SUMMARY PRODUCT INFORMATION

1. Name of the medicinal product

BUTOPAN 20mg/ml solution for injection.

2. Qualitative and quantitative composition

Active ingredient:

Hyoscine butyl bromide	20 mg/ml

Excipients:

Sodium Chloride	6.2 mg/ml

For excipients, see 6.1.

3. Pharmaceutical form

Solution for injection

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BUTOPAN is used in acute gastro-intestinal, biliary and Genito-urinary system spasms, including bile and renal colic, and in spasms during diagnosis or therapeutic procedures such as gastro-duodenal endoscopy and radiology.

4.2 Posology 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 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 frequency and duration of application:

It can be administered several times a day in adults without exceeding the highest daily dose of 100 mg. In infants and children, 1.5 mg per kg of body weight, which is the highest daily dose, should not be exceeded.

Method of administration:

BUTOPAN can be administered intramuscularly, subcutaneously, and slowly intravenously.

Special populations:
Renal / hepatic impairment:
It should be used carefully under medical supervision in patients with impaired liver and kidney function.

Pediatric population:

The maximum daily dose in infants should not exceed 1.5 mg per kilogram of body weight.

Geriatric population:

No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

4.3 Contraindications.

- Hypersensitivity to the active substance or to any of the excipients,
- Untreated narrow-angle glaucoma,
- Hypertrophy of the prostate with urinary retention,
- Mechanical stenosis in the gastrointestinal tract ,
- Tachycardia,
- Megacolon,
- Myasthenia gravis.

BUTOPAN should not be given by intramuscular injection to patients being treated with anticoagulant drugs since intramuscular haematoma may occur. In these patients, subcutaneous or intravenous route can be used.

4.3 Special warnings and precautions for use

Elevation of intraocular pressure may be produced by the administration of anticholinergic agents such as BUTOPAN 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 BUTOPAN.

After parenteral administration of BUTOPAN, cases of anaphylaxis including episodes of shock have been observed. As with all drugs causing such reactions, patients receiving BUTOPAN by injection should be kept under observation. Because of the possibility that anticholinergics may reduce sweating, BUTOPAN should be administered with caution to patients with pyrexia.

It should be used with caution in patients with narrow angle glaucoma, intestinal or urinary canal obstruction and also at risk of developing tachyarrhythmia such as thyrotoxicosis, heart failure and cardiac surgery. In such cases, Butopan should only be used under medical supervision and, if necessary, the dose should be reduced, or doses should be administered less frequently.

Excipients:

This medicinal product contains 6.2 mg / ml sodium. The product contains less than 1 mmol (23 mg) sodium per ml; so, it is basically "sodium free."

4.4 Interaction with other medicinal products and other forms of interaction

- The anticholinergic effect of drugs such as tricyclic antidepressants, antihistamines, quinidine, amantadine, phenothiazines, butyrophenones, disopyramide and other anticholinergics (e.g. tiotropium, ipratropium) intensified by BUTOPAN.
- 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 BUTOPAN.

4.5 Pregnancy and lactation:

General recommendations

Pregnancy category: C

Women with childbearing potential / Birth control (Contraception) There is insufficient data on the use of BUTOPAN in women with childbearing potential.

Pregnancy

As a result of long experience, no evidence of harmful effects during pregnancy has been observed. In terms of the use of BUTOPAN during pregnancy, general warnings about drug use should be taken into consideration, especially in the first trimester of pregnancy.

Lactation

There are no studies available about the safety of BUTOPAN use in breastfeeding women. The safety of BUTOPAN has not been established during lactation. Breastfeeding should stop during treatment with BUTOPAN.

Fertility

Studies on animals are insufficient in terms of effects on pregnancy / and-or / embryonal / fetal development and / or / birth / and-or / postpartum development (see section 5.3). The potential risk for humans is unknown.

4.6 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Some patients may experience impaired adaptation to seeing near and far (accommodation disorder). Since accommodation disorder may occur during BUTOPAN treatment, patients should not drive or use machines until vision returns to normal.

4.7 Undesirable effects

The frequency degrees of the adverse events listed below are defined as follows according to the system organ class:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to <1/100)
Rare	(≥ 1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data)

Many of the listed undesirable effects can be assigned to the anticholinergic properties of BUTOPAN. Anticholinergic side effects of BUTOPAN are usually mild and transient.

