This package insert is continually updated: Please read carefully before using a new pack.

Hyoscine Butylbromide & Paracetamol Tablets
Buscogast ® PLUS

Composition

Each film coated tablet contains:
Hyoscine butylbromide I.P…… 10mg
Paracetamol I.P. ……...…..325 mg
Excipients……q.s.
Colour: Titanium Dioxide I.P.

Indications

For spasmodic pain.

Paroxysmal pain in diseases of the stomach or intestine spastic pain and functional disorders in the biliary and urinary tracts and female genital organs (e.g. dysmenorrhoea)

Dosage and administration

Buscogast® PLUS should not be taken over prolonged period of time (for more than 3 days) without doctor's consultation.

Tablets
Adults
1 - 2 tablets 3 times daily.
The total daily dose should not exceed 6 tablets .
The tablets should not be chewed, but swallowed in whole with a sufficient amount of water.
Children from 10 years onward may use Buscogast® PLUS film-coated tablets , if required. The film coated tablets are not suitable for children under 10 years of age.

Contraindications

Buscogast® PLUS is contraindicated in:
- known hypersensitivity to hyoscine butylbromide, or paracetamol or other components of the drug
- myasthenia gravis
- mechanical stenosis in the gastrointestinal tract
- paralytical or obstructive ileus
- megacolon
- severe hepatocellular insufficiency (Child - Pugh C).

Special warnings and precautions

In case severe, unexplained abdominal pain persists or worsens, or occurs together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting or blood in stool, medical advice should immediately be sought.

To prevent overdosing, it should be ensured that any other drugs taken concurrently do not contain paracetamol, one of the active components of Buscogast® PLUS .
Liver damage may result if the recommended dosage for paracetamol is exceeded .

Buscogast® PLUS should be used with caution in:

- glucose-6-phosphate-dehydrogenase deficiency
- chronic alcohol use including recent cessation of alcohol intake
- severe renal insuficiency
- Gilbert's syndrome
- Mild to moderate hepatocellular insufficiency (Child - Pugh A/B)
- Low glutathione reserves.

In such cases Buscogast® PLUS should only be used under medical supervision and, if necessary, the dose reduced or the intervals between the individual administrations prolonged.

The blood count and renal and liver function should be monitored after prolonged use.

Extensive use of analgesics, especially at high doses, may induce headaches that must not be treated with increased doses of the drug.

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are very infrequently observed. Treatment must be discontinued at the first signs of a hypersensitivity reaction following the administration of Buscogast® PLUS .

Severe cutaneous adverse reactions (SCARs):
Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN) have been reported with the use of Buscogast® PLUS . Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should immediately stop Buscogast® PLUS treatment and seek medical advice.

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction.

Abrupt discontinuation of analgesics after a prolonged use at high doses may induce withdrawal symptoms (e.g. headache, tiredness, nervousness), that typically resolve within few days. Reintake of analgesics should depend upon physican’s advice, and withdrawal symptoms abated.

Buscogast® PLUS should not be taken for more than 3 days unless directed by a physician. The patient should be instructed to seek medical advice, if pain persists or gets worse, if new symptoms occur, or if redness or swelling is present, because these could be signs of a serious condition.

Because of the potential risk of anticholinergic complications caution should be used in patients prone to narrow angle glaucoma as well as in patients susceptible to intestinal or urinary outlet obstructions and in those inclined to tachyarrhythmia.

Interactions

Otherwise harmless doses of paracetamol may cause liver damage if taken together with drugs leading to enzyme induction such as certain hypnotics and anti-epileptics (e.g. glutethimide, phenobarbital, phenytoin, carbamazepin) as well as rifampicin. The same applies to potentially hepatotoxic substances and alcohol abuse.

Combination with chloramphenicol can prolong the half-life of chloramphenicol with the risk of increased toxicity.

Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K. Patients taking paracetamol and antivitamin K should be monitored for appropriate coagulation and bleeding complications.

Co-administration of flucloxacillin with paracetamol may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

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 Buscogast® PLUS.

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 Buscogast® PLUS .

Acceleration of gastric emptying, e.g. after administration of metoclopramide or domperidone, leads to an increase in the absorption rate of paracetamol.

