PROFESSIONAL INFORMATION FOR RUBITREND

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM:

Rubitrend 6,25 (tablets)

Rubitrend 12,5 (tablets)

Rubitrend 25 (tablets)

COMPOSITION:

Rubitrend 6,25: Each tablet contains 6,25 mg carvedilol
Contains sugar (lactose): 79,92 mg/tablet. Contains sugar (sucrose): 2 mg/tablet

Rubitrend 12,5: Each tablet contains 12,5 mg carvedilol
Contains sugar (lactose): 97,53 mg/tablet. Contains sugar (sucrose): 1,4 mg/tablet

Rubitrend 25: Each tablet contains 25 mg carvedilol
Contains sugar (lactose): 109,7 mg/tablet. Contains sugar (sucrose): 1,8 mg/tablet

Inactive ingredients: Lactose, sucrose, crospovidone, povidone, colloidal silicon dioxide, magnesium stearate, yellow iron oxide (E172 – 6,25 mg & 12,5 mg), red iron oxide (E172 – 12,5 mg only)

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

Pharmacodynamics:
Carvedilol is a competitive non selective beta 1 and 2 adrenergic blocking agent with also alpha 1 adrenergic blocking activity and no intrinsic sympathomimetic activity.
Carvedilol reduces peripheral vascular resistance through vasodilation and suppresses the renin- angiotensin-aldosterone system through beta blockade. Vasodilation has been shown to be mediated primarily by selective blockade of α1 -adrenoceptors.

Pharmacokinetics:
Carvedilol is rapidly absorbed from the gastrointestinal tract and extensively metabolised in the liver, primarily by aromatic ring oxidation and glucuronidation. Absolute bioavailability is about 25 % due to the considerable first-pass metabolism. Peak plasma concentration occurs approximately 1 to 2 hours after administration. There is a linear correlation between dose and serum concentration. Protein binding, especially to alpha-acid glycoprotein and albumin, is more than 98 %.
The absorption rate of carvedilol is slowed by food but the bioavailability appears not to be affected. The elimination half-life is 6 - 10 hours and excretion is mainly in the bile, with a small part (about 15 %) excreted via the kidneys.

Special populations:

The Elderly: The pharmacokinetics are affected by age: The plasma levels of carvedilol are an average of about 50 % higher in the elderly, compared with younger patients.

Hepatic insufficiency: The plasma levels of carvedilol are 5 times higher in patients suffering from liver cirrhosis, than in healthy subjects.

Renal insufficiency: The pharmacokinetic parameters are only modestly changed in patients with renal insufficiency, since the metabolites of carvedilol are mainly excreted via the biliary tract.

INDICATIONS:

- Treatment of mild to moderate essential hypertension.
- Treatment of mild to moderate stable symptomatic heart failure of ischaemic or cardiomyopathic origin in conjunction with standard therapy. **Rubitrend** may be used in patients unable to tolerate ACE inhibitors and in patients on digoxin.

CONTRAINDICATIONS:

- Hypersensitivity to carvedilol or any of the inactive ingredients of **Rubitrend**
- 2nd and 3rd degree A-V block
- Severe bradycardia (< 50/minute)
- New York Heart Association (NYHA) Class IV decompensated heart failure requiring intravenous inotropic support
- Metabolic acidosis
- Cardiogenic shock
- Sick sinus syndrome (including sino-atrial block)
- Severe hypotension (systolic blood pressure < 85 mmHg)
- Bronchospasm or asthma or patients with a history of obstructive airways disease
- Uncontrolled heart failure
- Hepatic function impairment
- Combination of **Rubitrend** and verapamil is contraindicated
- **Rubitrend** is contraindicated during pregnancy and lactation (see “Pregnancy and Lactation”)
- Safety in children has not been established

WARNINGS AND SPECIAL PRECAUTIONS:

- Patients with phaeochromocytoma should never receive **Rubitrend** without receiving concomitant alpha-adrenoceptor blocking therapy. **Rubitrend** should be prescribed with caution to patients suffering from allergic conditions involving the airways e.g. allergic rhinitis or glottis oedema.

Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines, which may give rise to a hypertensive crisis. If **Rubitrend** is administered in these circumstances, the alpha-receptor stimulation may potentiate this effect. If **Rubitrend** and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of **Rubitrend**, as severe rebound hypertension may occur.
Digitalisation of patients receiving long-term beta-blocking therapy may be necessary if congestive cardiac failure develops.
This combination may be considered despite the potentiation of negative chronotropic effect of the two medicines. Careful monitoring of the dosages and of the individual patient's response (and notably pulse rate), is essential in this situation.

