SOUTH AFRICAN PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

PREXOLAN 2,5 (film-coated tablet)

PREXOLAN 5 (film-coated tablet)

PREXOLAN 10 (film-coated tablet)

PREXOLAN IM (powder for solution for injection)

COMPOSITION

PREXOLAN 2,5 (film-coated tablet)

Each film-coated tablet contains olanzapine 2,5 mg.

Contains sugar: Lactose monohydrate 40 mg

PREXOLAN 5 (film-coated tablet)

Each film-coated tablet contains olanzapine 5 mg.

Contains sugar: Lactose monohydrate 80 mg

PREXOLAN 10 (film-coated tablet)

Each film-coated tablet contains olanzapine 10 mg.

Contains sugar: Lactose monohydrate 160 mg

Excipients:

Crospovidone, hydroxypropyl cellulose, lactose monohydrate, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide (C.I. 77891), xanthan gum.

PREXOLAN IM (powder for solution for injection)

Each vial contains olanzapine 10 mg.

Contains sugar: Maltose 72 mg

Excipients:

Citric acid monohydrate, maltose.

Diluent: Sterile water for injection.

CATEGORY AND CLASS

A 2.6.5 Tranquillisers - miscellaneous structures

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Olanzapine is an atypical antipsychotic medicine having affinity for $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamine D_4, D_3, D_1, D_2, cholinergic muscarinic receptors (m_1 - m_5), ALPHA-1 (α_1) adrenergic and histamine H_1 receptors.

Further studies also demonstrate that olanzapine selectively interacts with the mesolimbic system without significantly interacting with the extrapyramidal system.

Olanzapine's antagonism of muscarinic receptors (m_1 - m_5) may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this medicine. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this medicine.

Pharmacokinetic properties

Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food.

Olanzapine is metabolised in the liver by conjugative oxidative pathways. The major circulating metabolite is the 10-N-glucuronide which does not pass the blood-brain barrier. Other metabolites include the N-desmethyl and 2-hydroxymethyl metabolites neither of which has *in- vivo* pharmacological activity. The predominant pharmacologic activity is from the parent compound.

After oral administration the elimination half-life of olanzapine in healthy subjects varies with age and gender.

	< 65 years	≥ 65 years
Men	29 hours	49 hours
Women	39 hours	55 hours

The mean elimination half-life of olanzapine is about 1,5 times greater in the elderly (≥ 65 years) than in non-elderly subjects (< 65 years) (see WARNINGS AND SPECIAL PRECAUTIONS).

Plasma clearance of olanzapine is higher in smokers (see WARNINGS AND SPECIAL PRECAUTIONS).

The pharmacokinetic characteristics of olanzapine are similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by haemodialysis. The effect of renal impairment on metabolite elimination has not been studied.

The plasma protein binding of olanzapine is about 93 % over the concentration range of about 7 to about 1 000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Intramuscularly administered olanzapine results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. The peak concentration is about five fold higher than an equivalent oral dose. Area under the curve achieved after an intramuscular dose is equivalent to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics is linear over the clinical dosing range. Metabolic profiles after intramuscular administration are quantitatively similar and qualitatively identical to metabolic profiles after oral administration.

INDICATIONS

Oral PREXOLAN: PREXOLAN tablets are indicated for the management of the manifestations of schizophrenia.

It is recommended that responding patients be continued on PREXOLAN, at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment. Effectiveness for more than 6 weeks has not been established in controlled trials.

PREXOLAN is also indicated for the treatment of an acute episode of moderate to severe mania and for preventing recurrence of manic or depressive episodes of bipolar disorder.
Intramuscular PREXOLAN: PREXOLAN IM injection is indicated for the control of agitation and disturbed behaviour in patients with schizophrenia and related psychoses and in

patients with acute mania associated with Bipolar I disorder when oral therapy is not appropriate. Treatment with PREXOLAN IM should be discontinued and the use of PREXOLAN tablets should be initiated as soon as clinically appropriate.

