SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml ampoule contains

Metamizole sodium monohydrate: 2500 mg

Hyoscine butylbromide: 20 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A clear, slightly yellowish solution free from physical impurities.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute, severe colicky pains of the biliary, urinary and gastro-intestinal tract.

4.2 Posology and method of administration

Posology

Not to be given to children under 12 months of age.

1 ampoule of 5 ml by slow intravenous injection; if possible the patient should be in a lying position. The injection should be given over at least 5 minutes.

If necessary the same dose may be repeated 2 to 3 times daily at intervals of several hours.

Should intravenous injection be impossible, the preparation may be given by intramuscular injection.

Method of administration

Not to be administered subcutaneously.

The administration of BUSCOPAN COMPOSITUM 20 mg/2,5 g injection should be under medical supervision and be monitored.

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection should only be injected intravenously or intramusculary. Inadvertent intra-arterial use may cause necrosis in the distal vascular area.

Precaution

With intramuscular injection the following technique should be carefully observed:

Site of injection: Only in the upper, outer quadrant of the buttock.

Direction: Sagittally and directed towards the iliac crest.

Depth: A sufficiently long needle to ensure the injection reaches the muscle.

4.3 Contraindications

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection is contra-indicated in:

- patients who have demonstrated prior hypersensitivity to pyrazolone or pyrazolidines (e.g., metamizole, isopropylaminophenazone, propyphenazone, phenazone or phenylbutazone), or to hyoscine butylbromide, or to any other component of the product included in section 6.1. This includes patients who developed agranulocytosis, for example, following use of one of these substances.
- patients with granulocytopenia.
- patients with known analgesic-induced asthma syndrome or known analgesic intolerance of the urticaria-angioedema type, i.e. patients who develop bronchospasm or other anaphylactoid reactions in response to salicylates, paracetamol or other non-narcotic analgesics such as diclofenac, ibuprofen, indomethacin or naproxen.

- the potential of cross-sensitivity with aspirin and other non-steroidal anti-inflammatory agents exists. BUSCOPAN COMPOSITUM 20 mg/2,5 g injection should not be given to patients in whom aspirin or other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.
- impaired bone marrow function (e.g., after treatment with cytostatic agents) or diseases of the haemopoietic system.
- genetic glucose-6-phosphate-dehydrogenase deficiency (risk of haemolysis).
- patients with acute intermittent hepatic porphyria (risk of triggering a porphyria attack).
- Glaucoma
- hypertrophy of the prostate with urinary retention
- mechanical stenosis in the gastrointestinal tract
- paralytic or obstructive ileus
- pronounced tachycardia
- megacolon
- myasthenia gravis
- three months of pregnancy (see section 4.6)
- asthma
- patients with existing arterial hypotension and unstable circulatory state
- in patients being treated with anticoagulant drugs as intramuscular injection, since intramuscular haematoma may occur. In these patients, the intravenous route may be used.
- subcutaneous injection (see section 4.2)
- intraarterial injection (see section 4.2 and 4.4)
- in case of rare hereditary conditions that may be incompatible with an excipient of the product (see section 4.4)
- the third trimester of pregnancy (see section 4.6)
- children under 12 months of age. This medicinal product it is not recommended in children nor adolescents (under 18 years old), as safety and efficacy is not demonstrated in these patients.
- patients with existing arterial hypotension and unstable circulatory state

- subcutaneous injection (see section 4.2)
- intraarterial injection (see section 4.2 and 4.4)
- in case of rare hereditary conditions that may be incompatible with an excipient of the product (see section 4.4)

4.4 Special warnings and precautions for use

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

Haematologic reactions (such as agranulocytosis or pancytopenia)

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection contains metamizole, a derivative of pyrazolone, which presents a risk of agranulocytosis, which is rare but life-threatening (see section 4.8).

In the event of clinical signs of haematologic reactions (such as agranulocytosis, aplastic anaemia, thrombocytopenia or pancytopenia), treatment with BUSCOPAN COMPOSITUM 20 mg/2,5 g injection must be discontinued immediately and the blood count (including differential blood count) must be monitored until it has returned to normal (see section 4.8). Discontinuation of treatment must not be delayed until the results of the lab tests are available. All patients should be advised to immediately consult a physician if during treatment with BUSCOPAN COMPOSITUM 20 mg/2,5 g injection signs and symptoms occur which are suggestive of blood dyscrasia (e.g. general malaise, infection, persistent fever, bruising, bleeding or pallor).

