SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

BIO DOMPERIDONE 10 (Film-coated tablet)

COMPOSITION

Each film-coated tablet contains 10 mg domperidone.

Excipients

Core tablet: crospovidone, hydrogen vegetable oil, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose (PH 102), povidone (K 30), sodium lauryl sulphate.

Coating: hypromellose, polyethylene glycol.

Contains sugar: Lactose monohydrate 58,0 mg per tablet.

CATEGORY AND CLASS

A.5.7.2 Anti-emetics and anti-vertigo preparations

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Domperidone is a dopamine antagonist. It produces an anti-emetic effect through its action on the dopamine-receptor in the chemo-emetic trigger zone. Domperidone does not cross the blood-brain barrier to any significant degree and therefore exerts a relatively minor effect on cerebral dopaminergic receptors. Domperidone has been shown to increase the duration of antral and duodenal contractions thus improving gastric emptying. Domperidone does not alter gastric

secretions and has no effect in intracranial pressure.

Pharmacokinetic properties

Domperidone is absorbed after oral administration in the fasting state with peak plasma concentrations at approximately 1 hour after administration. Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. Due to this extensive first-pass hepatic and intestinal metabolism, the absolute bioavailability of oral domperidone is low (approximately 15 %).

Domperidone is 90 – 95 % bound to plasma proteins. The plasma half-life after a single oral dose is approximately 7 – 9 hours and is prolonged in patients with severe renal impairment.

Urinary and faecal excretion amount to 31 % and 66 % of the oral dose, respectively. The proportion of domperidone excreted unchanged is small (approximately 1 % of urinary and 10 % of faecal excretion).

INDICATIONS

BIO DOMPERIDONE 10 is indicated for:

- Delayed gastric emptying of functional origin with gastro-oesophageal reflux and/or dyspepsia.
- Control of nausea and vomiting of central or local origin.
- As an anti-emetic in patients receiving cytostatic and radiation therapy.
- Facilitates radiological examination of the upper gastrointestinal tract.

CONTRAINDICATIONS

BIO DOMPERIDONE 10 is contraindicated:

- In patients with a known hypersensitivity to domperidone or any of the ingredients of BIO

DOMEPRIDONE 10.

- In patients with a prolactin secreting or producing pituitary tumour (prolactinoma).
- When stimulation of gastric motility is to be avoided or could be harmful (e.g. in the presence of gastrointestinal haemorrhage, obstruction or perforation).
- In patients with moderate or severe hepatic impairment.
- Bradycardia or heart-block.
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.
- Known congenital long QT interval or family history thereof.
- Concomitant administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects (see INTERACTIONS).
- Concomitant administration with QT-prolonging medicines (see INTERACTIONS).
- The safe use during pregnancy and lactation has not been established (see HUMAN REPRODUCTION).
- Severe renal impairment (CrCl < 30 ml/min).
- Hypokalaemia. Hypomagnesemia.

WARNINGS AND SPECIAL PRECAUTIONS

Cardiovascular effects

BIO DOMPERIDONE 10 has been associated with prolongation of the QT interval on the electrocardiogram. Cases of QT prolongation and Torsades de Pointes have been reported in patients taking BIO DOMPERIDONE 10.

BIO DOMPERIDONE 10 use is associated with an increased risk of serious ventricular dysrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking

daily doses greater than 30 mg, and patients concurrently taking QT-prolonging medicine or CYP3A4 inhibitors (see CONTRAINDICATIONS).

BIO DOMPERIDONE 10 should be used at the lowest effective dose in adults and children.

BIO DOMPERIDONE 10 is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with signification electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see Contraindications). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the pro-dysrhythmic risk (see CONTRAINDICATIONS).

Treatment with BIO DOMPERIDONE 10 should be stopped if signs or symptoms occur that may be associated with cardiac dysrhythmia, and the patients should consult their medical practitioner.

Patients should be advised to promptly report any cardiac symptoms.

Use in children

BIO DOMPERIDONE 10 should not be administered to children under 12 years of age, or children weighing less than 35 kg.

Renal impairment

BIO DOMPERIDONE 10 should be used with caution in patients with mild to moderate renal impairment or in those at risk of fluid retention. In patients with severely impaired renal function, (creatinine clearance < 30 ml/minute, serum creatinine approximately 530 µmol/ℓ), the elimination half-life of BIO DOMPERIDONE 10 was increased from 7, 4 to 20, 8 hours, and BIO DOMPERIDONE 10 should not be used (see CONTRAINDICATIONS). The dosing frequency should be reduced to once or twice daily; depending on the severity of renal impairment. Patients who are on long-term therapy

should be monitored on a regular basis.

Hepatic impairment

BIO DOMPERIDONE 10 is contraindicated in patients with moderate to severe hepatic impairment (see CONTRAINDICATIONS). Caution is advised in patients with hepatic impairment and in the elderly since BIO DOMPERIDONE 10 is mainly metabolised in the liver.

Elderly

The risk of cardiac dysrhythmia or sudden death was increased in patients over 65 years of age.

Patients treated with Monoamine oxidase inhibitors

BIO DOMPERIDONE 10 should not be given to patients being treated with monoamine oxidase inhibitors (e.g. selegiline used for the treatment of Parkinson's disease or tranylcypromine and moclobemide used for the treatment of depression), (see INTERACTIONS), as dopamine levels can be increased.