- **Rubitrend** should be given to patients with congestive heart failure only after adequate clinical control is achieved, and only then with great caution, especially if the heart failure is controlled with digoxin, diuretics and/or ACE inhibitors as both digoxin and **Rubitrend** show A-V conduction. Before the dosage is increased, the patient should be evaluated for the symptoms of worsening heart failure or vasodilation. Transient heart failure and fluid retention should be treated with increased doses of a diuretic. It may be necessary to lower the **Rubitrend** dosage or to discontinue **Rubitrend** therapy temporarily in some cases. All symptoms of vasodilation or worsening heart failure must be stabilised before the dose of **Rubitrend** is increased in line with the recommended dosage instructions (see "Dosage and Directions for Use" and "Warnings and Special Precautions"). Digoxin levels should be monitored when initiating, adjusting or discontinuing **Rubitrend**.
- It is of the greatest importance that the anaesthetist be informed that a beta-blocker is being taken by the patient, prior to anaesthesia. **Rubitrend** therapy should be discontinued 48 hours prior to anaesthesia. If this is not possible, an agent such as atropine may be administered to counter increase in vagal tone.
- In the perioperative period it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or of hypertension. A patient's normal tachycardia response to hypovolaemia or blood loss may be obscured during and after surgery. Particular caution should be taken in this regard.
- Safety during long-term administration has not been demonstrated.
- Patients with peripheral vascular disease and/or Raynaud's syndrome should use **Rubitrend** with caution.
- Adverse reactions are more common in patients with renal decompensation, and in patients who receive the medicine intravenously.
- Acute renal failure and renal abnormalities have been reported in patients with heart failure who also suffer from diffuse vascular disease and/or renal impairment (see "Warnings and Special Precautions"). A dose reduction is necessary in elderly patients, or in patients suffering from renal dysfunction.
- Abrupt discontinuation of therapy with **Rubitrend** may cause exacerbation of angina pectoris or a sudden death in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual (over a period of 1 to 2 weeks) and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued (see "Dosage and Directions for Use").
- There is no clinical experience in the use of **Rubitrend** in patients suffering from Prinzmetal's variant angina. Caution is advised as **Rubitrend** may provoke chest pain in patients suspected of suffering from this disease.
- **Rubitrend** may cause bradycardia. A dose reduction is advised should the pulse rate drop to < 55 beats/minute (see "Contraindications").
- Early signs of acute hypoglycaemia may be masked or attenuated by the administration of **Rubitrend**. It may delay recovery from insulin-induced hypoglycaemia. Caution is advised when **Rubitrend** is prescribed to diabetic patients. A dose reduction of anti-diabetic medication or insulin may be necessary. In diabetic patients with congestive heart failure use of **Rubitrend** may be associated with worsening of blood glucose control.
- The symptoms of hyperthyroidism may be masked by **Rubitrend**.
- Wearers of contact lenses should be informed that there may be a reduction in lacrimation.
- Psoriasis may be aggravated.
- Patients with a history of anaphylaxis to an antigen may be more reactive to repeated challenge with the antigen while taking **Rubitrend**.
- **Rubitrend** contains sugar (sucrose) which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **Rubitrend**.
- **Rubitrend** contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **Rubitrend**.

Effects on ability to drive and operate machinery:
When dizziness or related symptoms are experienced, the patient should be advised not to drive or operate machinery.

INTERACTIONS:

It can be dangerous to administer **Rubitrend** concomitantly with the following medicines: hypoglycaemic agents, phenothiazines and various anti-dysrhythmic agents. Such interactions can have life-threatening consequences.

Rubitrend may potentiate the effect of other concomitantly administered antihypertensives. Anaesthetic agents causing myocardial depression should be avoided.
Rubitrend should be avoided in combination with cardio-depressant calcium channel blockers such as verapamil and diltiazem.
The hypotensive effects of **Rubitrend** are antagonised by non-steroidal anti-inflammatory agents (NSAIDS).
Rubitrend may potentiate anti-diabetic agents such as insulin or oral hypoglycaemics. The signs and symptoms of hypoglycaemia may be masked or attenuated (see Special Precautions).
Myocardial depressant agents, including Class I anti-dysrhythmic agents, e.g. disopyramide, quinidine, procainamide, lignocaine (lidocaine) and phenytoin, may have a negative inotropic effect on the heart and there may be a potentiation of the A-V conduction time when used concurrently with **Rubitrend**.