Patients who show an immunological reaction such as agranulocytosis to BUSCOPAN COMPOSITUM 20 mg/2,5 g injection are also at high risk of responding similarly to other pyrazolones and pyrazolidines.

Anaphylactic/anaphylactoid reactions

When choosing the administration route, it should be borne in mind that parenteral administration of BUSCOPAN COMPOSITUM 20 mg/2,5 g injection presents a higher risk of anaphylactic or anaphylactoid reactions. The risk of potentially severe anaphylactoid reactions to BUSCOPAN COMPOSITUM 20 mg/2,5 g injection is markedly higher for patients with:

- analgesic-induced asthma syndrome or analgesic intolerance of the urticaria-angioedema type (see section 4.3)
- bronchial asthma, in particular in the presence of rhinosinusitis and nasal polyps
- chronic urticaria
- intolerance to colouring agents (e.g. tartrazine) and/or preservatives (e.g. benzoates)
- alcohol intolerance. These patients react to even minute amounts of alcoholic drinks with symptoms such as sneezing, watering eyes and severe facial flushing. Alcohol intolerance of this kind may be an indication of as yet undiagnosed analgesic-induced asthma syndrome (see section 4.3).

Metamizole may cause the rare, but life-threatening risk of shock (see section 4.8).

The likelihood of anaphylactic shock is greater in susceptible patients. Particular caution is therefore required when using BUSCOPAN COMPOSITUM 20 mg/2,5 g injection in patients with asthma or atopy.

Prior to administration of BUSCOPAN COMPOSITUM 20 mg/2,5 g injection, the patient must be questioned appropriately. In patients at high risk of anaphylactoid reactions, BUSCOPAN COMPOSITUM 20 mg/2,5 g injection should only be used after consideration of the potential risks in relation to the expected benefit. If BUSCOPAN COMPOSITUM 20 mg/2,5 g injection is administered in such cases, the patient must be monitored very closely and emergency standby guaranteed.

Patients who show an anaphylactic or other immunological reaction to BUSCOPAN COMPOSITUM 20 mg/2,5 g injection are also at high risk of responding similarly to other pyrazolones, pyrazolidines and other non-narcotic analgesics.

Isolated hypotensive reactions

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection can cause hypotensive reactions (see section 4.8). These reactions may be dose-dependent and are more likely with parenteral rather than enteral administration.

The risk of such reactions is also increased in the case of:

- too rapid intravenous injection (see section 4.2)
- patient with e.g. previous arterial hypotension, volume depletion or dehydration, unstable circulation or incipient circulatory failure (such as patients with heart attack or polytrauma)
- patients with a high fever.

As a result, careful diagnosis and close monitoring is essential for these patients. Preventive measures (e.g., stabilization of the circulation) may be necessary in order to reduce the risk of hypotensive reactions. BUSCOPAN COMPOSITUM 20 mg/2,5 g injection requires close monitoring of the haemodynamic parameters when used in patients for whom a fall in blood pressure must be avoided at all costs, such as in the case of severe coronary artery disease or relevant stenosis of the cerebral blood vessels.

Severe skin reaction

Life-threatening skin reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were reported under treatment of metamizole. If signs or symptoms of SJS or TEN develop (such as skin rash often progressive with blisters or mucosal injury), treatment with BUSCOPAN COMPOSITUM 20 mg/2,5 g injection must be discontinued immediately and never be reintroduced.

Patients should be advised of the signs and symptoms of these severe skin reactions, so that in case they develop, medical advice is sought, and these reactions can be monitored closely, particularly in the first weeks of treatment.

Gastrointestinal bleeding

Gastrointestinal bleeding has been reported in patients treated with metamizole. Many patients had concomitantly received other treatment (e.g., NSAIDs) associated with gastrointestinal bleeding, or used an overdose of metamizole.

Intraocular pressure

Elevation of intraocular pressure may be produced by the administration of anticholinergic agents such as hyoscine butylbromide in patients with undiagnosed and therefore untreated narrow angle glaucoma. Therefore, patients should be advised to seek urgent ophthalmological advice in case they should develop a painful, red eye with loss of vision after the injection of BUSCOPAN COMPOSITUM 20 mg/2,5 g injection

Risk associated with incorrect route of administration

When administered parenterally, attention should be paid to proper injection technique. Inadvertent intraarterial use may cause necrosis potentially leading to amputation in the distal vascular area.

Risk in specific populations

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection should only be used after consideration of the benefit-risk ratio and appropriate precautions must be taken for elderly or patients with impaired renal or hepatic function (see section 4.2).