CONTRAINDICATIONS

PREXOLAN is contraindicated in:

- Patients who are hypersensitive to PREXOLAN or to any components of PREXOLAN.
- Patients with known risk of narrow-angle glaucoma.
- Paediatric use: safety and effectiveness in patients under 18 years of age have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

- During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.
- Discontinuation reactions may occur, usually within a week of discontinuing PREXOLAN. These reactions may consist of a cholinergic syndrome (diaphoresis, diarrhoea, sialorrhoea, nausea and vomiting, anxiety, agitation, insomnia and tremor). PREXOLAN should therefore be gradually discontinued.
- **Intramuscular use:** Serious/severe bradycardia and syncope may occur. In clinical studies there were cases with serious symptomatic hypotension, apnoea, ventricular tachydysrhythmias, including fatalities. In most of the serious cases there was a temporal relationship with the use of benzodiazepines. Patients should remain recumbent if drowsy or dizzy after injection, until examination has indicated that they are not experiencing hypotension, postural hypotension, bradycardia and/or hypoventilation. In view of the possibility of bradycardia and/or hypotension with PREXOLAN IM, caution should be considered in patients with serious cardiovascular disease where the occurrence of syncope,

or hypotension and/or bradycardia might put the patient at increased medical risk.

- **Hyperprolactinaemia:** PREXOLAN elevates prolactin levels and a modest elevation persists during chronic administration.
- **Neuroleptic malignant syndrome (NMS):** NMS has occurred infrequently in association with PREXOLAN. NMS is a potentially fatal symptom complex. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, rhabdomyolysis and acute renal failure. PREXOLAN should be discontinued should any of the clinical manifestations of NMS or high fever without additional clinical manifestations of NMS be observed.
- **Seizures:** PREXOLAN should be used cautiously in patients who have a history of seizures or who are subject to factors which may lower seizure threshold. Seizures have been reported to occur infrequently in patients treated with PREXOLAN. In most of these cases, a history of seizures or risk factor for seizures was reported.
- **Tardive dyskinesia:** PREXOLAN is associated with a low incidence of treatment emergent dyskinesia. If signs or symptoms of tardive dyskinesia appear in a patient on PREXOLAN, a dose reduction or discontinuation of treatment should be considered. However, some patients may benefit from continued treatment with PREXOLAN despite the presence of the syndrome. The risk of tardive dyskinesia increases with long-term exposure and symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

- **Hepatic impairment:** Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve and in patients who are being treated with potentially hepatotoxic medicines. Periodic assessment of transaminases is recommended in

patients with significant hepatic disease. A starting dose of 5 mg should be considered for patients with moderate hepatic impairment.

- **Transaminase elevations:** Transient elevations of liver transaminases (ALT, AST) have been observed. Caution should therefore be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve and in patients who are being treated with potentially hepatotoxic agents. In the event of elevated ALT and/or AST during treatment, follow-up should be organised and dose reduction should be considered. In cases where hepatitis has been diagnosed, PREXOLAN treatment should be discontinued.
- **Haematology:** Caution should be exercised when using PREXOLAN in the following types of patients:
    - In patients with low leucocyte and/or neutrophil counts due to any reason.
    - In patients with a history of medicine-induced bone marrow depression/toxicity.
    - In patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy.
    - In patients with hypereosinophilic conditions or with myeloproliferative disease. Thirty-two patients with clozapine-related neutropenia or agranulocytosis histories received PREXOLAN without decreases in baseline neutrophil counts.
- **Body temperature regulation:** Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents such as PREXOLAN. Appropriate care is advised when prescribing PREXOLAN for patients who will be experiencing conditions which may contribute to an elevation in core body temperature.
- **Dysphagia:** Oesophageal dysmotility and aspiration have been associated with antipsychotic medicines. PREXOLAN should be used with caution in patients at risk for aspiration pneumonia.
- **Suicide:** The possibility of suicide attempt is inherent in schizophrenia and close

supervision of high risk patients should accompany PREXOLAN treatment.

