PRESCRIBING INFORMATION AND CONSUMER INFORMATION

Buscopan®

Hyoscine Butylbromide, Tablets

Boehringer Ingelheim Standard, 10 mg

Hyoscine Butylbromide Injection, 20 mg/mL

Antispasmodic

Boehringer Ingelheim (Canada) Ltd.
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets, 10 mg	acacia, carnauba wax, castor oil, lactose, magnesium stearate, maize starch, sucrose, polyethylene glycol, shellac, talc, tartaric acid, titanium dioxide, and white wax
Parenteral	Ampoules, 20 mg/mL	sodium chloride and water for injection

INDICATIONS AND CLINICAL USE

BUSCOPAN (hyoscine butylbromide) tablets are indicated for:

- The relief of smooth muscle spasm of the gastrointestinal and genitourinary systems.

BUSCOPAN ampoules are indicated for:

- The relief of acute genitourinary or gastrointestinal spasm (e.g., renal or biliary colic), or to produce smooth muscle relaxation prior to radiological procedures such as pyelography or other diagnostic procedures where spasm may be a problem (e.g., gastro-duodenal endoscopy).

Geriatrics:
No data is available

Pediatrics:
No data is available

CONTRAINDICATIONS

- Hypersensitivity to hyoscine butylbromide, or atropinics (see WARNINGS AND PRECAUTIONS) or to any of the product excipients (See Dosage Forms, Composition and Packaging).

- BUSCOPAN (hyoscine butylbromide) tablets are contraindicated in patients with myasthenia gravis, megacolon, glaucoma or obstructive prostatic hypertrophy.

- Parenteral administration is contraindicated in patients with myasthenia gravis, untreated narrow angle glaucoma, prostatic hypertrophy with urinary retention, stenotic lesions of the gastrointestinal tract, tachycardia, angina, cardiac failure and megacolon.

- BUSCOPAN ampoules should not be given by intramuscular injection to patients being treated with anticoagulant drugs since intramuscular haematoma may occur. In these patients, the subcutaneous or intravenous routes may be used.

WARNINGS AND PRECAUTIONS

General

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

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.

Therapy should be discontinued if the patient reports any unusual visual disturbances or pressure pain within the eye.

Patients intolerant of one belladonna alkaloid or derivative may also be intolerant of other belladonna alkaloids or derivatives such as hyoscine butylbromide.

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

BUSCOPAN (hyoscine butylbromide) tablets and ampoules should be used with caution in patients with prostatic enlargement. BUSCOPAN may precipitate or aggravate urinary retention in patients with the following conditions: nonobstructive prostatic hypertrophy, urinary retention

(or the predisposition to) or obstructive uropathy such as a bladder neck obstruction due to prostatic hypertrophy (see CONTRAINDICATIONS). In addition, exercise caution in patients inclined to tachyarrhythmia.

One sugar-coated tablet of 10 mg contains 41.2 mg sucrose, resulting in 411.8 mg sucrose per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Cardiovascular

As large doses of anticholinergics/systemic antispasmodics may cause an increase in heart rate, due care is necessary in patients with cardiac disease, especially cardiac arrhythmias, congestive heart failure, coronary artery disease and mitral stenosis. The increase in heart rate may also be undesirable in patients with unstable cardiovascular status in an acute hemorrhage situation.

Gastrointestinal

Exercise caution in patients with reflux esophagitis or gastrointestinal tract obstructive disease (i.,e., achalasia and pyloroduodenal stenosis) due to the ability of anticholinergics/systemic antispasmodics to decrease smooth muscle motility and tone resulting in gastric retention.

Anticholinergics may aggravate hiatal hernia associated with reflux esophagitis, myasthenia gravis or pyloric obstruction.

In patients with ulcerative colitis, large anticholinergic doses may suppress intestinal motility, possibly causing paralytic ileus or resulting in obstruction; also, use may precipitate or aggravate toxic megacolon.

Ophthalmologic

The parenteral administration of hyoscine butylbromide, particularly of higher doses, has been reported to cause transient disturbances of accommodation which recede spontaneously. Therefore, patients should be cautioned about potential visual problems and the need to exercise care while driving or operating machinery after receiving BUSCOPAN ampoules.

The mydriatic effect of anticholinergics/systemic antispasmodics may result in increased intraocular pressure. BUSCOPAN should be used with caution in patients with angle-closure glaucoma or with this predisposition, as anticholinergics/systemic antispasmodics may precipitate an acute angle-closure glaucoma attack (see CONTRAINDICATIONS).

