1.6 PRODUCT INFORMATION

1.6.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
SPASMODEX-P (Paracetamol & Hyoscine Butylbromide Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains:
Paracetamol BP 500 mg
Hyoscine butylbromide BP 10 mg
Titanium Dioxide BP
Excipients QS

3. PHARMACEUTICAL FORM
Tablet, Solid dosage form

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
SPASMODEX-P is an antispasmodic-analgesic combination used for the relief from the pain of stronger abdominal cramps including menstrual cramps and urinary tract spasm.

4.2 Posology and method of administration
Hyoscine butylbromide + Paracetamol should not be taken over prolonged period of time (for more than 3 days) without a prescription from the physician.
The following doses are recommended: Adults: 1-2 tablets, 3 times daily.
The total daily dose should not exceed 6 tablets.
Pediatric population: Not suitable for children under 10 years of age.

Method of administration:
For oral administration only.
Should be swallowed whole with adequate water.

4.3 Contraindications
Hypersensitivity to any of Excipient used.
Myasthenia gravis, mechanical stenosis in the GIT, paralytic or obstructive ileus, megacolon, severe hepatocellular insufficiency (Child-Pugh C), rare hereditary conditions.

4.4 Special warnings and precaution for use
Spasmodex-P should be given with care in patients with impaired kidney or liver function in alcoholism and patients taking other drugs that affect the liver. Absorption of Paracetamol content in Spasmodex-P may be accelerated by Metoclopramide. Excretion of Paracetamol may be affected and plasma concentrations altered when administered with Probenecid. Spasmodex-P should be given with caution in patients with Myasthenia gravis, renal and hepatic impairment, diarrhea, glaucoma, hypertension, ulcerative colitis and down syndrome.

4.5 Interaction with other medicinal products and other forms of interaction
Hyoscine butylbromide + Paracetamol can be taken together with other drugs but not with the following:

certain hypnotics and anti-epileptics (e.g. glutethimide, phenobarbital, phenytoin, carbamazepine) as well as rifampicin. The same applies to potentially hepatotoxic substances and alcohol abuse.
Long-term use of paracetamol in patients being treated with oral anti-coagulants is only advisable under medical supervision.
Concomitant use of paracetamol and zidovudine (AZT or retrovir) enhances the tendency towards reducing leukocytes (neutropenia). Therefore, Hyoscine butylbromide + Paracetamol should only be taken together with zidovudine following medical advice.
The paracetamol dose should be reduced during concurrent administration with probenecid.
Cholestyramine reduces the absorption of paracetamol.
The anticholinergic effect of drugs such as tri- and tetracyclic antidepressants, antihistamines, antipsychotics, quinidine, amantadine, disopyramide and other anticholinergics (e.g. tiotropium, ipratropium, atropine-like compounds) may be intensified by Hyoscine butylbromide + Paracetamol.
Concomitant treatment with dopamine antagonists such as metoclopramide may result in diminution of the effects of both drugs on the gastrointestinal tract.
The tachycardic effects of beta-adrenergic agents may be enhanced by Hyoscine butylbromide + Paracetamol.

4.6 Pregnancy and Lactation
Pregnancy
Hyoscine butylbromide + Paracetamol Tablet may be unsafe to use during pregnancy.
Lactation
Hyoscine butylbromide + Paracetamol is safe to use during lactation.
Fertility
No studies on the effects on human fertility have been conducted.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
Because of possible visual accommodation disturbances patients should not drive or operate machinery if affected.

4.8 Undesirable effects
Gastrointestinal disturbances, staggering, skin rashes, conjunctivitis, anticholinergic side effects such as: dry mouth/skin, difficulty in swallowing, visual disturbances, flushings and drowsiness. Other adverse reactions include-liver damage in prolonged use or over dosage.

4.9 Overdose
Symptoms:
Signs of overdose of Hyoscine butylbromide may include pallor, nausea, vomiting, anorexia and abdominal pain. Patients may then experience a temporary subjective improvement but mild abdominal pain possibly indicative of liver damage may persist.
A single dose of paracetamol of approximately 6 g or more in adults or 140 mg/kg in children may cause hepatocellular necrosis. This may lead to complete irreversible necrosis and subsequently to hepatocellular insufficiency, metabolic acidosis and encephalopathy, which may in turn progress to coma and death.
Concurrent rises in liver transaminases (AST, ALT), lactate dehydrogenase and bilirubin and an increase in prothrombin time, occurring 12 - 48 hours after ingestion, have been observed. Clinical symptoms of liver damage are normally apparent after 2 days and reach a maximum after 4 - 6 days.
Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Other non-hepatic symptoms such as myocardial abnormalities and pancreatitis have also been reported to occur after paracetamol overdosage.

