1.3.1.1 Package Insert

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

COMPOSITION:

RUBITREND 6,25 (tablets)

RUBITREND 12,5 (tablets)

RUBITREND 25 (tablets)

RUBITREND 6,25: Each tablet contains 6,25 mg Carvedilol and 2,00 mg sucrose.

RUBITREND 12,5: Each tablet contains 12,5 mg Carvedilol and 1,40 mg sucrose.

RUBITREND 25: Each tablet contains 25 mg Carvedilol and 1,80 mg sucrose.

Contains: lactose

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

Carvedilol is a competitive non-selective beta 1 and 2-adrenergic blocking agent with also alpha-adrenergic blocking activity and no intrinsic sympathomimetic activity.
Carvedilol reduces peripheral vascular resistance through vasodilation and suppresses the renin-angiotensinaldosterone system through beta blockade.

Pharmacokinetics:

Carvedilol is 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 firstpass metabolism. Peak plasma concentration occurs approximately 1 hour after administration. Protein binding, especially to 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. The plasma level of carvedilol is an average of about 50% higher in the elderly, compared with younger patients. The plasma levels of carvedilol are 5 times higher in patients suffering from cirrhosis of the liver, than in healthy subjects.

INDICATIONS:

- Treatment of mild to moderate essential hypertension.
- Treatment of mild to moderate stable symptomatic heart failure of ischemic or cardiomyopathic origin in conjunction with standard therapy. **RUBITREND** has been used in patients unable to tolerate an ACE inhibitor and also in patients not receiving digitalis.

CONTRA INDICATIONS:

- Hypersensitivity to **RUBITREND**
- **RUBITREND** is contra-indicated in patients suffering from bronchospasm or asthma or patients with a history of obstructive airway disease, bronchitis and chronic respiratory disease.
- **RUBITREND** is contra-indicated in the following conditions:
- 2nd and 3rd degree atrioventricular block, severe bradycardia (< 50/minute)
- New York heart association (NYHA) Class IV decompensated heart failure requiring intravenous inotropic support
- Cardiogenic shock
- Sick sinus syndrome (including sino-atrial block)
- Hepatic function impairment

- Metabolic acidosis
- Peripheral vascular disease
- Raynaud's syndrome
- **RUBITREND** should not be prescribed to patients suffering from allergic conditions involving the airways e.g. allergic rhinitis or glottis oedema
- **RUBITREND** should not be used during pregnancy and lactation

WARNINGS:

Patients with phaechromocytoma should never receive **RUBITREND** without receiving concomitant alphaadrenoceptor blocking therapy.

RUBITREND should be given to patients with congestive heart failure only after adequate clinical control is achieved and only then with great caution.

Safety and efficacy in children have not been established.

INTERACTIONS:

Warning:

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 unopposed 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.

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

Special note:

Digitalisation of patients receiving long-term beta-blocking therapy may be necessary if congestive cardiac failure is likely to develop. This combination may be considered despite the potentiation of negative chronotropic effect of the two medicines. Careful control of the dosages and of the individual patients response (and notably pulse rate), is essential in this situation.

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 carvedilol are antagonised by non-steroidal anti-inflammatory agents (NSAIDS). **RUBITREND** may potentiate anti-diabetic agents such as insulin or sulphonylureas. Myocardial depressant agents, including anti-arrhythmic agents, e.g. Disopyramide, procainamide, lignocaine and phenytoin, may have a negative inotropic effect on the heart and there may be a potentiation of the AV conduction time when used concurrently with **RUBITREND .**

Enzyme inhibitors, such as quinidine may affect the metabolism and pharmacokinetics of **RUBITREND .** Reserpine and other medicines that can deplete catecholamines, as well as adrenergic neuron blocking agents such as guanethidine and bethanidine, may cause hypotension and severe bradycardia. Beta-adrenoreceptor stimulating agents, such as isoprenaline, diminish the effect of Carvedilol. Alphaadrenoreceptor stimulating agents such as noradrenaline and mixed alpha- and beta-adrenoreceptor stimulating agents, such as adrenaline, may enhance the peripheral vasoconstrictor effects of Carvedilol and may reverse the hypotensive effects.

Rifampicin may decrease the systemic availability of **RUBITREND .**

Digoxin levels should be monitored when Carvedilol dosages are changed. Concurrent therapy with cimetidine may result in a 30% increase in the systemic bioavailability of **RUBITREND ,** but has no effect on Cmax. Hydralazine and alcohol may increase the plasma concentration of Carvedilol by delaying the hepatic metabolism of **RUBITREND .**

PREGNANCY AND LACTATION:

RUBITREND should not be used during pregnancy and lactation (see **"CONTRA-INDICATIONS").**

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

DOSAGE AND DIRECTIONS FOR USE:

Essential hypertension:

ADULTS:

Initial dose: 6.25mg twice daily, for 1 to 2 weeks.

Maintenance dose: 12.5mg twice daily.

or

Initial dose: 12.5mg once daily, for 2 days.

Maintenance dose: 25mg once daily.

At doses higher than 25mg the incidence of side-effects increases significantly with only a marginal increase in efficacy.

ELDERLY:

Usual dose: 12.5mg once daily

If necessary the dosage may be increased as tolerated, at intervals of at least 2 weeks, to 25mg once daily or in divided doses.

Heart failure (in conjunction with standard therapy):

To reduce the incidence of orthostatic effects **RUBITREND** should be taken with food to slow the rate of absorption. The bioavailability of **RUBITREND** is not affected by food. It is advised that the dosage be individualised and that the patient be closely monitored by a medical practitioner experienced in the management of heart failure, during up-titration. Patients receiving digitalis, diuretics and/or angiotensin-converting enzyme (ACE) inhibitors, should be stabilized prior to carvedilol therapy.

