light headedness, tingling, headache, drowsiness, weakness, nervousness, numbness, mental confusion and/or excitement (especially in elderly persons), dyskinesia, lethargy, syncope, speech disturbance, insomnia.

Ophthalmologic: blurred vision. diplopia, mydriasis, cycloplegia, increased ocular tension

Dermatological/Allergic: rash, urticaria, itching, and other dermal manifestations; severe allergic reaction or drug idiosyncrasies including anaphylaxis. **Genitourinary:** urinary hesitancy, urinary retention

Cardiovascular: tachycardia. palpitations

Respiratory: Dyspnea, apnea, asphyxia

Other: decreased sweating, nasal stuffiness or congestion, sneezing, throat congestion, impotence. suppressron of lactation)

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

4.9 Overdose

Dicyclomine Hydrochloride:

The signs and symptoms of overdosage with Dicyclomine are headache; nausea; vomiting; blurred vision; dilated pupils; hot, dry skin; dizziness; dryness of the mouth; difficulty in swallowing; and CNS stimulation. A curare-like action may occur (i.e., neuromuscular blockade leading to muscular weakness and possible paralysis). Treatment should consist of gastric lavage, emetics, and activated charcoal. Sedatives (e.g., short-acting barbiturates, benzodiazepines) may be used for management of overt signs of excitement. If indicated, an appropriate parenteral cholinergic agent may be used as an antidote.

Paracetamol:

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum

acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

5. PHARMACOLOGICAL PROPERTIES

Dicyclomine relieves smooth muscle spasm of the gastrointestinal tract. Animal studies indicate that this action is achieved via a dual mechanism:

(1) a specific anticholinergic effect (antimuscarinic) at the acetylcholine-receptor sites with approximately 1/8 the milligram potency of atropine (in vitro, guinea pig ileum); and (2) a direct effect upon smooth muscle (musculotropic) as evidenced by Dicyclomine's antagonism of bradykinin- and histamine-induced spasms of the isolated guinea pig ileum. Atropine did not affect responses to these two agonists. In vivo studies in cats and dogs showed Dicyclomine to be equally potent against acetylcholine (ach)- or barium chloride ($bacl_2$)-induced intestinal spasm while atropine was at least 200 times more potent against effects of ach than $bacl_2$. Tests for mydriatic effects in mice showed that Dicyclomine was approximately 1/500 as potent as atropine; antisialagogue tests in rabbits showed Dicyclomine to be 1/300 as potent as atropine.

The smooth muscles of the biliary tree, renal tissue, uterus, fallopian tube etc have been shown to go into a stage of spasm in colic. Animal studies indicate that this effect is mediated by the binding of acetylcholine to its muscarinic type of receptors situated in various organs of the abdominal and pelvic viscera. Animal studies do indicate that this action of acetylcholine can be blocked by muscarinic blocking agents like atropine.

Recent studies indicate that there are basically five types of muscarinic receptors designated as M1, M2, M3, M4 and M5 receptors. Of these various types, muscarinic receptors of type 1 (M1) is said to be involved in the spasm of the smooth muscles of the abdomen and pelvis. Muscarinic agonists such as acetylcholine liberate

arachidonic acid from membrane phospholipids (Bymaster 1999) which induce spasm of the smooth muscles. Hence, blockade of the receptors of M1 type would be useful in the treatment of disorders associated with altered smooth muscle contractility or tone (Wallis 1995).

An in vitro study carried out to assess the antispasmodic effect of Dicyclomine found Dicyclomine to produce competitive inhibition of acetylcholine induced contraction of the smooth muscles (Khanna et al 1979). Giachetti and co workers while studying the selectivity profile of various muscarinic receptor antagonists found Dicyclomine to have the highest affinity for M1 muscarinic receptor subtype (Giachetti et al 1986).

Dicyclomine displays low affinity for cardiac muscarinic receptors as well as glandular muscarinic receptors. Dicyclomine displayed a high affinity for M1 receptor in the smooth muscles of the abdomen and distinguishes between the various muscarinic receptors (Klibinger and Stein 1988).

Paracetamol I (Acetaminophen) is a para-aminophenol derivative. It has analgesic and antipyretic actions and weak anti-inflammatory actions. Acetaminophen is a peripherally acting analgesic and is well absorbed orally. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat regulating center.

5.1 Pharmacodynamics Properties

DE-SPAS tablets are effective in relief of pain inflammation and smooth muscle spasm by the antispasmodic, anti-cholinergic and analgesic actions of Dicyclomine and Paracetamol respectively.