Caution is required when administering parenterally BUSCOPAN COMPOSITUM 20 mg/2,5 g injection to patients with a history of cardiovascular disease risk factors. Special monitoring is required in patient suffering from tachycardia.

Patients receiving BUSCOPAN COMPOSITUM 20 mg/2,5 g injection should be monitored for hypotension and tachycardia, especially those with a history of cardiac disease or hypertension.

Interference with laboratory tests

In diabetic patients the pyrazolone derivative can affect the enzymatic blood sugar assay by the glucose-oxidase method (GOD).

4.5 Interaction with other medicines and other forms of interaction

Methotrexate

Concomitant administration of BUSCOPAN COMPOSITUM 20 mg/2,5 g injection with methotrexate may increase blood toxicity of methotrexate particularly in elderly patients. Therefore, this combination should be avoided.

Chlorpromazine

Concomitant use of metamizole and chlorpromazine can cause severe hypothermia.

Acetylsalicylic acid

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection can reduce the antiplatelet effect of acetylsalicylic acid if administered concomitantly. BUSCOPAN COMPOSITUM 20 mg/2,5 g injection should therefore be used with caution in patients who are taking low-dose acetylsalicylic acid for cardioprotection.

Bupropion

Blood levels of bupropion can be reduced by metamizole. Caution is therefore required if metamizole and bupropion are used concomitantly.

Cyclosporin

If BUSCOPAN COMPOSITUM 20 mg/2,5 g injection is taken concomitantly with cyclosporin, cyclosporin blood levels may be reduced and should therefore be monitored.

Medicines with anticholinergic effects

The anticholinergic effect of medicines 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 COMPOSITUM 20 mg/2,5 g injection.

Dopamine antagonists

Concomitant treatment with dopamine antagonists such as metoclopramide may result in diminution of the effects of both medicines on the gastrointestinal tract.

Beta-adrenergic agents

The tachycardic effects of beta-adrenergic agents may be enhanced by BUSCOPAN COMPOSITUM 20 mg/2,5 g injection.

Alcohol

The effect of alcohol and BUSCOPAN COMPOSITUM 20 mg/2,5 g injection can be potentiated when taken concurrently.

Additional interactions of pyrazolones

Pyrazolones may also cause interactions with oral anticoagulants, captopril, lithium and triamterene. The efficacy of antihypertensives and diuretics may be affected by pyrazolones. It is not known to what extent metamizole causes these interactions

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection may also alter the effect of other active substances such as digoxin.

4.6 Fertility, pregnancy and lactation

Pregnancy and Breastfeeding

Hyoscine butylbromide:

Safety during pregnancy and lactation has not been established.

Metamizole sodium monohydrate:

Metamizole sodium monohydrate passes the placental barrier and is excreted in breast milk and should therefore only be used during pregnancy and lactation after careful consideration of the indications.

The breakdown products of metamizole are excreted into breast milk in considerable amounts and a risk to the breastfed infant cannot be excluded. Especially the repeated use of metamizole during breastfeeding must therefore be avoided. In case of a single administration of metamizole mothers are advised to collect and discard the breastmilk for 48 hours from its administration.

Fertility

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

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. Patients should be advised that they may experience undesirable effects such as accommodation disturbances and dizziness during parenteral treatment with hyoscine butylbromide. If taken in the recommended dose, metamizole is not expected to affect concentration or reactions. As a precaution, at least if higher doses are taken, the possibility of impaired reactions should be borne in mind, and patients should be advised not to drive, operate machinery or conduct hazardous activities. This applies in particular in combination with alcohol.

4.8 Undesirable effects

Hyoscine butylbromide:

Side-effects of antimuscarinic agents include dryness of the mouth with difficulty of swallowing and talking, thirst, dilation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitation and arrhythmias, and urinary urgency, difficulty and retention, as well as reduction in the tone and mobility of the gastro-intestinal tract leading to constipation. Occasionally vomiting, giddiness and staggering may occur. Retrosternal pain may occur due to increased gastric reflux. Tricyclic anti-depressants, quinidine and amantadine can potentiate the anticholinergic effect of hyoscine butylbromide. Hyoscine butylbromide does not readily cross the blood-brain barrier, so central effects are rare.

Hyoscine butylbromide may cause drowsiness; patients so affected should not drive or operate machinery. Patients should abstain from alcohol.