Adults:

Initial dose: 3.125mg twice daily for two weeks.

Increase to: 6.25mg twice daily for two weeks.

Maintenance dose: 25mg twice daily for patients weighing< 85kg (maximum dose).

Increase to: 50mg twice daily for patients weighing> 85kg (maximum dose).

An interval of at least two weeks should be allowed after each dose increase. Before the dosage is increased, the patient should be evaluated for 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 carvedilol therapy temporarily in some cases. Should treatment be discontinued for two weeks or more, it is advised that therapy be reinstated at 3, 125mg twice daily for two weeks and the dosage then increased in line with the abovementioned dosage instructions. Symptoms of vasodilation (headache, dizziness, postural hypotension) may initially be managed by a dose reduction of the diuretic.

Should the symptoms persist; the dose of the ACE inhibitor may be reduced, followed by a reduction in the dose of **RUBITREND ,** if necessary. All symptoms of vasodilation or

worsening heart failure must be stabilized before the dose of carvedilol is increased in line with the recommended dose instructions.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

SIDE-EFFECTS:

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention:

very common(= 1/10); common(= 1/100, < 1/10); uncommon(= 1/100, < 1/100); rare(= 1/10000, < 1/1000); very rare (= < 1/10 000); including isolated reports. Adverse events are listed separately for chronic heart failure because of differences in the background diseases.

In Chronic Heart Failure

Haematological disorders:	
Rare:	Thrombocytopenia Leucopoenia has been reported in isolated cases.
Metabolic disorders:	
Common:	Weight increase and hypercholesterolemia. Hyperglycaemia, hypoglycaemia and worsening control of blood glucose are also common in patients with preexisting diabetes mellitus.
Central Nervous system disorders:	
Very common:	Dizziness, headache are usually mild and occur particularly at the start of treatment, asthenia (including fatigue)

Cardiovascular disorders:	
Common:	Bradycardia, postural hypotension, hypotension, oedema (including generalized, peripheral, dependent and genital oedema, oedema of the legs, hypervolaemia and fluid overload)
Uncommon:	Syncope (including presyncope), AV block and cardiac failure during up titration
Gastro-intestinal disorders:	
Common:	Nausea, diarrhoea and vomiting
Skin and appendages disorders: Dermatitis and increased sweating	
Others:	
Common:	Vision abnormalities
Rare:	Acute renal failure and renal function abnormalities in patients with diffuse vascular disease and/or impaired renal function (see **"Special Precautions")**
The frequency of adverse experiences is not dose dependent, with the exception of dizziness, abnormal vision and bradycardia.	
In Hypertension and Angina The profile is similar to that observed in chronic heart failure although the incidence of events is generally lower in patients with hypertension or angina treated with **RUBITREND** **.**	
Blood chemistry and haematological	

Isolated cases of changes in serum transaminases, thrombocytopenia, and leucopoenia have been reported.	
Central Nervous system disorders:	
Common:	Dizziness, headache and fatigue, which are usually mild and occur particularly at the start of treatment
Uncommon:	Depressed mood, sleep disturbance, parathesia, asthenia
Cardiovascular disorders:	
Common:	Bradycardia, postural hypotension, especially at the beginning of treatment
Uncommon:	Syncope, hypotension, disturbances of peripheral circulation (cold extremities, PVD, exacerbation of intermittent claudication and Raynauds phenomenon). AV block, angina pectoris (including chest pain), symptoms of heart failure and peripheral oedema
Gastro-intestinal disorders:	
Common:	Gastro-intestinal upset (with symptoms such as nausea, abdominal pain, diarrhoea)
Uncommon:	Constipation and vomiting
Skin and appendages disorders:	

Uncommon:	Skin reactions (e.g. allergic exanthema, dermatitis, urticaria, pruritis, lichen planus-like reactions and increased sweating). Psoriatic skin lesions may occur or existing lesions exacerbated.
Others:	
Common:	Pain in the extremities, reduced lacrimation
Uncommon:	Cases of sexual impotence and disturbed vision
Rare:	Dryness of the mouth and disturbances of micturition and eye irritation Isolated cases of allergic reactions have been reported.
Post-marketing experience Isolated cases of urinary incontinence in women, which resolved upon discontinuation of the medication, have been reported.	

Special Precautions:

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 digitalis, diuretics and/or ACE inhibitors.

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. 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. Adverse reactions are more common in patients with renal decompensation, and in patients who receive the medicine intravenously. A dose reduction is necessary in elderly patients, or in patients suffering from renal dysfunction. Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischemic 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. Patients with phaechromocytoma should receive concomitant alpha-adrenoceptor blocking therapy. 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.

Early signs of acute hypoglycaemia may be masked by the administration of **RUBITREND .** Caution is advised when **RUBITREND** is prescribed to diabetic patients. A dose reduction of anti-diabetic medication or insulin may be necessary.

The symptoms of hyperthyroidism may be masked by **RUBITREND .**

When dizziness or related symptoms are experienced, the patient should be advised not to drive or operate machinery.

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 .**

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage may produce bradycardia and severe hypotension. Bronchospasm and cardiac failure may occur in some patients.

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. If further measures are required, noradrenaline may be preferable in restoring circulation. The recommended starting dose for 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 glucagons intravenously, followed by intravenous infusion at a rate of 2 - 2.5 mg/hour.

Bronchospasm should be treated with intravenous aminophylline and cardiac failure with glucagons 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 .**

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, 500 or 1000 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

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