Dicyclomine relieves smooth muscle spasm not only through blockade of muscarinic receptors but also through a direct effect upon the smooth muscle as evidenced by Dicyclomine antagonism of histamine and bradykinin induced spasm of the guinea ileum. In vitro studies in dogs and cats indicate that Dicyclomine is equally effective against acetylcholine or barium induced intestinal spasm.

Paracetamol acts by inhibiting cyclooxygenase enzyme in brain, thus inhibiting the formation of prostaglandins. It is a poor inhibitor of prostaglandin sysnthesis in peripheral tissues. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat regulating center.

5.2 Pharmacokinetic Properties

Pharmacokinetics of Dicyclomine Hydrochloride:

Absorption

In man, Dicyclomine is absorbed rapidly from the gastrointestinal tract following oral administration. Peak concentrations in the plasma are attained 60 to 90 min after oral administration.

Distribution

The mean volume of distribution is approximately 3.65 L/kg suggestive extensive distribution in tissues.

Elimination

Approximately 80 % of an oral dose is excreted in the urine and 10 % in the feces. The mean plasma elimination half-life is approximately 1.8 h. Although the elimination half-life has been shown to be only 1.8h with short duration pharmacokinetic studies, studies with longer follow up indicate a terminal elimination half-life of 8 h.

Pharmacokinetics of Paracetamol:

Absorption

Paracetamol is absorbed readily from the gastrointestinal tract following oral administration. Peak concentrations in the plasma are attained 10 to 60 min after oral administration.

Distribution

Paracetamol is distributed throughout most tissues & fluids of the body. It crosses the placenta and is present in the breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism:

It is metabolized predominantly in the liver and excreted mainly as glucoronide and sulphate conjugates.

Elimination

The plasma elimination half-life ranges from 1 to 4 hours for acetaminophen. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

5.3 Preclinical Safety Data

Dicyclomine Hydrochloride:

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no known human data on long-term potential for carcinogenicity or mutagenicity.

Long-term studies in animals to determine carcinogenic potential are not known to have been conducted. In studies in rats at doses of up to 100 mg/kg/day, Dicyclomine hydrochloride produced no deleterious effects on breeding, conception, or parturition.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 33 times the maximum recommended human dose based on 160 mg/day (3 mg/kg) and have revealed no evidence of impaired fertility or harm to the fetus due to Dicyclomine. Epidemiologic studies in pregnant women with products containing

Dicyclomine hydrochloride (at doses up to 40 mg/day) have not shown that Dicyclomine increases the risk of fetal abnormalities if administered during the first trimester of pregnancy. There are, however, no adequate and well-controlled studies in pregnant women at the recommended doses (80-160 mg/day). Because animal reproduction studies are not always predictive of human response, Dicyclomine hydrochloride as indicated for functional bowel/irritable bowel syndrome should be used during pregnancy only if clearly needed.

Nursing Mothers

Since Dicyclomine hydrochloride has been reported to be excreted in human milk, Dicyclomine Hydrochloride Is contraindicated In Nursing Mothers.

Paediatric Use

Dicyclomine hydrochloride is contraindicated in infants less than 6 months of age. Safety and effectiveness in paediatric patients have not been established.

Geriatric Use

Clinical studies of Dicyclomine Hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Paracetamol:

Human carcinogenicity data

In the previous monograph on Paracetamol, a positive association with cancer of the ureter (but not of other sites in the urinary tract) was observed in an Australian case–control study. None of the other three case–control studies showed an association with cancer in the urinary tract. Nine new—mainly population-based—case–control studies of cancers of the urinary tract have been published, many of which addressed more than one subsite.

None of six studies from Australia, Europe and North America, including a very large international study, found a consistent association between renal-cell cancer and regular intake of Paracetamol at any level. In one study from the United States which included patients with renal cancer (type not specified), the risk increased with increasing cumulative intake of Paracetamol, to reach statistical significance at the highest exposure; however, this result was not adjusted for intake of other analgesics. In one study from Australia which included patients with cancer of the renal pelvis, a non-significant twofold increase in risk was seen among people in the highest

exposure category, with no excess risk in the two lower exposure categories. Another, large case–control study of cancer of the renal pelvis and ureter from the United States showed no association with regular intake of paracetamol.

Of the three new studies that included patients with urinary bladder cancer, which conducted in Sweden showed an elevated risk without providing details. The other two (both from the United States) showed only a slight or no association.