Pregnancy And Lactation

Pregnancy
There are no adequate data on use of Buscogast® PLUS during pregnancy.
Long experience with the mono substances has shown insufficient evidence of adverse effects during human pregnancy.
After use of hyoscine butylbromide, preclinical studies in rats and rabbits did not show either embryotoxic or teratogenic effects.

During pregnancy prospective data on overdose of paracetamol showed no increase in the risk of malformations. Reproductive studies to investigate oral use showed no signs to suggest malformations of fetotoxicity. Under normal conditions of use, paracetamol can be used throughout pregnancy after careful review of the risk-benefit ratio.

During pregnancy, paracetamol should not be taken for prolonged periods, in high doses, or in combination with other medicinal products as the safety has not been confirmed in such cases.
Therefore, Buscogast® PLUS is not recommended during pregnancy.

Lactation
For hyoscine butylbromide safety during lactation has not yet been established. However, adverse effects on the newborn have not been reported.
Paracetamol enters breast milk, but is not likely to affect the infant when therapeutic doses are used.
As a precautionary measure, it is preferable to avoid the use of Buscogast® PLUS during lactation.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

Adverse Reactions

Blood and lymphatic system disorders	Not known: Agranulocytosis, thrombocytopenia, neutropenia, leukopenia, hemolytic anemia in particular in patients with underlying glucose 6-phosphate-deshydrogenase deficiency

Immune system disorders	Uncommon: Skin reactions, sweating abnormal, , Rare: blood pressure decreased including shock, Not known: anaphylactic reactions, , dyspnoea, Not known: Hypersensitivity such as anaphylactic shock, angioedema
Cardiac disorders	Rare: tachycardia
Respiratory, thoracic and mediastinal disorders:	Not known: Bronchospasm (especially in patients with a history of bronchial asthma or allergy)
Skin and subcutaneous disorders	Very rare: erythema, urticaria, rash Not known: Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption
Gastrointestinal disorders	Uncommon: Dry mouth
Hepatobiliary disorders	Not known: cytolytic hepatitis, which may lead to acute hepatic failure
Renal and urinary disorders	Not known: Urinary retention

Overdose

Elderly persons, small children, patients with liver disorder, chronic alcohol consumption or chronic malnutrition, as well as patients co-administered with enzyme-inducing drugs are at an increased risk of intoxication, including fatal outcomes.

Signs And Symptoms

Hyoscine butylbromide
In the case of overdose, anticholinergic effects have been observed.

Paracetamol
Symptoms normally occur during the first 24 hours and 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.
Overdosage with paracetamol may cause hepatic cytolysis which can lead to hepatocellular insufficiency, gastrointestinal bleeding, metabolic acidosis, encephalopathy, disseminated intravascular coagulation, coma and death.
Increased levels of hepatic transaminases, lactate deshydrogenase and bilirubin with a reduction in prothrombin level can appear 12 to 48 hours after acute overdosage.
It can also lead to pancreatitis, acute renal failure and pancytopenia .

Management

Hyoscine butylbromide
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. Catheterisation may be required for urinary retention. In addition, appropriate supportive measures should be used as required.

Paracetamol
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.

Interferences With Laboratory And Diagnostic Test

Intake of paracetamol may impact the lab determination of uric acid by phosphotungstic acid and of blood glucose by glucose oxidase-peroxidase.

Pharmacological properties

Hyoscine butylbromide contained in Buscogast® PLUS exerts a spasmolytic action on the smooth muscle of the gastro-intestinal, biliary and genito-urinary tracts.
As a quaternary ammonium derivate, hyoscine butylbromide does not enter the central nervous system. Therefore, anticholinergic side effects at the central nervous system do not occur. Peripheral anticholinergic action results from a ganglion-blocking action within the visceral wall as well as from an anti-muscarinic activity.

Paracetamol contained in Buscogast® PLUS has analgesic and antipyretic actions, together with a very weak anti-inflammatory effect. Its mechanism of action is not fully understood. It strongly inhibits central prostaglandin synthesis but only weakly inhibits peripheral prostaglandin synthesis. It also inhibits the effect of endogenous pyrogens on the temperature regulation centre in the hypothalamus.