Metamizole:

Severe anaphylactic reaction may occur. Other signs of allergy which can affect the skin, mucosa, the granulopoetic system (leucopoenia, agranulocytosis) or the circulation (shock) may also occur. Very serious or even life-threatening bullous skin reactions, generally with mucous membrane involvement (Stevens-Johnson Syndrome, Lyell Syndrome), have been reported with medications containing metamizole. Should such a reaction occur, BUSCOPAN COMPOSITUM 20 mg / 2,5 g injection should be discontinued at once and a physician immediately consulted.

Patients suffering from existing disturbances of blood cell formation (e.g. under cytostatic treatment) should only use BUSCOPAN COMPOSITUM under medical supervision.
Particular care is required in patients with systolic blood pressure values below 100 mm Hg in patients with unstable circulation (myocardial infarction, multiple injuries, initial shock).
Should symptoms of agranulocytosis, such as high fever, chills, sore throat, difficulty in swallowing, inflammation in the mouth, nose and throat as well as in the genital or anal region, occur during treatment, it should be discontinued immediately and the doctor concerned informed at once.
Shock may occur immediately or up to 1 hour after administration. If anaphylactic shock should occur intensive treatment for shock should be commenced without delay. In parenteral administration the injection should be stopped immediately at the first sign of shock; the cannula should be left in the vein or access to the vein should be sought; the patient should be laid on his side and the respiratory passages kept free of obstruction.
Counter-measures: administration of adrenaline, monitoring of pulse rate and blood pressure (attention : dysrhythmia!); anti-histamine agents; glucocorticoids (e.g. prednisolone up to 1 g i.v.); administration of plasma volume expanders; artificial respiration.]

Frequency of undesirable effects is classified according to MedDRA system:

Very common ≥ 1/10

Common ≥ 1/100, < 1/10

Uncommon ≥ 1/1000, < 1/100

Rare ≥ 1/10 000, < 1/1000

Very rare < 1/10 000, including isolated reports

Not known (cannot be estimated from available data)

Blood and lymphatic system disorders

Uncommon: leukopenia, agranulocytosis (including fatal cases)

Very rare: thrombocytopenia

Not known: sepsis (including fatal cases), aplastic anaemia, pancytopenia (including fatal cases). These are presumably immunological reactions. They can occur even if BUSCOPAN COMPOSITUM 20 mg/2,5 g injection was administered on previous occasions without complications.

There are signs to suggest that the risk of agranulocytosis may be elevated if BUSCOPAN COMPOSITUM 20 mg/2,5 g injection is used for more than one week. Agranulocytosis is manifest in the form of pyrexia, chills, oropharyngeal pain, dysphagia, stomatitis, rhinitis, pharyngitis, genital tract inflammation, and anal inflammation. These signs may be minimal in patients on antibiotics. There is little or no lymphadenopathy or splenomegaly. The red blood cell sedimentation rate is markedly increased; the granulocytes are considerably reduced or absent altogether.

Haemoglobin, red blood cell count and platelet counts may be abnormal.

It is strongly recommended that BUSCOPAN COMPOSITUM 20 mg/2,5 g injection be discontinued immediately and a doctor be consulted, and not only when the lab test results are available, if there is an unexpected deterioration in the patient's general condition, the fever does not subside or reappears, or if there are painful changes in the mucosa of the mouth, nose and throat.

Immune system disorders, skin and subcutaneous tissue disorders

Uncommon: drug eruption, skin reactions.

Rare: anaphylactic reaction, anaphylactoid reaction (especially after parenteral administration), asthma in patients with analgesic asthma syndrome, rash maculo-papular

Very rare: toxic epidermal necrolysis, Stevens-Johnson syndrome

Not known: anaphylactic shock including fatal outcome, dyspnoea; hypersensitivity; sweating abnormal

Milder reactions (e.g. skin and mucosal reactions, such as pruritus, burning sensation, erythema, swelling, as well as dyspnoea and gastro-intestinal disorders) may lead on to more severe reactions (e.g. generalised urticaria, severe angioedema including the laryngeal region, severe

bronchospasm, arrhythmia, decreased blood pressure with sometimes initially increased blood pressure). BUSCOPAN COMPOSITUM 20 mg/2,5 g injection must therefore be discontinued immediately if skin reactions occur. In case of severe skin reactions, a physician should immediately be consulted.