- The combined effects of age, smoking and gender could lead to substantial pharmacokinetic differences. The clearance in young smoking males for example, may be 3 times higher than that in elderly non-smoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of PREXOLAN.
- **Elderly patients:** Caution should be exercised in dosing the elderly, especially if there are other factors that might additively influence medicine metabolism and/or pharmacodynamic sensitivity. In general, there is no indication of any different tolerability of PREXOLAN in the elderly compared to younger adults. The presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to PREXOLAN should lead to consideration of a lower starting dose. As postural hypotension was infrequently observed in the elderly in clinical trials, it is recommended that blood pressure is measured periodically in patients over 65 years.
- **Safety experience in elderly patients with dementia-related psychosis:** In elderly patients with dementia-related psychosis, the efficacy of PREXOLAN has not been established.

  Risk factors that may predispose this patient population to increased mortality when treated with PREXOLAN include age ≥ 80 years, sedation, concomitant use of benzodiazepines,

  or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).
- **Hyperglycaemia and Diabetes mellitus:** There is an increased prevalence of diabetes amongst patients with schizophrenia. Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during PREXOLAN treatment. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk

factors for developing diabetes mellitus. Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with PREXOLAN. Patients with an established diagnosis of diabetes mellitus who are started on PREXOLAN should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes), who are starting treatment with PREXOLAN should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with PREXOLAN should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when PREXOLAN was discontinued, however, some patients required continuation of anti-diabetic treatment despite discontinuation of PREXOLAN.

- **Concomitant illnesses:** Clinical experience with PREXOLAN in patients with concomitant illnesses is limited. As PREXOLAN demonstrates anticholinergic activity *in-vitro* caution is advised when prescribing for patients with symptomatic prostatic enlargement, or paralytic ileus and related conditions.
- PREXOLAN has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Because of the risk of orthostatic hypotension with PREXOLAN, caution should be observed in cardiac patients.
- **Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia:** Cerebrovascular adverse events (e.g. stroke, transient ischaemia attack), including fatalities, were reported especially in elderly patients with dementia-related psychosis. All patients who experienced a cerebrovascular event had pre-existing risk factors known to be associated with an increased risk for a CVAE (e.g. history of previous CVAE or transient ischaemic attack, hypertension, cigarette smoking) and presented with concurrent medical conditions and/or concomitant medications having a

temporal association with CVAE. PREXOLAN is not approved for the treatment of patients with dementia-related psychosis.

- **Orthostatic hypotension:** PREXOLAN may induce orthostatic hypotension associated with dizziness, tachycardia and in some patients, syncope, especially during the initial treatment period.

Applicable to the IM formulation only

Post injection delirium/Sedation syndrome

Following intramuscular administration of PREXOLAN IM, signs and symptoms consistent with PREXOLAN overdose have been reported. These include symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension or possible convulsions (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS for other potential manifestations of PREXOLAN overdose).

In most cases, signs and symptoms have been observed 1 to 3 hours following the injection, and in all cases a full recovery was reported to have occurred within 24 to 72 hours post injection. The potential for onset of an event is greatest within the first hour. Healthcare providers are advised to discuss this potential risk with patients each time they prescribe and administer PREXOLAN IM.

PREXOLAN IM should be administered in a healthcare facility. Appropriately qualified healthcare providers administering PREXOLAN IM should observe the patient for at least 3 hours following the injection, ensuring the patient is alert, orientated, and absent of signs and symptoms consistent with PREXOLAN overdose.

Hypotension and/or bradycardia have been observed during PREXOLAN IM administration. Patients should remain recumbent if drowsy or dizzy after injection, until examination has indicated that they are not experiencing hypotension, postural hypotension, bradycardia and/or hypoventilation. In view of the possibility of bradycardia and/or hypotension with PREXOLAN IM, caution should be considered in patients with serious cardiovascular disease where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Simultaneous injection of PREXOLAN IM and parenteral benzodiazepines has not been studied and is therefore not recommended (see also INTERACTIONS). If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least 1 hour after PREXOLAN IM administration. If the patient has received parenteral benzodiazepines, PREXOLAN IM administration should only be considered after careful evaluation of clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression.

