

**Carvetrend 6,25 mg**

**Carvetrend 12,5 mg**

**Carvetrend 25 mg**

**SCHEDULING STATUS:**

S3

**PROPRIETARY NAME AND DOSAGE FORM:**

Carvetrend 6,25 mg tablet

Carvetrend 12,5 mg tablet

Carvetrend 25 mg tablet.

**COMPOSITION:**

Each Carvetrend 6,25 mg tablet contains 6,25 mg carvedilol.

Each Carvetrend 12,50 mg tablet contains 12,50 mg carvedilol.

Each Carvetrend 25,00 mg tablet contains 25,00 mg carvedilol.

**PHARMACOLOGICAL CLASSIFICATION:**

A: 7.1.3 Other hypotensives

**PHARMACOLOGICAL ACTION:**

In the same dosage range, carvedilol exhibits both non-selective beta-blocking properties and acts as an **antihypertensive** agent having vasodilating properties.

Carvedilol is a competitive, non-selective antagonist of beta<sub>1</sub>- and beta<sub>2</sub>-adrenoreceptors; as demonstrated in both *in vitro* and *in vivo* animal studies.

Its beta-blockade activity leads to a reduction of peripheral vascular resistance via suppression of the renin-angiotensin-aldosterone system and vasodilation. Selective blockade of alpha1-adrenoreceptors is responsible mainly for vasodilation.

Carvedilol has no intrinsic sympathomimetic activity.

The pharmacological action of carvedilol in **congestive heart failure** has not been established.

See INDICATIONS for details.

**Pharmacokinetics:**

Carvedilol undergoes extensive first-pass hepatic metabolism resulting in a low and variable absolute bioavailability of 25%. Metabolism is primarily hepatic. Linear correlation between dose and serum concentration has been observed.

Carvedilol is extensively (approximately 98%) bound to plasma protein (primarily alpha-acid glycoproteins and also albumin).

The average elimination half-life is 6 to 10 hours.

The rate of absorption (time to reach maximum serum concentration), but not the extent of absorption (bioavailability) is decreased by food.

Elimination is primarily biliary.

Dosage adjustment in renally impaired patients is not required.

Peak plasma carvedilol concentrations and bioavailability are significantly increased in patients with severe hepatic impairment, and therefore not recommended in these patients (see CONTRA-INDICATIONS).

### **INDICATIONS:**

Carvetrend is indicated for the treatment of:

- ❖ Essential mild to moderate hypertension.
- ❖ Mild to moderate stable symptomatic congestive heart failure either of cardiomyopathic or ischaemic origin. Used as an adjunct to standard therapy. Has been used in patients that are not tolerant to ACE (angiotensin-converting-enzyme) inhibitors. Has been used in patients who may, or may not, be on digitalis therapy.

### **CONTRA-INDICATIONS:**

Hypersensitivity to any of the ingredients.

Bronchial asthma, chronic obstructive pulmonary disease, severe bradycardia (< 50 bpm), sick sinus syndrome including sino-atrial block, second or third degree atrioventricular block, unstable heart failure, decompensated heart failure (New York Heart Association (NYHA) class IV requiring intravenous inotropic support), cardiogenic shock, clinically manifest liver impairment, and severe hypotension (systolic BP < 85 mmHg).

*Children:* Safety has not been established.

### **WARNINGS:**

Use with extreme caution in patients with congestive heart failure who have previously achieved adequate clinical control.

Phaeochromocytoma patients should first be controlled with alpha-blockers before initiating CARVETREND treatment.

Use with caution in patients with renal impairment.

Do not use in patients with obstructive airway diseases, bronchospasm, or allergic conditions involving the airways (example, glottis oedema, allergic rhinitis).

Do not use in patients with metabolic acidosis, partial heart block, or sinus bradycardia.

## **INTERACTIONS:**

Concomitant administration of carvedilol:-

- May result in the potentiation of the effect when used with other antihypertensives or medicines that result in hypotension as a side-effect.
- May result in an increase of approximately 16% in steady state trough digoxin concentrations in hypertensive patients. Digoxin levels should be monitored when carvedilol therapy is initiated, adjusted or discontinued.
- May result in the increase of systemic bioavailability (approximately 30%) of carvedilol without affecting Cmax when administered with cimetidine.
- May lead in the reduced systemic availability of carvedilol when administered with rifampicin.
- With insulin or oral hypoglycaemics may lead to their effects being increased. Regular blood glucose monitoring is recommended as hypoglycaemic signs and symptoms are either hidden or aggravated.
- May lead to an increase in carvedilol plasma levels when administered with hydralazine and alcohol as they are metabolised by the liver.
- May result in the synergism of effects when administered with diltiazem.
- With medicines that lead to catecholamine depletion; e.g., reserpine, or adrenergic neuron blocking agents like guanethidine or bethanidine may lead to hypotension and/or severe bradycardia. These patients should be closely monitored for these signs and symptoms.
- With beta-adrenoreceptor stimulating agents; e.g., isoprenaline could result in diminished carvedilol effects.
- With alpha-adrenoreceptor stimulating agents such as noradrenaline or agents with both alpha- and beta-adrenoreceptor stimulating properties such as adrenaline may lead to increased peripheral vasoconstrictor effects and reversal of the hypotensive effects of carvedilol; bradycardia could occur.

