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

Hyoscine Butylbromide Tablets
BUSCOGAST®

Composition

Each sugar-coated tablet contains:
Hyoscine butylbromide I.P. 10mg
Excipients q.s.
Colour: Titanium Dioxide I.P.

Indications

Gastro-intestinal tract spasm, spasm and dyskinesia of the biliary system, genito-urinary tract spasm.

For targeted relief from abdominal pain and cramps.

Dosage and administration

Unless otherwise prescribed by the physician, the following dosages are recommended:

ORAL

Sugar-coated tablets:
Adults and children over 6 years: 3 times daily 1 - 2 s.c.(sugar coated) tablets.

BUSCOGAST® should not be taken on a continuous daily basis or for extended periods without investigating the cause of abdominal pain.

Contraindications

BUSCOGAST® is contraindicated in:

- patients who have demonstrated prior hypersensitivity to hyoscine butylbromide or any other component of the product
- myasthenia gravis
- mechanical stenosis in the gastrointestinal tract
- paralytical or obstructive ileus
- megacolon

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.
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

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®.

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®.

Fertility, pregnancy and lactation

There is limited data from the use of hyoscine butylbromide in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (please refer to "toxicology").

There is insufficient information on the excretion of BUSCOGAST® and its metabolites in human milk.

As a precautionary measure, it is preferable to avoid the use of BUSCOGAST® during pregnancy and lactation.

No studies on the effects on human fertility have been conducted.

In rats and rabbits hyoscine butylbromide oral administration did not affect fertility and breeding capacity.

Effects on ability to drive and use machines

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

Side effects

Many of the listed undesirable effects can be assigned to the anticholinergic properties of BUSCOGAST®, but are generally mild and self-limited.

Immune system disorders
Not known: Anyphylactic shock, anaphylactic reactions, dyspnoea, and hypersensitivity.

Cardiac disorders
Uncommon: Tachycardia

Gastrointestinal disorders
Uncommon: dry mouth

Skin and subcutaneous tissue disorders
Uncommon : skin reactions, urticaria, pruritus, abnormal sweating
Not Known: Rash, erythema

Renal and urinary disorders
Rare: Urinary retention

Overdose

Symptoms
In the case of overdose, anticholinergic effects may be observed

Management
If required, parasympathomimetic drugs should be administered. Ophthalmological advice should be sought in cases of glaucoma urgently. 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.

Pharmacological properties

BUSCOGAST® exerts a spasmolytic action on the smooth muscle of the gastro-intestinal, biliary and genito-urinary tracts. As a quaternary ammonium derivative, 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.

Pharmacokinetics

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%.

Due to a first pass metabolism the absolute bioavailability following oral administration is only around 0.3 - 0.8%.

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*.
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:
The main metabolic pathway is the hydrolytic cleavage of the ester bond. The mean total clearance after intravenous administration is approximately 1.2 L/min, approximately half of it being renal.

Elimination:
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 105 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.

NONCLINICAL SAFETY DATA:

i) Repeat- Dose Toxicity:
Acutely, hyoscine butylbromide has a low index of toxicity: oral LD_{50} 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 LD_{50} 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 = "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.
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.
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:
Hyoscine butylbromide revealed no mutagenic or clastogenic potential in the Ames test, in the in vitro gene mutation assay in mammalian V79 cells (HPRT test) and in an in vitro chromosome aberration test in human peripheral lymphocytes. In vivo, hyoscine butylbromide was negative in the rat bone marrow micronucleus assay.

iii) Carcinogenicity:
There are no in vivo carcinogenicity studies. Nevertheless, hyoscine butylbromide did not show a tumorigenic potential in two oral 26-week-studies in rats given up to 1000 mg/kg.

iv) Reproductive and Developmetal Toxicity:
Hyoscine butylbromide was neither embryotoxic nor teratogenic at oral doses of up to 200 mg/kg in the diet (rat) or 200 mg/kg by gavage or 50 mg/kg s.c. (rabbit). Fertility was not impaired at doses of up to 200 mg/kg p.o.
Like other cationic drugs, hyoscine butylbromide interacts with the choline transport system of human placental epithelial cells *in vitro*. Transfer of hyoscine butylbromide to the foetal compartment has not been proved.

v) Other Toxicity Studies:
In special studies concerning local tolerability, a repeated i.m. injection of 15 mg/kg BUSCOGAST® over 28 days was studied in dogs and monkeys. Small focal necroses at the site of injection were seen only in dogs. BUSCOGAST® was well tolerated in arteries and veins of the rabbit´s ear. In vitro, 2 % BUSCOGAST® injectable solution showed no haemolytic action when mixed with 0.1 ml human blood.

Storage condition
BUSCOGAST® Tablets:
Store at a temperature not exceeding 30°C protected from light and moisture.
Keep out of reach of children.

Presentation
BUSCOGAST® Tablets:

- Strip of 10 tablets
- 20 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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