NEW ZEALAND DATA SHEET

ADIRAMEDICA HYOSCINE BUTYLBROMIDE

1 PRODUCT NAME

- ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg film-coated tablets
- ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hyoscine-N-butylbromide 10 mg film-coated tablet, and 20 mg film coated tablet.
Excipient with known effect: Lactose Monohydrate For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Oral, Film-Coated Tablet

Presentation

ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE

BUTYLBROMIDE 20 mg tablets are both: White to off-white coloured, round, biconvex, film coated tablet plain on both sides.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Muscle spasm of the gastrointestinal tract.

4.2 DOSE AND METHOD OF ADMINISTRATION

AdiraMedica Hyoscine Butylbromide 10 mg:
Adults and children over 6 years: 2 tablets four times a day

ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg tablets should be swallowed whole with a glass of water.

ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg should not be taken on a continuous daily basis or for extended periods without investigating the cause of abdominal pain.

AdiraMedica Hyoscine Butylbromide 20 mg:
Adults and children over 6 years: 1 tablet four times a day.

ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg tablets and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg tablet should be swallowed whole with a glass of water.

ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg tablets should not be taken on a continuous daily basis or for extended periods without investigating the cause of abdominal pain.

4.3 CONTRAINDICATIONS

ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg 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 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

ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg tablets should be used with caution in conditions characterised by tachycardia such as thyrotoxicosis, cardiac insufficiency or failure and in cardiac surgery where it may further accelerate the heart rate. Due to the risk of anticholinergic complications, caution should be used in patients susceptible to intestinal or urinary outlet obstructions. Because of the possibility that anticholinergics may reduce sweating, ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg should be administered with caution to patients with pyrexia.

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

Elevation of intraocular pressure may be produced by the administration of anticholinergics such as ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20mg 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 taking of ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg.

One film-coated tablet of 10 mg contains 63.8 mg lactose monohydrate, resulting in 510.4 mg lactose monohydrate per maximum recommended daily dose and One film-coated tablet of 20 mg contains 127.6 mg lactose, resulting in 510.4 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.

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 ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg.

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 ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg.

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 ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg 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

In rare cases ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg may cause drowsiness, if affected, patients should not drive or operate machinery.

4.8 UNDESIRABLE EFFECTS

Many of the listed undesirable effects can be assigned to the anticholinergic properties of ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg.
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.

Cardiac disorders

Common: tachycardia

Gastrointestinal disorders

Common: dry mouth

Skin and subcutaneous tissue disorders
Not known: dyshidrosis

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 ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE 20 mg 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Quanternary 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 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 ($t1/2\alpha$ = 4 min, $t1/2\beta$ = 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

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 the hyoscine butylbromide.

The half-life of the terminal elimination phase ($t1/2\gamma$) 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 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 in the diet.

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

ADIRAMEDICA HYOSCINE BUTYLBROMIDE 10 mg and ADIRAMEDICA HYOSCINE BUTYLBROMIDE
20 mg film-coated tablets:
Excipients: Lactose monohydrate, microcrystalline cellulose, povidone K30, magnesium stearate, and Film Coating Opadry II 85G18490 white (Medsafe reference number: 03-2-75).

6.2 INCOMPATIBILIES

None known.

6.3 SHELF LIFE

36 months from the date of manufacture, when stored at or below 25°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mg film-coated tablets: 10s and 20s Aluminium/Opaque PVC film blister pack

20 mg film-coated tablets: 10s Aluminium/Opaque PVC film blister pack

7 MEDICINE SCHEDULE

Pharmacist Only Medicine

8 SPONSOR

AdiraMedica Pty Ltd
C/O Core Business Services Ltd
2 Khyber Pass Road, Grafton,
Auckland-1023 New Zealand
aucontact@adiramedica.com

9 DATE OF FIRST APPROVAL:

9.2.2023

10 DATE OF REVISION OF THE TEXT

1 July 2024

SUMMARY TABLE OF CHANGES:

Section changed	Description	Date
6.3	Change of shelf life from 24 months to 36 months	1.7.2024