Treatment:
If required, parasympathomimetic drugs should be administered. Opthalmological advice should be sought urgently in cases of glaucoma. Cardiovascular complications should be treated according to usual therapeutic principles. In case of respiratory paralysis: intubation, artificial respiration should be considered. Catherisation may be required for urinary retention. In addition, appropriate supportive measures should be used as required.
Where paracetamol intoxication is suspected, intravenous administration of SH group donators such as N-acetylcysteine within the first 10 hours after ingestion is indicated.
Although N-acetylcysteine is most effective if initiated within this period, it can still offer some degree of protection if given as late as 48 hours after ingestion; in this case, it is taken for longer. The plasma concentration of paracetamol can be decreased by dialysis. Determinations of the plasma concentration of paracetamol are recommended.
Further measures will depend on the severity, nature and course of clinical symptoms of paracetamol intoxication and should follow standard intensive care protocols.

5. PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Antispasmodic-analgesic
Paracetamol: N02BE01, Hyoscine Butylbromide: A03BB01

5.1 Pharmacodynamic properties
Mechanism of action
Hyoscine butylbromide and Paracetamol/Acetaminophen, which relieves abdominal pain and cramps. Hyoscine butylbromide is an anti-cholinergic which works by relaxing the muscles in your stomach and gut (intestine). It stops sudden muscle contractions (spasms), thereby relieving cramps, pain, bloating, and discomfort.
Paracetamol/Acetaminophen is an analgesic (pain reliever) which works by blocking the release of certain chemical messengers that cause pain.

5.2 Pharmacokinetic properties
Absorption

As a quaternary ammonium compound, hyoscine butylbromide is highly polar and hence only partially absorbed following oral (8%) or rectal (3%) administration. After oral administration of single doses of hyoscine butylbromide in the range of 20 to 400 mg, mean peak plasma concentrations between 0.11 ng/mL and 2.04 ng/mL were found at approximately 2 hours. In the same dose range, the observed mean AUC_{0-tz}-values varied from 0.37 to 10.7 ng h/mL. The median absolute bioavailabilities of different dosage forms, i.e. coated tablets, suppositories and oral solution, containing 100 mg of hyoscine butylbromide each were found to be less than 1%.

Distribution

Because of its high affinity for muscarinic receptors and nicotinic receptors, hyoscine butylbromide is mainly distributed on muscle cells of the abdominal and pelvic area as well as in the intramural ganglia of the abdominal organs. Plasma protein binding (albumin) of hyoscine butylbromide is approximately 4.4%. Animal studies demonstrate that hyoscine butylbromide does not pass the blood-brain barrier, but no clinical data to this effect is available. Hyoscine butylbromide (1 mM) has been observed to interact with the choline transport (1.4 nM) in epithelial cells of human placenta *in vitro*.

Metabolism and elimination

Following oral administration of single doses in the range of 100 to 400 mg, the terminal elimination half-lives ranged from 6.2 to 10.6 hours. The main metabolic pathway is the hydrolytic cleavage of

the ester bond. Orally administered hyoscine butylbromide is excreted in the faeces and in the urine. Studies in man show that 2 to 5% of radioactive doses is eliminated renally after oral, and 0.7 to 1.6% after rectal administration. Approximately 90% of recovered radioactivity can be found in the faeces after oral administration. The urinary excretion of hyoscine butylbromide is less than 0.1% of the dose. The mean apparent oral clearances after oral doses of 100 to 400 mg range from 881 to 1420 L/min, whereas the corresponding volumes of distribution for the same range vary from 6.13 to 11.3 x 10^5 L, probably due to very low systemic availability. The metabolites excreted via the renal route bind poorly to the muscarinic receptors and are therefore not considered to contribute to the effect of the hyoscine butylbromide.

Paracetamol BP

Absorption

Paracetamol is readily absorbed from the gastrointestinal tract.

Distrubution

Peak plasma concentrations occur about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Biotransformation

It is metabolised in the liver. A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause tissue damage.

Elimination

It is excreted in the urine, mainly as the glucuronide and sulfate conjugates. The elimination half-life varies from about 1 to 4 hours.

5.3 Preclinical safety data

In limited reproductive toxicity studies hyoscine butylbromide showed no evidence of teratogenicity in rats at 200 mg/kg in the diet or in rabbits at 200 mg/kg by oral gavage or 50 mg/kg by subcutaneous injection. Fertility in the rat was not impaired at doses of up to 200 mg/kg in the diet.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Citric Acid
Maize Starch
PVPK-30
Magnesium Stearate
Colloidal silicon Dioxide
Crosscarmellose Sodium
Pregelatinised Starch
Instamoist Shield IC-MS- 2398
Instaglow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30^0 C. Protect from light and moisture.

Keep Medicine Out of Reach of Children

6.5 Nature and contents of container
3 Blisters of 10 tablets each are packed in carton along with Product insert. (3×10's Alu-Alu Blisters pack)

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER
Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION
Not Applicable