Reserpine and other medicines that can deplete catecholamines, as well as adrenergic neuron blocking agents should be closely observed for hypotension and/or severe bradycardia.
Beta-adrenoreceptor stimulating agents, such as isoprenaline, dopamine and dobutamine diminish the effects of **Rubitrend**.
Alpha-adrenoreceptor stimulating agents such as pseudoephedrine, phenylephrine and norepinephrine (noradrenaline) and mixed alpha- and beta-adrenoreceptor stimulating agents, such as epinephrine (adrenaline), may enhance the peripheral vasoconstrictor effects of **Rubitrend** and may reverse the hypotensive effects.
Concomitant therapy of **Rubitrend** with inducers of the cytochrome p-450 enzyme system such as phenytoin, phenobarbital and rifampicin may decrease the systemic availability of **Rubitrend**.
Following concurrent administration of **Rubitrend** and digoxin, steady state trough concentrations of digoxin may be increased by approximately 16 % in hypertensive patients.
Ciclosporin concentrations should be monitored closely after initiation of **Rubitrend** therapy and adjusted as appropriate.
Concurrent therapy with inhibitors of the cytochrome P-450 enzyme system, such as cimetidine, quinidine, fluoxetine and paroxetine may increase the systemic bioavailability of **Rubitrend**. Although cimetidine may result in a 30 % increase in the systemic bioavailability of **Rubitrend**, it has no effect on the C_{max}.
Phosphodiesterase type 5 inhibitors, such as sildenafil may enhance the hypotensive effect of **Rubitrend**.
Hydralazine and alcohol may increase the plasma concentration of **Rubitrend** by delaying the hepatic metabolism of **Rubitrend**.
The absorption of **Rubitrend** may be decreased by cholestyramine, aluminium salts and colestipal.

PREGNANCY AND LACTATION:

Rubitrend should not be used during pregnancy and lactation (see “Contraindications”). Administration to pregnant mothers shortly before giving birth or during labour, may result in the newborn infant being born hypotonic, collapsed and hypoglycaemic.
Rubitrend and/or its metabolites are excreted in breast milk; breastfeeding is therefore not recommended during administration of **Rubitrend**.

DOSAGE AND DIRECTIONS FOR USE:

Essential hypertension:

Adults:
The recommended dose for initiation of therapy is 12,5 mg once a day for the first two days. Thereafter the recommended dose is 25 mg once a day. Combination with a diuretic may also give the desired response.

Elderly:
The recommended dose for initiation of therapy is 12,5 mg once daily which has provided satisfactory control in some patients. If the response is inadequate, the dose may be titrated at intervals of at least two weeks up to the recommended daily dose of 25 mg once a day or in divided doses.
In hypertensive patients, it is not necessary to time the dose in relation to meals.
At doses higher than 25 mg, the incidence of side-effects increases significantly with only a marginal increase in efficacy.

Treatment of symptomatic congestive heart failure:
To reduce the incidence of orthostatic effects **Rubitrend** should be taken with food to slow the rate of absorption. Dosage must be individualised and closely monitored by a medical practitioner experienced in the management of heart failure, during up-titration.
For those patients receiving digoxin, diuretics and angiotensin-converting enzyme (ACE) inhibitors, dosing of these medicines should be stabilised prior to initiation of **Rubitrend** treatment.
The recommended dose for initiation of therapy is: 3,125 mg twice daily for at least two weeks. If this dose is tolerated, the dosage may subsequently be increased, at intervals of not less than 2 weeks, to 6,25 mg twice daily, followed by 12,5 mg twice daily and thereafter 25 mg twice daily.
Dosing should be increased to the highest level tolerated by the patient. The maximum recommended dose is 25 mg twice daily in patients weighing less than 85 kg and 50 mg twice daily in patients weighing more than 85 kg.
Before each dose increase, the patient should be evaluated by the medical practitioner for symptoms of worsening heart failure or vasodilation. Transient worsening of heart failure or fluid retention should be treated with increased doses of diuretics, although occasionally it may be necessary to lower the **Rubitrend** dose or to temporarily discontinue **Rubitrend** treatment.
If **Rubitrend** treatment is discontinued for more than two weeks, therapy should be recommenced at 3,125 mg twice daily and up-titrated in line with the above dosing recommendation.
Symptoms of vasodilation such as headache, dizziness and postural hypotension may be managed initially by a reduction in the dose of diuretics. If symptoms persist, the dose of ACE inhibitor (if used) may be reduced, followed by a reduction in the dose of **Rubitrend**, if necessary. Under these circumstances, the dose of **Rubitrend** should not be increased until symptoms of worsening heart failure or vasodilation have been stabilised.

SIDE-EFFECTS:

The frequency of adverse experiences is not dose dependent, with the exception of dizziness, abnormal vision and bradycardia.