If parenteral benzodiazepines are required for the management of adverse reactions following the injections, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

For the remainder of the day following intramuscular administration, patients should not drive or operate machinery. Patients should be advised to seek medical assistance should they experience any symptoms consistent with post injection adverse reactions.

Effects on ability to drive and use machines

PREXOLAN may cause somnolence. Patients should be cautioned about operating

hazardous machinery, including motor vehicles, until they are reasonably certain that PREXOLAN therapy does not affect them adversely (see SIDE EFFECTS).

Excipients

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take PREXOLAN.

INTERACTIONS

Given the primary CNS effects of PREXOLAN, caution should be exercised when PREXOLAN is taken in combination with other centrally acting agents (especially those that can cause CNS depression) and alcohol.

As it exhibits *in-vitro* dopamine antagonism, PREXOLAN may antagonise the effects of levodopa and dopamine agonists. Because of the potential for inducing hypotension, PREXOLAN may enhance the effects of certain antihypertensive agents.

Caution should be exercised when PREXOLAN is prescribed with medicines known to increase the QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Hypotension and/or bradycardia have been observed during intramuscular administration of PREXOLAN IM.

PREXOLAN IM has α-1 adrenergic antagonist activity.

Caution should be exercised in patients who receive treatment with medicinal products that

can lower blood pressure by mechanisms other than α-1 adrenergic antagonism.

Potential interactions affecting PREXOLAN: Since PREXOLAN is metabolised by CYP1A2, substances that can specifically induce, inhibit or act as a substrate to this isoenzyme may affect the pharmacokinetics of PREXOLAN.

Potential for other medicines to affect PREXOLAN: Single doses of antacid (aluminium, magnesium) or cimetidine do not affect the oral bioavailability of PREXOLAN. However, the concomitant administration of activated charcoal reduces the oral bioavailability of PREXOLAN by 50 to 60 % and should be taken at least 2 hours before or after PREXOLAN.

Fluoxetine in combination with PREXOLAN may cause an increase in the maximum concentration of PREXOLAN and a decrease in PREXOLAN clearance. The effect of repeat dosage of PREXOLAN and higher dosages has not been evaluated. Combination therapy is not advised.

Administration of intramuscular lorazepam one hour after PREXOLAN IM does not significantly affect the pharmacokinetics of PREXOLAN IM, unconjugated lorazepam or total lorazepam. However, co administration of intramuscular lorazepam and intramuscular PREXOLAN IM injection adds to the somnolence observed with either medicine alone.

Induction of CYP1A2: The metabolism of PREXOLAN may be induced by concomitant smoking or by carbamazepine therapy causing slightly to moderately lower PREXOLAN plasma levels. Clinical monitoring is recommended and an increase of PREXOLAN may be considered if necessary.

Inhibition of CYP1A2: Known potent inhibitors of CYP1A2 activity may decrease PREXOLAN clearance. Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of PREXOLAN. A lower starting dose of PREXOLAN should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin or ketoconazole. A decrease in the dose of PREXOLAN should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Potential for PREXOLAN to affect other medicines: PREXOLAN may antagonise the effects of direct and indirect dopamine agonists. In clinical trials with single doses of PREXOLAN, no inhibition of the metabolism of imipramine/desipramine (P450-CYP2D6 or P450-CYP3A/1A2), warfarin (P450-CYP2C9), theophylline (P450-CYP1A2) or diazepam (P450-CYP3A4 and P450-CYP2C19) was evident. PREXOLAN showed no interaction when co administered with lithium or biperiden. Also, in *in-vitro* studies with human liver microsomes, PREXOLAN showed little potential to inhibit cytochromes P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6, and -CYP3A4.

Studies *in-vitro* using human liver microsomes, determined that PREXOLAN has little potential to inhibit the glucuronidation of valproate, the major metabolic pathway for valproate. Further, valproate was found to have little effect on the metabolism of PREXOLAN *in-vitro*. Daily concomitant *in-vivo* administration of 10 mg PREXOLAN for 2 weeks did not affect steady state plasma concentrations of valproate. Therefore, concomitant PREXOLAN administration does not require dosage adjustment of valproate.

