NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Gastro-soothe 20 mg/ mL injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gastro-soothe ampoules contain 20 mg/ 1 mL hyoscine butylbromide per ampoule.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMCEUTICAL FORM

Gastro-soothe is a clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Muscle spasm of the gastrointestinal tract

4.2 DOSE AND METHOD OF ADMINISTRATION

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 100 mg should not be exceeded.
Infants and young children:	In severe cases, 0.3 - 0.6 mg/kg body weight, 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.

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

4.3 CONTRAINDICATIONS

Gastro-soothe injections 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, Gastro-soothe injection should not be administered in the following disorders: untreated narrow angle glaucoma; tachycardia and hypertrophy of the prostate with urinary retention.

By intramuscular injection, Gastro-soothe 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.

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, Gastro-soothe 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 Gastro-soothe, patients with visual accommodation disturbances should not drive or operate machinery until vision has normalised.

Because of the potential risk of anticholinergic complications, Gastro-soothe 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 Gastrosoothe 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 Gastro-soothe.

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

Caution is needed in patients with cardiac conditions submitted to parenteral treatment with Gastro-soothe. Monitoring of these patients is advised.

Gastro-soothe 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.

Paediatric use

Refer to Section 4.2 for information on paediatric dosing.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 Gastro-soothe.

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 Gastro-soothe.

4.6 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 Section 5.3).

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

As a precautionary measure, it is preferable to avoid the use of Gastrosoothe 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 Gastro-soothe 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 ADVERSE EFFECTS (UNDESIREABLE EFFECTS)

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

Adverse events have been ranked under headings of frequency using the following convention:

Very common ≥ 1/10

Common ≥ 1/100, < 1/10

Uncommon ≥ 1/1,000, <1/100

Rare ≥ 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

Common: accommodation disorders

Not known: mydriasis, increased intraocular pressure

Cardiac disorders

Common: tachycardia

Vascular disorders

Not known: blood pressure decreased, dizziness, flushing

Gastrointestinal disorders

Common: dry mouth

Skin and subcutaneous 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 suspected adverse effects

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 Gastro-soothe 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 (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Quanternary ammonium derivate, ATC code: A03BB01. Hyoscine butylbromide exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary and 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 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 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 AUC0-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

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 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 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 radiolabelled 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 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 = “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 hyoscine butylbromide over 28 days was studied in dogs and monkeys. Small focal necroses at the site of injection were seen only in dogs. Hyoscine butylbromide was well tolerated in arteries and veins of the rabbit´s ear. *In vitro*, 2 % hyoscine butylbromide 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

Sodium chloride

Hydrochloric acid

Water for injection

6.2 INCOMPATIBILITIES

None known

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Gastro-soothe injection is supplied in a glass ampoule. Five vials are packed in a carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For single use only. Any unused solution should be discarded.

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

AFT Pharmaceuticals Ltd.

Auckland

Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

5 October 2023