Anaphylactic reactions can develop during or immediately after injection, but can also develop some hours later. Reactions generally occur, however, within the first hour of administration. Appropriate tr*eatment should be started as soon as signs/symptoms of anaphylaxis appear.*

Eye disorders

Uncommon: accommodation disorders

Not known: mydriasis; increased intraocular pressure

Cardiac disorders

Not known: tachycardia, Kounis Syndrome

Vascular disorders

Common: hypotension, dizziness

Uncommon: shock, injection site pain; flushing

Very rare: phlebitis

Not known: injection site reaction

Hypotensive reactions occurring during or after use may be medicine-induced, and do not go hand in hand with other signs of anaphylactoid and/or anaphylactic reactions. Such a reaction can lead to a severe fall in blood pressure. Rapid intravenous injection increases the risk of hypotensive reactions.

In case of hyperpyrexia, or after a too rapid injection, there may be a dose-dependent and critical drop in blood pressure with no other signs of medicine intolerance.

Gastrointestinal disorders

Common: dry mouth

Not known: gastrointestinal haemorrhage

Renal and urinary disorders:

Very rare: acute renal failure, anuria; interstitial nephritis, oliguria, proteinuria, renal impairment

Not known: urinary retention, chromaturia

Excretion of rubazonic acid, a harmless metabolite of metamizole, may cause a red colouration of the urine, which disappears on discontinuation of treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BUSCOPAN COMPOSITUM is important. It allows continued monitoring of the benefit/risk balance of BUSCOPAN COMPOSITUM. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8, or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

Symptoms:

Hyoscine butylbromide:

In the case of overdose, anticholinergic effects may be observed.

Toxic doses cause tachycardia, rapid respiration, hyperpyrexia and central nervous system stimulation marked by restlessness, confusion and, excitement, paranoid and psychotic reactions, hallucinations and delirium, and occasionally seizures or convulsions. A rash may appear on the face and upper trunk.

After very high doses, elimination of the metabolic rubazonic acid can cause reddish discolouration of the urine.

Metamizole:

Acute overdosage or chronic use in excessive dosage lead to dizziness, nausea, emesis, gastro-intestinal pains, state of agitation, convulsion, clonic cramp, shock, coma, respiratory paralysis,

liver and renal damage, sodium and fluid retention with pulmonary oedema in cardiac patients, risk of allergy and anaphylactic reactions, leucopoenia, thrombocytopenia, agranulocytosis and aplastic anaemia.]

Therapy:

Hyoscine butylbromide:

Treat spastic conditions first - diazepam 10 - 20 mg i.v./i.m. Symptoms of BUSCOPAN COMPOSITUM overdosage respond to parasympathomimetics. In patients with glaucoma, pilocarpine should be used locally.

Further treatment: Symptomatic and supportive.

If required, parasympathomimetic medicines should be administered.

Opthalmological advice should be sought urgently in cases of glaucoma.

Cardiovascular complications should be treated according to usual therapeutic principles. In case of respiratory paralysis: intubation or artificial respiration should be considered. Catheterisation may be required for urinary retention. In addition, appropriate supportive measures should be used as required.

Metamizole:

There is no known specific antidote for metamizole. If metamizole was administered only recently, absorption-reducing measures (e.g. activated charcoal) can be administered in an effort to limit absorption by the body. The major metabolite (4-N-methyl-amino-antipyrine) can be eliminated by means of haemodialysis, haemofiltration, haemoperfusion or plasma filtration. Treatment of intoxication and prevention of severe complications may require general and specific intensive medical monitoring and treatment.

Acute measures in the event of severe medicine intolerance (shock):

At the first signs (e.g. skin reactions such as urticaria and flushing, restlessness, headache, profuse sweating, nausea) stop the administration immediately.

Leave the cannula in the vein or set up a venous access. In addition to the usual emergency measures such as tilting the head and upper body back, maintaining the airways, administering oxygen, it may be necessary to administer sympathomimetics, volume expanders or glucocorticoids.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 11.2 Gastro-intestinal antispasmodics and cholinolytics (anticholinergic)

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection has a selective antispasmodic action on the smooth muscle of the gastro-intestinal, biliary and genito-urinary tracts. It also has analgesic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

Tartaric acid

6.2 Incompatibilities

BUSCOPAN COMPOSITUM 20 mg/2,5 g injection should not be added to pH correcting intravenous solutions of high volume or parenteral nutrition (amino acids, lipids).

Because of the possibility of incompatibilities, BUSCOPAN COMPOSITUM 20 mg/2,5 g injection must not be mixed with other drugs in the same syringe (see section 4.2).

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. [Keep out of reach of children.]

6.5 Nature and contents of container

Ampoules of 5 ml in boxes of three ampoules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street,

1685, Midrand, SA

8. REGISTRATION NUMBER

E/11.2/504

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 March 1994

10. DATE OF REVISION OF THE TEXT

03 February 2021

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