Major reconstitution incompatibilities: See DOSAGE AND DIRECTIONS FOR USE - Reconstitution.

HUMAN REPRODUCTION

Safety of PREXOLAN during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Psychotic disorders: PREXOLAN tablets should be administered on a once a day schedule without regard to meals, generally beginning with an initial dose of 5 mg to 10 mg per day, with a target dose of 10 mg per day within several days.

In order to evaluate efficacy and guard against side effects, dosage increases should not be considered before one week, since steady state for PREXOLAN would not be achieved for approximately one week. The dose range is from 5 mg to 20 mg per day. Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment.

A starting dose of 5 mg should be considered for patients with hepatic impairment and may also be considered for the elderly patient.

Acute mania in bipolar disorder: PREXOLAN should be administered on a once a day schedule without regard to meals, generally beginning with 10 mg. Dosage adjustments, within the dose range of 5 mg to 20 mg per day, if indicated, should generally occur at intervals of not less than 24 hours.

Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg per day. For patients who have been receiving PREXOLAN for treatment of manic episode, continue therapy for preventing recurrence at the same dose. An increase to a dose greater than the recommended starting dose, within the dose range of 5 mg to 20 mg per day, is advised only after appropriate clinical assessment,

and should generally occur at intervals of not less than 24 hours.

The safety of doses above 20 mg per day has not been evaluated in clinical trials.

Gradual tapering of the dose should be considered when discontinuing PREXOLAN (see WARNINGS AND SPECIAL PRECAUTIONS).

Intramuscular dosing: PREXOLAN IM should be administered in a healthcare facility. For patients who have never been given PREXOLAN IM, it is recommended to establish response and tolerability with oral PREXOLAN prior to initiating treatment with PREXOLAN IM.

PREXOLAN IM is for intramuscular use only.

Do not administer intravenously or subcutaneously. The recommended dose for PREXOLAN IM injection is 10 mg administered as a single intramuscular injection. On the basis of individual clinical status, a second injection of up to 10 mg may be administered as early as 2 hours after the first injection, and a third injection of up to 10 mg may be administered as early as 4 hours after the second injection. If oral supplementation with PREXOLAN tablets is required, then the combined total dose of both formulations should not exceed the corresponding maximum oral dose of 20 mg daily. The safety of total daily doses greater than 30 mg has not been evaluated in clinical trials. Treatment with PREXOLAN IM injection should be discontinued and oral PREXOLAN tablets in a range of 5 mg to 20 mg per day should be initiated as soon as clinically appropriate.

Elderly patients: A lower starting dose of 2,5 mg to 5 mg per injection should be considered for elderly patients.

Reconstitution:

Reconstitution of PREXOLAN IM (Powder for injection) with sterile water for injection:

- Reconstitute using 2,0 ml of sterile water for injection.

Major reconstitution incompatibilities:

- **PREXOLAN IM should be reconstituted with sterile water for injection only.**
- **PREXOLAN IM should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed.**
- **Lorazepam injection should not be used to reconstitute PREXOLAN IM as this combination results in a delayed reconstitution time.**
- **PREXOLAN IM should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade PREXOLAN IM over time.**

SIDE EFFECTS

Blood and the lymphatic system disorders

Frequent: Eosinophilia

Less frequent: Leucopenia, thrombocytopenia, neutropenia

Frequency unknown: Agranulocytosis

Immune system disorders

Less frequent: Allergic reaction

Metabolic and nutritional disorders

Frequent: Weight gain, increased appetite

Less frequent: Diabetic coma, diabetic ketoacidosis, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia

Frequency unknown: Increased risk of glucose intolerance and diabetes mellitus, abnormalities of glucose homoeostasis

Psychiatric disorders

Frequent: Hallucinations

Frequency unknown: Mania

Nervous system disorders

Frequent: Asthenia, akathisia, dizziness, somnolence, abnormal gait, falls, parkinsonism, speech disorder, tremor

Less frequent: Seizures, extrapyramidal effects, neuroleptic malignant syndrome

Frequency unknown: Discontinuation symptoms (sweating, insomnia, tremor, anxiety, nausea and vomiting has been reported when PREXOLAN is stopped abruptly), sedation, tardive dyskinesia, stuttering