Patients should seek urgent ophthamological advice in case they should develop a painful eye with loss of vision after injection of BUSCOPAN.

Special Populations

Fertiliy, 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.

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

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

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

Pediatrics:
BUSCOPAN is not currently recommended for use in children.

Geriatrics:
Geriatric patients are especially susceptible to the anticholinergic side effects of constipation, dryness of mouth and urinary retention (especially in males). If these side effects continue or are severe, discontinuation of medication should be considered.

Due care is necessary when anticholinergics are administered to geriatric patients due to the danger of precipitating undiagnosed glaucoma.

Administration of anticholinergics/systemic antispasmodics to elderly patients with intestinal atony or in debilitated patients may result in obstruction.

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 BUSCOPAN® 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 REACTIONS

Adverse Drug Reaction Overview

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

Accumulated clinical and postmarketing experience indicates that the following adverse

reactions can be expected with the use of BUSCOPAN Ampoules and Tablets: Xerostomia (dry mouth), dyshidrosis, visual accomodation disorders, mydriasis, increased intraocular pressure, tachycardia, dyspnea, and urinary retention.

There have been rare reports of dizziness, blood pressure decreased and flushing.

Skin reactions (e.g. urticaria, rash, erythema, pruritus) and other hypersensitivity, angioedema and fixed drug eruptions have been reported rarely.
There have been very rare reports of anaphylactic reactions and anaphylactic shock including fatal outcome.

Adverse events reported during therapy with BUSCOPAN include increased pulse rate, diarrhea, nausea, retinal pigmentation, and glaucoma.

DRUG INTERACTIONS

Overview

As hyoscine butylbromide can reduce the motility and secretory activity of the gastrointestinal system, the systemic absorption and pharmacologic effects of other oral medications may be delayed.

Drug-Drug Interactions

Table 1 - Established or Potential Drug-Drug Interactions

Hyoscine Butylbromide	Effect	Clinical comment
Tri-and tetracyclic antidepressants Antipsychotics Atropine-like compounds	Can potentiate the anticholinergic effect.	
Antihistamines	Can potentiate the anticholinergic effect.	
Quinidine	Can potentiate the anticholinergic effect.	
Disopyramide	Can potentiate the anticholinergic effect.	
Amantadine	Can potentiate the anticholinergic effect.	
MAO inhibitors	May result in intensified anticholinergic side effects. Also, may block detoxification of anticholinergics thus potentiating their action.	

Hyoscine Butylbromide	Effect	Clinical comment
Anticholinergics	May intensify anticholinergic effects. May increase the severity of potassium chloride induced gastrointestinal lesions.	
Dopamine antagonists such as metoclopramide.	May result in diminution of the effects of both drugs on the gastrointestinal tract.	
Beta-adrenergic agents	May enhanced tachycardic effects.	
Antacids or adsorbent antidiarrheals	May reduce the absorption of anticholinergics, resulting in decreased therapeutic effectiveness.	Anticholinergics such as hyoscine butylbromide should be given at least one hour before these medications.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Individual response to BUSCOPAN (hyoscine butylbromide) may vary and doses should be adjusted accordingly.

Recommended Dose and Dosage Adjustment

Tablets:
One to two 10 mg tablets per day up to a maximum of 6 tablets per day. In prolonged illness which requires repeated dosing, 1 tablet 3 to 5 times a day is recommended.

Ampoules:
One half (10 mg/0.5mL) to one ampoule (20 mg/1mL) administered parenterally by intramuscular, subcutaneous, or intravenous routes, at an injection rate of 1 mL/min. No dilution of the ampoule is necessary prior to administration. The maximum dose should not exceed 100 mg/day (5 ampoules).

Missed Dose
In case a dose has been missed, take the next dose as scheduled. Do not double the dose.

Administration
Tablets should be swallowed whole with a glass of water.

The rapid action of injected BUSCOPAN is advantageous in acutely ill patients and in those situations where prompt spasmolytic activity facilitates diagnostic procedures such as radiological examinations. BUSCOPAN ampoules may also be used intramuscularly 10-15 minutes before radiological examinations of the stomach to slow peristaltic movements.

