

## DATA SHEET

### 1 BUSCOPAN AND BUSCOPAN FORTE

BUSCOPAN® 10 mg tablet and 20 mg/ml injection

BUSCOPAN® FORTE 20 mg film coated tablet

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hyoscine-N-butylbromide 10 mg tablet, 20 mg film coated tablet and 20 mg/ml injection

Excipient with known effect: Lactose\*

\*Only applicable for the product BUSCOPAN® FORTE 20 mg film coated tablet.

For the full list of excipients, see Section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet 10 mg: white, unmarked, biconvex, sugar-coated.

Tablet 20 mg: white, round, biconvex, film coated tablets embossed with the letter 'B' on one side and the number '20' on the other side.

Injection 20 mg/ml: clear, colourless solution in glass ampoules.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Muscle spasm of the gastrointestinal tract.

#### 4.2 DOSE AND METHOD OF ADMINISTRATION

##### Oral:

Adults and children over 6 years: 2 BUSCOPAN 10 mg tablets (20 mg) four times a day

or

1 BUSCOPAN FORTE 20 mg tablet four times a day.

The tablets should be swallowed whole with adequate fluid.

**Parenteral:**

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

Infants and young children: In severe cases, 0.3 - 0.6 mg/kg bodyweight, to be administered by slow intravenous, intramuscular or subcutaneous injection several times a day. The maximum daily dose of 1.2 mg/kg should not be exceeded.

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

**4.3 CONTRAINDICATIONS**

BUSCOPAN and BUSCOPAN FORTE are contraindicated in myasthenia gravis, mechanical stenosis in the gastrointestinal tract, paralytical or obstructive ileus, megacolon and in patients who have demonstrated prior hypersensitivity to hyoscine butylbromide or any other component of the products.

In addition, BUSCOPAN should not be administered parenterally in the following disorders: untreated narrow angle glaucoma; tachycardia and hypertrophy of the prostate with urinary retention.

By intramuscular injection BUSCOPAN is contraindicated in patients being treated with anticoagulant drugs since intramuscular haematoma may occur. In these patients, the subcutaneous or intravenous routes may be used.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to Section 4.4) the use of the product is contraindicated.

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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 where appropriate diagnostic measures are needed to investigate the etiology of the symptoms.

Hyoscine may cause drowsiness: patients so affected should not drive or operate machinery. Patients should abstain from alcohol. However, as a quaternary ammonium compound with low lipid

solubility, BUSCOPAN cannot cross the blood/brain barrier easily and only rarely causes the central nervous system side effects associated with atropine and hyoscine.

After parenteral administration of BUSCOPAN, patients with visual accommodation disturbances should not drive or operate machinery until vision has normalised.

Because of the potential risk of anticholinergic complications, BUSCOPAN and BUSCOPAN FORTE tablets should be administered with caution in patients susceptible to narrow angle glaucoma, intestinal or urinary outlet obstruction, and those inclined to tachyarrhythmia.

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

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.

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

BUSCOPAN injection can cause tachycardia, hypotension and anaphylaxis, therefore use with caution in patients with cardiac conditions such as cardiac failure, coronary heart disease, cardiac arrhythmia or hypertension, and in cardiac surgery. Monitoring of these patients is advised. Emergency equipment and personnel trained in its use must be readily available.

One sugar-coated tablet of 10 mg contains 41.2 mg sucrose, resulting in 329.6 mg sucrose per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

One film-coated tablet of 20 mg contains 138.5 mg lactose, resulting in 554 mg lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### **Paediatric use**

Refer to Section 4.2 for information on paediatric dosing.

## **4.5 INTERACTION WITH OTHER MEDICINES 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 BUSCOPAN and BUSCOPAN FORTE.

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 BUSCOPAN and BUSCOPAN FORTE.

#### **4.6 FERTILITY, PREGNANCY AND LACTATION**

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

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (please refer to Section 5.3).

There is insufficient information on the excretion of hyoscine-N-butylbromide and its metabolites in human milk.

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

No studies on the effects on human fertility have been conducted (please refer to Section 5.3).

#### **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. However, patients should be advised that they may experience undesirable effects such as accommodation disorder or dizziness during treatment with BUSCOPAN injection. 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.

#### **4.8 UNDESIRABLE EFFECTS**

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

Adverse events have been ranked under headings of frequency using the following convention: Very common  $\geq 1/10$

Common  $\geq 1/100, < 1/10$

Uncommon  $\geq 1/1,000, < 1/100$

Rare  $\geq 1/10,000, < 1/1,000$

Very rare  $< 1/10,000$

Not known cannot be estimated from the available data

### Immune system disorders

Not known: anaphylactic shock including fatal outcome, anaphylactoidic reactions, dyspnoea, skin reactions (e.g. urticaria, rash, erythema, pruritus) and other hypersensitivity.