Pharmacokinetics

Hyoscine butylbromide

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 $AUC_{0\text{-}tz}$-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.
After intravenous administration, the substance is rapidly cleared from the plasma during the first 10 minutes with a half life of 2 - 3 minutes The volume of distribution (Vss) is 128 L. Following oral and intravenous administration, hyoscine butylbromide concentrates in the tissue of the gastrointestinal tract, liver and kidneys Despite the briefly measurable extremely low blood levels, hyoscine butylbromide remains available at the site of action because of its high tissue affinity. Autoradiography confirms that hyoscine butylbromide does not pass the blood-brain barrier. Hyoscine butylbromide has low plasma protein binding.

Metabolism and elimination
The mean total clearance after intravenous administration is approximately 1.2 L/min, approximately half of it being renal. The terminal elimination half life is approximately 5 hours.

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
Absorption and Distribution
Following oral administration paracetamol is rapidly and almost completely absorbed from the small intestine with peak plasma concentrations occurring about 0.5 to 2 h after ingestion After rectal administration absorption of paracetamol is less and slower than after oral administration with an absolute bioavailability of about 30 to 40% and peak plasma concentrations at 1.3 - 3.5 h.

The drug is rapidly and evenly distributed into the tissues and crosses the blood brain barrier. The absolute bioavailability after oral administration ranges between 65% and 89% indicating a first pass effect of about 20 - 40%. Fasting accelerates absorption but has no influence on bioavailability . Protein binding is low (about 5 to 20%) at therapeutic doses.

Metabolism
Paracetamol is extensively metabolized in the liver mainly to inactive conjugates of glucuronic (about 60%) and sulphuric acid (about 35%). At supratherapeutic doses, the latter route rapidly becomes saturated. A small amount is metabolized by cytochrome P450 isoenzymes (mainly CYP2E1), leading to the formation of a toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), which is normally rapidly detoxified by glutathione and excreted as mercaptopurine and cysteine conjugates. Following massive overdose, however, the levels of NAPQI are increased.

Elimination
Glucuronide and sulphate conjugates are completely excreted via the urine within 24 hours,. Less than 5% of the dose is excreted as the unchanged parent compound. Total clearance is about 350 mL/min..The plasma half-life is 1.5 - 3 hours at therapeutic doses . In young children the half-life is prolonged and sulfate conjugation is the dominant metabolic pathway. Plasma paracetamol half-life is also prolonged in chronic liver disease and in patients with severely impaired renal function..

Bioavailability of a combination of hyoscine butylbromide and paracetamol
A study in healthy volunteers on the bioavailability of hyoscine butylbromide and paracetamol from three different formulations of Buscogast® PLUS (tablets, suppositories, oral solution) showed that the bioavailability of the two compounds was comparable to the results obtained in previous studies with the respective single compounds and that a relevant effect on the bioavailability due to combined administration could not be observed.

NONCLINICAL SAFETY DATA
i) Repeat Dose Toxicity:
The acute oral toxicity of the combination paracetamol/hyoscine butylbromide in the ratio 50/1 in mice and rats was low. The LD50 in mice was 980 mg/kg, in rats in the range of 3000 mg/kg. Signs of toxicity were apathy, reduced motility, bristled fur and loss of weight. Animals died between 1.25 and 48 h after the administration. There was no difference in the sensitivity to the drug between the genders.

Acutely, hyoscine butylbromide has a low index of toxicity: oral LD50 values were 1000 - 3000 mg/kg in mice, 1040 - 3300 mg/kg in rats, and 600 mg/kg in dogs. Toxic signs were ataxia and

decreased muscle tone, additionally, in mice tremor and convulsions, in dogs mydriasis, dry mucous membranes and tachycardia. Deaths from respiratory arrest occurred within 24 h. The intravenous LD50 values of hyoscine butylbromide were 10 - 23 mg/kg in mice and 18 mg/kg in rats.

In repeated oral dose toxicity studies over 4 weeks, rats tolerated 500 mg/kg equivalent to no observed adverse effect level (NOAEL). At 2000 mg/kg, by the action on parasympathetic ganglia of visceral area, hyoscine butylbromide paralysed the gastrointestinal function resulting in obstipation. Eleven out of 50 rats died. Haematology and clinical chemistry results did not show dose-related variations.