Dilution and Stability of Parenteral BUSCOPAN:

Although dilution prior to administration is not required, BUSCOPAN solution is compatible with the following solutions, should dilution be desirable:

Ringers Solution
Ringers Lactate
NaCl 0.9%
Laevulose 5%
Glucose 10%

Solutions must be mixed under sterile conditions and are stable for 8 hours.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms
Single oral doses of up to 590 mg and quantities of active drug up to 1090 mg within 5 hours have produced dry mouth, tachycardia, slight drowsiness and transient visual disorders. Other symptoms include urinary retention, reddening of the skin, and inhibition of gastrointestinal motility.

Other symptoms which occurred in animals and which may be encountered in humans include: shock, Cheyne-Stokes respiration, respiratory paralysis, clonic spasms, paresis of the striated muscle, coma, paralytic ileus and cystoparalysis.

Treatment
In the case of an oral overdose, perform gastric lavage with activated charcoal followed by magnesium sulfate (15%). BUSCOPAN overdose symptoms respond to parasympathomimetics.

For patients with glaucoma, administer pilocarpine locally. If necessary, parasypathomimetics should be administered, e.g. neostigmine 0.5-2.5 mg i.m. or i.v.. Cardiovascular complications should be treated according to usual therapeutic principles. In case of respiratiory paralysis: intubation, artificial respiration.

Catheterisation may be required for urinary retention.

Other overdosage symptoms should be treated with standard supportive therapy.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BUSCOPAN (hyoscine butylbromide) is an antispasmodic agent which relaxes the smooth muscle of the gastrointestinal, biliary and urinary tracts. It is believed to act predominantly at the parasympathetic ganglia in the walls of the viscera of these organs. Structurally, BUSCOPAN exists as a quaternary ammonium compound and as a single positively charged cation throughout the entire pH range.

Pharmacokinetics

Ampoules

Absorption and distribution

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). 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

The main metabolic pathway is the hydrolytic cleavage of the ester bond. The half-life of the terminal elimination phase ($t_{1/2\gamma}$) is approximately 5 hours. The total clearance is 1.2 L/min. 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.

Tablets

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, suppositoires 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.

STORAGE AND STABILITY

BUSCOPAN tablets and ampoules should be protected from light and heat. BUSCOPAN ampoules should be protected from freezing. Products should be stored at room temperature and are stable up to the expiration date indicated on the label.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

Tablets: Round, white, sugar-coated tablets each containing 10 mg of hyoscine butylbromide.

Ampoules: Containing 20 mg of hyoscine butylbromide in 1 mL aqueous solution.

Composition

Tablets: hyoscine-N-butylbromide. Non-medicinal ingredients include acacia, carnauba wax, castor oil, lactose, magnesium stearate, maize starch, sucrose, polyethylene glycol, shellac, talc, tartaric acid, titanium dioxide, and white wax.

Ampoules: hyoscine-N-butylbromide. Non-medicinal ingredients include sodium chloride and water for injection.

Packaging

Tablets: Bottles of 100 and 500 tablets.

Ampoules: Packages of 10 ampoules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: hyoscine butylbromide

Chemical name: (1S,3S,5R,6R,7S)-8-Butyl-6,7-epoxy-3-[(S)-tropoyloxy] tropanium bromide

Molecular formula and molecular mass: $C_{21}H_{30}BrNO_4$, 440.4

Physicochemical properties: A white or almost white, odourless or almost odourless, powder, soluble 1 to 1 in water, 1 in 50 of alcohol, and 1 in 5 of chloroform. 10% solution in water has a pH of 5.5 to 6.5.

PART III: CONSUMER INFORMATION

Buscopan®
Hyoscine Butylbromide

This leaflet is part III of a three-part "Product Monograph" published when BUSCOPAN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BUSCOPAN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
BUSCOPAN tablets are used for the relief of smooth muscle spasm (cramps) of the gastrointestinal and genitourinary system.

BUSCOPAN ampoules are used for relief of acute genitourinary or gastrointestinal spasm, or to produce smooth muscle relaxation prior to radiological procedures where spasm may be a problem.

What it does:
Stomach cramps are caused by sudden, irregular tightening up of muscles in the wall of the intestine. BUSCOPAN works by relaxing the tight muscles, so relieving the cramps.

When it should not be used:
Do not use Buscopan if:

- You are hypersensitive (allergic) to hyoscine butylbromide or atropinics or to any of the nonmedicinal ingredients (See What the important nonmedicinal ingredients are).

Tablets:

- You have myasthenia gravis (a muscle wasting disease), megacolon (enlarged colon), untreated narrow angle glaucoma or obstructive prostatic hypertrophy (enlarged and blocked prostate).