### Eye disorders (BUSCOPAN injection)

Common: accommodation disorders

Not known\*: mydriasis, increased intraocular pressure.

### Cardiac disorders

Common: tachycardia

### Vascular disorders (BUSCOPAN injection)

Not known: blood pressure decreased, dizziness, flushing.

### Gastrointestinal disorders

Common: dry mouth

### Skin and subcutaneous tissue disorders

Not known: dyshidrosis, abnormal sweating.

### Renal and urinary disorders

Not known: impaired micturition, urinary retention

### Nervous system disorders

Very rarely in the national post marketing surveillance data base, there have been isolated reports following parenteral administration of coma, hallucinations, dystonia, confusion, agitation and dizziness from which the patient recovered after drug withdrawal and appropriate treatment. In very rare cases, dyspnoea has been reported.

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## 4.9 OVERDOSE

### Symptoms

Serious signs of poisoning following acute overdosage have not been observed in man. In case of overdose, anticholinergic symptoms such as urinary retention, dry mouth, reddening of skin, tachycardia, inhibition of gastrointestinal motility, and transient visual disturbances may occur.

### Therapy

In the case of oral poisoning, gastric lavage with activated charcoal should be followed by magnesium sulphate (15%). Symptoms of BUSCOPAN and BUSCOPAN FORTE overdosage respond to parasympathomimetics. For patients with glaucoma, urgent ophthalmological advice should be sought and pilocarpine should be given locally. If necessary, parasympathomimetics should be administered, e.g. neostigmine 0.5-2.5 mg i.m. or i.v. Cardiovascular complications as a result of using this medicine 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.

In the case of overdose, immediately contact the Poisons Information Centre, in New Zealand, called 0800 764 766.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Quaternary ammonium derivate, ATC code: A03BB01 Hyoscine-N-butylbromide exerts a spasmolytic action on the smooth muscle of the

gastrointestinal, biliary and urinary tracts. As a quaternary ammonium derivative, hyoscine-N-butylbromide does not enter the central nervous system. Therefore, anticholinergic side effects at the central nervous system do not occur. Peripheral anticholinergic effects result from a ganglion-blocking action within the visceral wall as well as from anti-muscarinic activity.

### 5.2 PHARMACOKINETIC PROPERTIES

#### Absorption

As a quaternary ammonium compound, hyoscine-N-butylbromide is highly polar and hence only partially absorbed following oral (8%) 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<sub>0-tz</sub>-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**

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 ( $V_{ss}$ ) 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**

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<sup>5</sup> 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

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.

## **5.3 PRECLINICAL SAFETY DATA**

Acutely, hyoscine butylbromide has a low index of toxicity: oral LD<sub>50</sub> 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<sub>50</sub> 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 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.

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.

Hyoscine butylbromide-suppositories were locally well tolerated.

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

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.

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.



## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

**10 mg Tablets:** dibasic calcium phosphate, maize starch, starch soluble, aerosil 200, tartaric acid, stearic acid, polyvidone saccharose, talc, acacia, titanium dioxide, polyethylene glycol 6000, carnauba wax, beeswax white.

**20 mg Tablets:** povidone, lactose, cellulose - microcrystalline, magnesium stearate and Opadry II white 85G18490.

**Injection:** sodium chloride, water for injection

### **6.2 INCOMPATIBILITIES**

None known.

### **6.3 SHELF LIFE**

**10 mg Tablets:** Shelf life is 36 months (3 years) from manufacture.

**20 mg Tablets:** Shelf life is 36 months (3 years) from manufacture.

**Injection Ampoules:** Shelf life is 60 months (5 years) from manufacture.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

**10 mg Tablets:** Store below 25°C.

**20 mg Tablets:** Store below 30°C.

**Injection Ampoules:** Store below 30°C.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

**10 mg Tablets:** 100s. PVC/PVDC/Al Blister pack or Plastic Bottle

**20 mg Tablets:** 10s. PVC/Al Blister pack

**Injection Ampoules:** 20 mg/mL, 1 mL, 5s. Ampoules

Not all pack sizes or pack types may be marketed.

### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING**

**Injections:** For single use only. Any unused solution should be discarded

## **7 MEDICINE SCHEDULE**

**10 mg Tablets:** Prescription Medicine.

**20 mg Tablets:** Restricted Medicine.

**Injection Ampoules:** Prescription Medicine.

## **8 SPONSOR**

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## **9 DATE OF FIRST APPROVAL**

BUSCOPAN: 31 December 1969

BUSCOPAN FORTE: 26 February 2016

## **10 DATE OF REVISION OF THE TEXT**

20 January 2021

BUSCOPAN® is a registered trademark.

## **SUMMARY TABLE OF CHANGES**

<b>Section changed</b>	<b>Summary of new information</b>
4.8	Update with safety information