Animal carcinogenicity data

Paracetamol was tested for carcinogenicity by oral administration in mice and rats. An early study indicated an increased incidence of liver adenomas and carcinomas at a markedly toxic dose in mice of one strain; however, this result was not corroborated in a later study in mice, also at a dose greater than the maximal tolerated dose. A more recent, well-conducted study showed no evidence of a carcinogenic effect in mice. Paracetamol had no carcinogenic effect in rats of several strains, but in rats of one inbred strain, increased incidences of liver and bladder neoplasms were recorded in males at the high dose and an increased incidence of bladder tumours in females at the low dose. A more recent, well-conducted study showed no treatment-related carcinogenic effect in rats.

Paracetamol did not promote urinary bladder carcinogenesis in rats and reduced the incidence of intestinal tumours in a two-stage model of intestinal carcinogenesis in rats. It enhanced the incidence of renal adenomas induced by one renal carcinogen but not those induced by another.

Other relevant data

Activation of a relatively small percentage of Paracetamol to N-acetyl-parabenzoquinone imine by cytochrome P450, predominantly CYP 2E1, has been found to be involved in the mechanism of hepatic and, perhaps, renal toxicity. Most Paracetamol is metabolized by glucuronidation, sulfation and conjugation with glutathione, which protects the liver at therapeutic doses. Doses of 300 mg/kg bw per day paracetamol and higher saturate conjugation reactions, deplete glutathione and result in binding of the benzoquinone imine to cellular proteins; this has been proposed to be the mechanism of hepatocellular injury in rodents and humans. Several protein

adducts have been found in humans and rodents in vivo after exposure to Paracetamol. DNA adducts were not observed in mice.

In humans, an association was reported in two case–control studies between daily use of Paracetamol and renal disease; however, a causal relationship has not been established. Humans and rodents exposed to doses of Paracetamol well above the therapeutic range have experienced centrilobular hepatotoxicity and nephrotoxicity involving the proximal renal tubule. In experimental animals, hepatic, renal and testicular damage occurred only at oral doses that exceeded 300 mg/kg bw per day in rats and 900 mg/kg bw per day in mice. At lower doses, toxic effects in rodents are minimal or absent.

Teratogenicity:

Paracetamol does not present a teratogenic risk to humans at doses associated with severe maternal toxicity. It did not affect reproductive performance of mice in a continuous breeding protocol, although growth and birth weights were reduced. Sperm abnormalities have been observed in mice.

Although Paracetamol does cross the placenta the occasional use of therapeutic doses in healthy women does not seem to be associated with an increased risk of malformation and has not been proved to be teratogenic. There seems to be the same degree of renal and hepatotoxicity in the baby as in the mother, so large doses of Paracetamol that cause severe maternal toxicity have been associated with foetal kidney and liver damage. There is structural damage (i.e. affecting organ formation) in a 1st trimester exposure and functional damage (i.e. affecting organ maturation and/or function) in 2nd and 3rd trimester exposures. There is also an association with foetal anaemia and neonatal jaundice if the overdose is taken near term.

Mutagenicity & Genotoxicity:

The results of studies of the cytogenetic effects of Paracetamol in humans are inconclusive. Paracetamol induced sister chromatid exchange in human cells in vivo, and it was aneugenic and induced chromosomal aberrations but not micronuclei in mammalian cells in vivo. It induced DNA single-strand breaks in mice treated in vivo.

Paracetamol induced sister chromatid exchange and chromosomal aberrations in human cells in vitro. It weakly induced cell transformation in a mouse cell line. It

induced chromosomal aberrations, micronuclei and sister chromatid exchange in mammalian cells in vitro. It did not induce gene mutation, and the results of tests in mammalian cells in vitro for unscheduled DNA synthesis and DNA damage were inconclusive. Overall, Paracetamol was genotoxic in mammalian cells in vivo and in vitro. It was not mutagenic to insects but was clastogenic in plant cells. It was not mutagenic in any standard assay in bacteria.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Pregelatinised Starch, Microcrystalline Cellulose, Maize Starch, Gelatin, Sodium Maize Starch, Gelatin, Sodium Methyl Hydroxybenzoate, Sodium Propyl Hydroxy benzoate, Magnesium Stearate, Sodium Starch Glycolate (Type 1) and Purified Water.

6.2 Incompatibilities:

None reported

6.3 Shelf Life:

36 months

6.4 Special Precaution for Storage:

Do not store above 30°C. Protect from light & moisture. Keep out of reach of children.

6.5 Nature and Contents of Container:

2 x 10’s blisters packed in a mono carton with a package insert; 5 such mono cartons packed in an outer carton.

6.6 Special Precautions for Disposal:

No special instructions needed.

7. REGISTRANT:

STEDMAN PHARMACEUTICALS PRIVATE LTD.

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