Cardiac disorders

Frequent: Bradycardia, tachycardia

Vascular disorders

Frequent: Orthostatic hypotension, peripheral oedema, hypotension

Less frequent: Venous thromboembolism

Frequency unknown: Pulmonary embolism

Respiratory, thoracic and mediastinal disorders

Frequent: Pneumonia

Frequency unknown: Hypoventilation

Gastrointestinal disorders

Frequent: Dry mouth, constipation

Frequency unknown: Pancreatitis

Hepato-biliary disorders

Frequency unknown: Acute hepatocellular cholestatic jaundice

Skin and subcutaneous tissue disorders

Less frequent: Photosensitivity reaction, rash

Musculoskeletal, connective tissue and bone disorders

Less frequent: Rhabdomyolysis

Renal and urinary disorders

Frequent: Urinary incontinence

Reproductive system and breast disorders

Less frequent: Priapism

General disorders and administration site conditions

Less frequent: Fatigue

Frequency unknown: Hypothermia

Investigations

Frequent: Increased ALT, increased AST, increased prolactin

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

Frequent symptoms reported in PREXOLAN overdose include tachycardia,

agitation/aggressiveness, dysarthria, various extrapyramidal symptoms and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of PREXOLAN overdose include delirium, convulsion, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac dysrhythmias and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg, but survival has also been reported following acute overdose of 1 500 mg.

Treatment

The possibility of multiple medicine involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose, may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias.

There is no specific antidote to PREXOLAN, therefore, appropriate symptomatic and supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents. Induction of emesis is not recommended. Do not use epinephrine (adrenaline), dopamine or other sympathomimetics with β-agonist activity, since β-stimulation may worsen hypotension in the setting of PREXOLAN induced α-blockade.

Close medical supervision and monitoring should continue until the patient recovers.

IDENTIFICATION

PREXOLAN 2,5: White, round, biconvex, film-coated tablets with dimensions 6,1 mm ± 0,1 mm in diameter and 2,6 mm ± 0,2 mm in thickness.

PREXOLAN 5: White, round, biconvex, film-coated tablets with dimensions 8,1 mm ± 0,1 mm in diameter and 3,1 mm ± 0,2 mm in thickness.

PREXOLAN 10: White, round, biconvex, film-coated tablets with dimensions 10,1 mm ± 0,1 mm in diameter and 4,1 mm ± 0,2 mm in thickness.

PREXOLAN IM: Yellow lyophilised spongy powder.

Reconstituted solution: Clear, yellow solution free of foreign particles.

PRESENTATION

PREXOLAN tablets: 28 or 30 film-coated tablets are packed in a polyamide, aluminium, polyvinyl chloride film and sealed with an aluminium foil backing. The blister strips (7 tablets/blister or 10 tablets/blister) are packed into an outer cardboard carton together with a leaflet.

PREXOLAN IM: 1 x 7 ml clear Type 1 glass vial containing a yellow lyophilised powder is sealed with a bromobutyl rubber stopper together with an aluminium flip off cap.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

PREXOLAN tablets: Store at or below 25 °C protected from light and moisture.

Keep the blisters in the carton until required for use.

PREXOLAN IM: Store at or below 25 °C. Protect from light and moisture.

After reconstitution with sterile water for injection: Stable for one hour when stored at or below 25 °C. Do not freeze (see DOSAGE AND DIRECTIONS FOR USE).

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

PREXOLAN 2,5: 43/2.6.5/0908

PREXOLAN 5: 43/2.6.5/0909

PREXOLAN 10: 43/2.6.5/0910

PREXOLAN IM: 43/2.6.5/0911

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

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Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Dates of registration:

PREXOLAN 2,5: 06 March 2014

PREXOLAN 5: 06 March 2014

PREXOLAN 10: 06 March 2014

PREXOLAN IM: 06 March 2014

Date of the most recent amendment to the professional information as approved by the Authority: 06 March 2014

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