Ampoules:

- You have myasthenia gravis, untreated narrow angle glaucoma, difficulty in urination due to inflammation of the prostate, stenotic lesions (narrowing of a duct/canal) of the gastrointestinal tract, tachycardia (fast heartbeat), angina, heart failure and megacolon (enlarged colon).

What the medicinal ingredient is:
Hyoscine butylbromide

What the important nonmedicinal ingredients are:
Tablets: acacia, carnauba wax, castor oil, lactose, magnesium stearate, maize starch, sucrose, polyethylene glycol, shellac, talc, tartaric acid, titanium dioxide, and white wax.

Ampoules: sodium chloride and water for injection

What dosage forms it comes in:
Tablets, 10 mg
Ampoules, 20 mg/mL

WARNINGS AND PRECAUTIONS

BEFORE you use BUSCOPAN talk to your doctor or pharmacist if:

- you are pregnant, likely to become pregnant or if you are breast feeding as it is recommended that you do not use BUSCOPAN in these conditions
- you are a man who suffers from prostate problems
- you have narrow angle glaucoma, megacolon or myasthenia gravis
- you have a very fast heart rate or other heart problems
- you have reflux esophagitis or ulcerative colitis
- you are hypersensitive or "allergic" to hyoscine-N-butylbromide or any of the other ingredients
- you have previously been treated by a doctor for a severe sweating disorder
- you are taking antidepressants, major tranquilizers, antihistamines, antivirals, dopamine antagonists (e.g. metoclopramide) or medicines to treat heart problems
- you have sudden or severe abdominal pain along with symptoms such as fever, nausea, vomiting, blood in the stool, or low blood pressure (e.g., lightheadedness) , contact your doctor immediately
- you have a rare hereditary condition of fructose (a sugar) intolerance you should not take this medication as it contains lactose.

If in doubt, ask your doctor or pharmacist.

If you experience dizziness or blurred vision, avoid driving or operating machinery.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with BUSCOPAN include: tricyclic antidepressants, antihistamines, quinidine, disopyramide, amantadine, MAO inhibitors, anticholinergics, dopamine antagonists such as metoclopramide, beta-adrenergic agents, antacids or adsorbent antidiarrheals.

PROPER USE OF THIS MEDICATION

Usual adult dose:
Tablets: One to two 10 mg tablets per day up to a maximum of 6 tablets per day. In prolonged illness, the doctor may recommend repeated dosing of one tablet 3 to 5 times a day. Swallow tablets whole with a glass of water.

Ampoules: One half (10 mg/0.5 mL) to one ampoule (20 mg/mL) administered parenterally by intramuscular, subcutaneous, or

intravenous routes, at an injection rate of 1 mL/min. No dilutions of the ampoule is necessary prior to administration. The maximum dose should not exceed 100 mg/day (5 ampoules).

Overdose:

In case of drug overdose, contact a health care practitioner (or doctor), hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

When using the product, the patient should not take more doses than directed. Particularly in the case of overdose, the side effects listed below may be observed.

Your doctor will advise you that certain antacids or adsorbent antidiarrheals should be taken at least one hour before Buscopan.

Missed Dose:
In case a dose has been missed, take the next dose as scheduled. Do not double the dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

After taking BUSCOPAN tablets:
All medicines sometimes cause side-effects. BUSCOPAN may occasionally cause a dry mouth, blurred vision, mydriasis (pupil dilation), increased eye pressure, diarrhea, nausea, reduced ability to sweat, an increase in heart rate and the inability to pass urine.

Other possible rare side-effects include, dizziness, flushing, allergic reactions (particularly skin rash and itching), skin reactions (e.g., hives, rash, skin redness, itching), angioedema (swelling of the lips), decreased blood pressure, and difficulty in breathing (usually in patients who suffer with asthma or allergy).

There have been very rare reports of anaphylactic reactions and anaphylactic shock including death.

If you experience any of these effects and they persist or become troublesome, consult your doctor.

Should you suffer from a painful red eye with loss of vision, seek urgent medical advice.

If you experience any other effects not mentioned above, consult your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking BUSCOPAN, contact your doctor or pharmacist.

HOW TO STORE IT

BUSCOPAN tablets and ampoules should be protected from light and heat.

BUSCOPAN ampoules should be protected from freezing.

Products should be stored at room temperature and are stable up to the expiration date indicated on the label.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the Prescribing Information, prepared for health professionals can be found at:
http://www.boehringer-ingelheim.ca
or by contacting the sponsor, Boehringer Ingelheim (Canada) Ltd., at:
1-800-263-5103 ext. 84633

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