For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

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

Hyoscine Butylbromide Ampoules

BUSCOGAST® Ampoules

Composition

Each one ml ampoule contain
Hyoscine Butylbromide IP …. 20 mg
Excipients ……q.s.

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

Adults and adolescents over 12 years:
1 - 2 ampoules of BUSCOGAST® (20 - 40 mg) may be administered by slow intravenous, intramuscular or subcutaneous injection several times daily.
The maximum daily dose of 100 mg should not be exceeded.

Infants and children:
In severe cases: 0.3 - 0.6 mg/kg bodyweight, to be administered by slow intravenous, intramuscular or subcutaneous injection several times daily.

The maximum daily dose of 1.5 mg/kg bodyweight should not be exceeded.

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

Contraindications

BUSCOGAST® ampoules are contraindicated in:
- patients who have demonstrated prior hypersensitivity to hyoscine butylbromide or any other component of the product
- untreated narrow angle glaucoma
- hypertrophy of the prostate with urinary retention
- mechanical stenosis in the gastrointestinal tract
- paralytical or obstructive ileus
- megacolon
- tachycardia
- myasthenia gravis

By intramuscular injection, BUSCOGAST® ampoules are contraindicated:
- in patients being treated with anticoagulant drugs since intramuscular haematoma may occur. In these patients, the subcutaneous or intravenous routes may be used.

Special warnings and precautions for Use

In severe cases, 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.

Elevation of intraocular pressure may be produced by the administration of anticholinergic agents such as BUSCOGAST® in patients with undiagnosed and therefore untreated narrow angle glaucoma. Therefore, patients should seek urgent ophthalmological advice in case they should develop a painful, red eye with loss of vision after the injection of BUSCOGAST®.

After parenteral administration of BUSCOGAST®, cases of anaphylaxis including episodes of shock have been observed. As with all drugs causing such reactions, patients receiving BUSCOGAST® by injection should be kept under observation.

Caution is needed in patients with cardiac conditions submitted to parenteral treatment with BUSCOGAST®. Monitoring of these patients is advised.

Interactions with other medicinal products and other forms of interaction

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®.

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.
However, patients should be advised that they may experience undesirable effects such as accommodation disorder or dizziness during treatment with BUSCOGAST® ampoules. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience accommodation disorder or dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

Adverse Reaction

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

Immune system disorders
Not Known: Anaphylactic shock, anaphylactic reactions, dyspnoea, and hypersensitivity.

Eye disorders
Common: Accommodation disorders
Not Known: Mydriasis, increased intraocular pressure.

Cardiac disorders
Common: Tachycardia

Vascular disorders
Not Known: Blood pressure decreased, flushing.
Common: dizziness

Gastrointestinal disorders
Common: Dry mouth

Skin and subcutaneous tissue disorders
Not Known: Skin reactions, urticaria, pruritus, abnormal sweating, rash, erythema.

Renal and urinary disorders
Not Known: Urinary retention

Overdose

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

Therapy
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:
After intravenous administration hyoscine butylbromide is rapidly distributed ($t_{1/2\alpha}$ = 4 min, $t_{1/2\beta}$ = 29 min) into the tissues. The volume of distribution (Vss) is 128 L (corresponding to approx. 1.7 L/kg).

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

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

Clinical studies with radiolabeled hyoscine butylbromide show that after intravenous injection 42 to 61% of the radioactive dose is excreted renally and 28.3 to 37% faecally. The portion of unchanged active ingredient excreted in the urine is approximately 50%. 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 gastro-intestinal function was depressed and deaths occurred. The NOAEL of the 39-week oral (capsule) dog study was 30 mg/kg. The majority of clinical findings was 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 Developmental Toxicity:
Hyoscine butylbromide was neither embryotoxic nor teratogenic at oral doses of up to 200 mg/kg in the diet (rat) and 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 [99]. 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
Store at a temperature not exceeding 30ºC, protected from light and moisture.

Presentation
BUSCOGAST® Injection
- Ampoule of 1 ml
- 10 Ampoules of 1 ml in a tray
- 5 trays of 10 ampoules each in a carton

Manufactured in India by: Sovereign Pharma Pvt. Ltd., Survey no 46/1-4, Kadaiya Village, Nani Daman – 396210, India

Marketed by : Sanofi Healthcare India Private Limited
Regd Office: Sanofi House, CTS No. 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai – 400072

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