Effects on ability to drive and use machines

BIO DOMPERIDONE 10 can cause dizziness. Patients should not drive a vehicle and use machines until they know how their ability to react are impaired.

BIO DOMPERIDONE 10 contains lactose. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take BIO-DOMPERIDOME 10.

INTERACTIONS

The main metabolic pathway of BIO DOMPERIDONE 10 is through CYP3A4. *In vitro* data suggest that the concomitant use of a medicine that significantly inhibits this enzyme may result in increased plasma levels of BIO-DOMPERIDOME 10.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated:

QTc prolonging medicines

- anti-dysrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- anti-dysrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal medicines (e.g., pentamidine)
- certain antimalarial medicines (in particular halofantrine, lumefantrine)
- certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride), and anti-cholinergic medicines (e.g. hyoscine bromide)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone)
- grapefruit juice.

(see CONTRAINDICATIONS).

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:

- protease inhibitors

- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin, telithromycin).

(see CONTRAINDICATIONS).

The effect of BIO DOMPERIDONE 10 may be antagonised by anti-muscarinic agents and opioid analgesics.

Due to the gastro-kinetic effects of BIO DOMPERIDONE 10, the absorption of concomitant oral medication (particularly sustained release or enteric coated formulations) can be influenced.

BIO DOMPERIDONE 10 increases with serum prolactin levels, and therefore may interfere with other hypoprolactaemic medicines and with some diagnostic tests.

BIO DOMPERIDONE 10 should not be taken concomitantly with anti-acids, anti-secretory medicines (histamine H_2-receptor antagonists such as cimetidine; proton pump inhibitors; selective antimuscarinics or prostaglandin analogues), or sodium bicarbonate as they lower the oral bioavailability of BIO DOMPERIDONE 10.

Reduced gastric acidity impairs the absorption of BIO DOMPERIDONE 10.

BIO DOMPERIDONE 10 suppresses the peripheral effects (digestive disorders, nausea and vomiting) of dopaminergic agonists (e.g.carbegoline), by antagonism of dopamine receptors in the chemoreceptor trigger zone.

HUMAN REPRODUCTION

BIO DOMPERIDONE 10 should not be administered to pregnant or lactating women (see CONTRAINDICATIONS).

Administration to pregnant mothers shortly before giving birth, or during labour, may result in the new-born infant being born hypotonic, collapsed and hypoglycaemic.

DOSAGE AND DIRECTIONS FOR USE

Acute conditions (nausea and vomiting)

Adults and children over 12 years and weighing 35 kg or more: One tablet (10 mg) three to four times per day, 15 to 30 minutes before meals.

Do not exceed maximum dose of 30 mg /day.

Treatment duration should not exceed one week.

Tablets are not recommended for children weighing less than 35 kg.

Children < 12 years: The formulation is not suitable for this indication, in children.

SIDE EFFECTS

Immune system disorders

Frequency unknown: Anaphylactic reaction (including anaphylactic shock).

Psychiatric disorders

Less frequent: Loss of libido; anxiety.

Frequency unknown: Agitation; nervousness.

Nervous system disorders

Less frequent: Headache; dizziness; irritability; somnolence; thirst and ataxia.

Frequency unknown: Convulsion; extrapyramidal manifestations.

Where the blood brain barrier is not fully developed (mainly in young babies) or is impaired, the possible occurrence of neurological side effects cannot be excluded.

Eye disorders

Less frequent: Conjunctivitis.

Frequency unknown: Oculogyric crisis.

Endocrine disorders

Less frequent: Endocrinological effects, increased prolactin).

Reproductive system and breast disorders

Less frequent: Mastalgia (breast pain); galactorrhoea; breast tenderness; menstrual irregularities.

Frequency unknown: Gynaecomastia; amenorrhoea.

Skin and subcutaneous tissue disorders

Less frequent: Pruritus; rash.

Frequency unknown: Urticaria; angioedema.

General disorders and administration site conditions

Less frequent: Stomatitis; asthenia; lethargy.

Renal and urinary disorders

Less frequent: Change in urinary frequency; dysuria.

Frequency unknown: Urinary retention.

Gastrointestinal disorders

Frequent: Dry mouth.

Less frequent: Abdominal cramps; change in appetite; constipation; diarrhoea and heartburn.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Leg cramps.

Cardiac disorders

Less frequent: Palpitations.

Frequency unknown: Ventricular dysrhythmias; sudden cardiac death; QTc prolongation and Torsade de Pointes.

Vascular disorders

Frequency unknown: Hot flushes, hypertensive crisis in patients with pheochromocytoma may occur with administration of BIO DOMPERIDONE 10.

Investigations

Frequency unknown: Liver function test abnormal; blood prolactin increased.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The following are the clinical effects of an overdose: dysrhythmia (dizziness, fainting, and irregular heartbeat); drowsiness; disorientation; extrapyramidal reactions, especially in children and hypotension.

There is no specific antidote or specific medicine for domperidone overdose. In the event of overdosage gastric lavage as well as the administration of activated charcoal may be useful. Symptomatic and supportive measures are recommended. Anticholinergic medicines, anti-parkinson medicine or antihistamines with anticholinergic properties may be useful in controlling the extrapyramidal effects associated with domperidone toxicity.

IDENTIFICATION

White, round, film-coated, biconvex tablets.

PRESENTATION

BIO DOMPERIDONE tablets are available in transparent PVC-Aluminium blister packs of 10 or 100 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Keep the blister in the outer carton until required for use.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

42/5.7.2/0836

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