In man, acute intoxication was observed for paracetamol. The lethal dose for paracetamol is about 10 g (hepatotoxicity).
Repeat-dose toxicity of the combination paracetamol/hyoscine butylbromide in the ratio 50/1 was investigated in a 13-week study in rats . At doses > 250/5 mg/kg/day of the combination, adverse effects included reduced body weight gain, anemia, polydipsia, an increase of SGPT, SGOT and SAP and an atrophy of testes with impairment of spermiogenesis. All these findings were reversible or showed a clear tendency to reversibility during the recovery period of 5 weeks.

In both, the single-dose studies and the 13-week study, signs of toxicity and the toxic dose range were related to paracetamol, the major-part of the combination product Buscogast® PLUS.
In the combination, no potentiation of toxicity or new toxic effects of hyoscine butylbromide or paracetamol were observed.

Over 26 weeks, rats tolerated 200 mg/kg, while at 250 and 1000 mg/kg, the gastrointestinal function was depressed and deaths occurred. The NOAEL for a 39-week oral (capsule) dog study was 30 mg/kg.
The majority of clinical findings were attributable to acute effects of hyoscine butylbromide at high dosages (200 mg/kg). No adverse histopathological findings were observed.

Studies with the individual ingredients however can be regarded as relevant supplemental data for the evaluation of the toxic potential of Buscogast® PLUS.

A repeated intravenous dose of 1 mg/kg was well tolerated by rats in a 4-week study. At 3 mg/kg, convulsions occurred immediately after injection. Rats dosed with 9 mg/kg died from respiratory paralysis.

Dogs treated intravenously over 5 weeks at 2 x 1, 2 x 3 and 2 x 9 mg/kg, showed a dose-dependent mydriasis in all treated animals, in addition at 2 x 9 mg/kg, ataxia, salivation and decreased body weight and food intake were observed. The solutions were locally well tolerated.

After repeated i.m. injection, the dose of 10 mg/kg was systemically well tolerated, but lesions of muscles at the site of injection were distinctly increased if compared to control rats. At 60 and 120 mg/kg, mortality was high and local damages were dose-dependently-increased.

ii) Genotoxicity:
Investigations on reproduction, mutagenicity and cancerogenicity with the combination have not been performed.

Hyoscine butylbromide revealed no mutagenic or clastogenic potential in the Ames test, in the gene mutation assay in mammalian V79 cells (HPRT test) and in a chromosomal aberration test in human peripheral lymphocytes as well as in micronucleus test in rats. There are no carcinogenicity studies of hyoscine butylbromide; however, no tumorigenic potential was revealed in two oral 26-week studies in rats when given up to 1000 mg/kg.
Comprehensive investigations did not indicate any evidence of a clinically relevant genotoxic risk from paracetamol in the therapeutic, i.e. non-toxic, dose range.

iii) Carcinogenicity:
There were heterogeneous results of genotoxicity and carcinogenicity studies performed in rats and mice. On the basis of data from NTP bioassays in rats and mice, the International Agency for Research on Cancer (IARC) classified paracetamol as non-genotoxic and non-carcinogenic.

iv) Reproductive and Developmental Toxicity:
In reproduction studies with oral administration in rats and rabbits hyoscine butylbromide did not show a teratogenic potential and did not affect fertility and breeding capacity. Paracetamol crosses the placenta. Paracetamol has been reported not to be teratogenic for animals and humans. No reports of paracetamol-induced impairment on fertility and peri/postnatal development are available in laboratory animals and humans.
Doses > 250/5 mg/kg/day of the combination paracetamol/hyoscine butylbromide administered for 13 weeks to rats produced testicular atrophy and inhibition of spermatogenesis; the relevance of this finding to use in humans is not known.

Storage condition
Store at a temperature not exceeding 30^0C protected from light and moisture.
Keep out of reach of children.

Presentation
BUSCOGAST® PLUS Tablets:
- Strip of 10 tablets
- 10 strips in a carton

Manufactured in India by:
Recipharm Pharmaservices Pvt. Ltd., Khata No. 845/713 and 1108/ 970/1, 34th KM, Tumkur Road, T-Begur, Nelamangala, Bangalore Rural - 562123, India

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