Blood and the lymphatic system disorders:
Frequent: Thrombocytopenia
Less frequent: Leukopenia, changes in serum transaminases

Metabolic and nutrition disorders:
Frequent: Weight increase and hypercholesterolaemia; hyperglycaemia. Hypoglycaemia and worsening control of blood glucose in patients with pre-existing diabetes mellitus

Nervous system disorders:
Frequent: Dizziness, headaches and fatigue
Less frequent: Paraesthesia

General disorders and administrative site conditions:
Frequent: Asthenia, pain in the extremities

Cardiac disorders:
Frequent: Bradycardia
Less frequent: Syncope (including presyncope), A-V block and exacerbation of cardiac failure, acute myocardial infarction, cardiomegaly, angina pectoris (including chest pain), symptoms of heart failure, wheezing, flu-like symptoms

Vascular disorders:
Frequent: Oedema (including generalised, peripheral, dependent and genital oedema, oedema of the legs, hypervolaemia and fluid overload), postural hypotension (especially at the beginning of treatment), hypotension
Less frequent: Disturbances of peripheral circulation (cold extremities, PVD, exacerbation of intermittent claudication and Raynaud's phenomenon).

Gastro-intestinal disorders:
Frequent: Nausea, diarrhoea and vomiting, abdominal pain
Less frequent: Constipation, dryness of the mouth

Eye disorders:
Frequent: Vision abnormalities, reduced lacrimation
Less frequent: disturbed vision, eye irritation

Renal and urinary disorders:
Less frequent: Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function, urinary incontinence in women, disturbances of micturition,

Psychiatric disorders:
Less frequent: Depressed mood, sleep disturbance

Skin and subcutaneous tissue disorders:
Less frequent: Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritus, lichen planus-like reactions and increased sweating). Psoriatic skin lesions may occur or existing lesions exacerbated.

Respiratory system disorders:
Frequent: Bronchoconstriction
Less frequent: Nasal congestion, dyspnoea

Reproductive system and breast disorders:
Less frequent: Sexual impotence

Immune system disorders:
Less frequent: Allergic reactions

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage may produce bradycardia, severe hypotension, cardiogenic shock, heart failure and/or cardiac arrest. Bronchospasm, vomiting, seizures and disturbed consciousness may occur in some patients.

Treatment: The patient should be placed in a supine position to improve blood supply to the brain. Bradycardia and severe hypotension should be treated with intravenous atropine. Incremental doses of up to 3 mg should be given immediately. If necessary, this should be followed by a slow intravenous infusion of isoprenaline/dobutamine/adrenaline (epinephrine). If further measures are required, norepinephrine (noradrenaline) may be preferable in restoring circulation. The recommended starting dose for norepinephrine (noradrenaline) is 5 – 10 µg given intravenously, and should be repeated according to the patient's response. Alternatively, it may be given by intravenous infusion at a rate of 5 µg/minute until a response is achieved.
In case of therapy-resistant bradycardia, pacemaker therapy should be performed.

In severe overdosage the following regime may be preferred:
Initially 1 – 10 mg glucagon intravenously, followed by intravenous infusion at a rate of 2 – 2,5 mg/hour.
Bronchospasm should be treated with intravenous aminophylline or B2 adrenergics and cardiac failure with glucagon and/or pacing.
Peripheral vasodilation may be treated with noradrenaline with continuous monitoring of the circulation.
In the event of seizures, diazepam or clonazepam may be given as slow intravenous injection.
Since a prolonged elimination half-life of **Rubitrend** can be expected, treatment with antidotes must be continued for a sufficiently long period of time when there are symptoms of shock, following severe intoxication with **Rubitrend**.
Rubitrend is not eliminated by dialysis.

IDENTIFICATION:

Rubitrend 6,25 – Pale yellow to off white, round, flat tablet with central break-line
Rubitrend 12,5 – Pink coloured, circular flat tablets
Rubitrend 25 – White coloured, round, flat tablet with central break-line

PRESENTATION:

Unit carton containing 28 (2 x 14) or 30 (3 x 10) tablets in clear PVC/silver Al blister packs White HDPE container and cap with 30, 100 or 500 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a dry place. Do not remove tablets from blister until required for use.
Protect from light and moisture. Keep HDPE containers tightly closed.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER(S):

Rubitrend 6,25 – 43/7.1.3/0951
Rubitrend 12,5 – 43/7.1.3/0952
Rubitrend 25 – 43/7.1.3/0953

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

Gulf Drug Company (Pty) Ltd
22 Burnside Drive,
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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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