Immune system disorders
Not known anaphylactic shock including cases with fatal outcome, anaphylactic reactions, hypersensitivity reactions

Eye disorders
Common: accommodation disorders

Cardiac disorders
Common: tachycardia

Vascular disorders
Common: dizziness
Not known: blood pressure decreased, flushing.

Gastrointestinal disorders
Common: dry mouth
Skin and subcutaneous tissue disorders
Not known: Dyshidrosis (A Skin Disease Caused By Abnormal Sweating Especially On The Hands And Feet)
Rare: skin redness
Very rare: allergic reactions in the style of exanthema.
Renal and urinary disorders:
Not known: urinary retention

Hyoscine butylbromide, the active ingredient of BUTOPAN, due to its chemical structure as a quaternary ammonium derivate, is not expected to enter the central nervous system. Hyoscine butylbromide does not readily pass the blood-brain barrier. However, it cannot totally be ruled out that under certain circumstances psychiatric disorders (e.g. confusion) may also occur after administration of BUTOPAN.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Turkey Pharmacovigilance Central at: (www.titck.gov.tr; e- post: tufam@titck.gov.tr; Tel: 0800 314 00 08; fax: O312 218 35 99)

4.8 Overdose and treatment

Symptoms
In the case of overdosage, anticholinergic symptoms such as urinary retention, dry mouth, reddening of the skin, tachycardia, inhibition of gastrointestinal motility and transient visual disturbances may occur, and Cheynes-Stokes respiration has been reported.
Treatment
Symptoms of hyoscine butylbromide overdosage respond to parasympathomimetics. For patients with glaucoma, an ophthalmologist should promptly be consulted, pilocarpine should be given locally. Cardiovascular complications should be treated according to usual therapeutic principles. In case of respiratory paralysis, intubation and artificial respiration. Catheterisation may be required for urinary retention. In addition, appropriate supportive measures should be used as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Belladonna and Derivatives, Drugs used in GIS functional diseases
ATC code: A03BB01 Hyoscine butylbromide.
Hyoscine-N-butylbromide has a spasmolytic effect on smooth muscles in the gastro-intestinal, bile and urinary tract ducts. Hyoscine butylbromide, due to its chemical structure as a quaternary ammonium derivate, is not expected to enter the central nervous system. Therefore, it does not cause anticholinergic side effects in the central nervous system. Peripheral anticholinergic effects depend on the blocker effect and antimuscarinic effect on visceral ganglia.

5.2 Pharmacokinetic properties

Absorption:
It is easily absorbed after intramuscular and subcutaneous administration.
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).
Hyoscine-N-butylbromide cannot cross the blood-brain barrier and its binding to plasma proteins is low. The highest concentrations of hyoscine-N-butylbromide in rats are found in the gastro-intestinal tract, liver and kidneys.
Metabolism:
The half-life of the terminal elimination phase ($t_{1/2}\gamma$) is approximately 5 hours.
Elimination:
Following intravenous administration, its total clearance is 1.2 L/min and approximately half of the clearance occurs through the kidneys. The metabolites excreted via the renal route bind poorly to the muscarinic receptors

Linearity / Nonlinear situation:
No particular.

Special population
None founded.

5.3 Preclinical safety data

In animal experiments no teratogenic, carcinogenic effects or any negative effects on fertility were observed.

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.

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.

The hyoscine-N-butylbromide suppository formulation is locally well tolerated.

In special studies concerning local tolerability, a repeated i.m. injection of 15 mg/kg BUTOPAN over 28 days was studied in dogs and monkeys. Small focal necroses at the site of injection were seen only in dogs. BUTOPAN was well tolerated in arteries and veins of the rabbit´s ear. In vitro, 2 % BUTOPAN 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
Water for injections

6.2 Incompatibilities

There are no studies on incompatibility. This medicinal product should not be mixed with other medicinal products.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

It should be stored at room temperature under 30 ° C. Should be protected from light.

6.5 Nature and contents of container

1 ml of solution in 6 amber colored ampoules in a plastic separator in the box.
1 ml of solution in 100 amber colored ampoules in the separator In the box (hospital packaging).

6.6 Special precautions for disposal and other handling

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulation".

7. Marketing authorisation holder

STOT PHARMA İlaç San. ve Dış Tic. Ltd. Şti.
Emek Mah. 29. Sk. No:4 A Antakya-Hatay

8. Marketing authorisation number(s)

2019/383

9. Date of first authorisation date /renewal of the authorisation

First authorisation date: 08.08.2019
renewal of the authorization date:

10. Date of revision of the text