Caution should be exercised when carvedilol is administered with:-

- Calcium antagonist, especially verapamil. This particular combination is contra-indicated in patients with disturbed heart function.
- Myocardial depressant agents including anti-arrhythmic like quinidine, disopyramide, lignocaine, procainamide and phenytoin due to the probability of increased AV conduction time and a negative inotropic effect.

Other:

- In patients undergoing anaesthesia, carvedilol use has not been established. It is recommended that carvedilol therapy be discontinued at least 48 hours before anaesthesia.

- When clonidine and carvedilol therapy are discontinued simultaneously, it is recommended that carvedilol be withdrawn first followed by a gradual decrease of the clonidine dosage a few days after.

## **PREGNANCY AND LACTATION**

*Pregnancy:* Safety has not been established.

*Lactation:* As carvedilol is excreted into breast milk, it should not be administered when breastfeeding.

## **DOSAGE AND DIRECTIONS FOR USE:**

Tablets should be taken after meals. Treatment should be started with low doses, and gradually titrated upwards until an optimal effect is achieved.

### Essential Hypertension:

*Adults:* The initial recommended dose is 12,5 mg once daily for the first 2 days. Dosage is then increased to 25 mg daily thereafter.

Combination with a diuretic may assist in attaining the desired clinical response.

*Elderly:* The initial recommended dose is 12,5 mg once daily. If the clinical response is inadequate, the dose should be increased at 14 day intervals up to 25 mg once daily or in divided doses.

The incidence of side-effects increases significantly with doses higher than 25 mg with only a slight increase in efficacy.

### Symptomatic Congestive Heart failure:

CARVETREND should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Dosage must be individualised and closely monitored by a medical practitioner experienced in the management of heart failure, during up-titration.

Patients on concomitant digitalis, diuretics and ACE-inhibitors should have dosing stabilised for these medicines before initiating treatment with CARVETREND.

Treatment should be initiated with 3,125 mg twice a day for at least 14 days; if this dose is tolerated, the dosage should be increased at intervals of not less than 14 days to 6,25 mg twice a day, 12,5 mg twice a day and then 25 mg twice a day.

Maximum recommended dose for patients weighing:

- less than 85 kg is 25 mg twice a day and
- more than 85 kg is 50 mg twice a day.

The medical practitioner should assess the patient for symptoms of worsening heart failure or vasodilation before the dose increments. The diuretic should be increased to treat the transient

worsening heart failure or fluid retention; sometimes lowering the CARVETREND dose or temporary discontinuing CARVETREND may be necessary. When treatment of CARVETREND has been discontinued for longer than 14 days, the dosage regimen should be initiated from the starting point reflected above. Reduction of the diuretic dose may assist in the management of vasodilation symptoms (such as dizziness, headache and postural hypotension). The ACE-inhibitor dose may be reduced if symptoms continue. If necessary, the CARVETREND dose may be reduced.

CARVETREND dose should not be increased until the symptoms of worsening heart failure or vasodilation have been stabilised.

Elderly:

Carvedilol plasma levels are approximately 50% higher in elderly subjects when compared to young subjects; appropriate dosage adjustment should be made.

Cirrhosis:

Carvedilol plasma levels are 5 times higher in patients with liver cirrhosis than in healthy subjects; appropriate dosage adjustment should be made.

**SIDE-EFFECTS AND SPECIAL PRECAUTIONS:**

With the exception of bradycardia, abnormal vision and dizziness; the adverse event frequency is not dose dependent. These effects are usually mild, short-term and usually occur at the beginning of treatment.

Gastro-intestinal disorders:

Vomiting, nausea, diarrhoea, abdominal pain, infrequently constipation are commonly reported.

Vascular disorders:

Oedema of the legs, dependent and genital oedema, peripheral, generalised, fluid overload and hypervolaemia are commonly reported. Pain in the extremities is commonly reported.

Cardiac disorders:

Hypotension, bradycardia, postural hypotension are commonly reported. The latter has mainly been observed on product initiation or when the dose is increased but the occurrence is reduced when the product is used as recommended.

AV block, cardiac failure during dosage increase, syncope, angina pectoris or progression of heart failure is reported less frequent.

It has been reported that the frequency of side-effects are lower in hypertensive patients treated with CARVETREND than in congestive heart failure.

Blood and lymphatic system disorders:

Thrombocytopenia and hypercholesterolaemia are commonly reported. Reduced peripheral circulation, Raynaud's phenomenon or symptom exacerbation of intermittent claudication is reported less frequent. Leucopenia and changes in serum transaminases have been reported in isolated cases.

Endocrine disorders:

Hyperglycaemia (patients with pre-existing diabetes mellitus) is commonly reported. It is possible for latent diabetes mellitus to become evident and existing diabetes to be exacerbated due to the beta-blocking properties of CARVETREND.

Respiratory, thoracic and mediastinal disorders:

Asthma and dyspnoea in predisposed patients are commonly reported. Flu-like symptoms, stuffy nose and wheezing are reported less frequent.

Eye disorders:

Vision abnormalities and reduced lacrimation are commonly reported. Eye irritation, disturbed vision has been reported less frequently.

Renal and urinary disorders:

Renal abnormalities in patients with diffuse vascular disease and/or impaired function, micturition disturbances and acute renal failure are reported less frequently.

Skin and subcutaneous tissue disorders:

Existing lesions can be aggravated, psoriatic skin lesions may occur, isolated or less frequently skin reactions, e.g., pruritis, urticaria, lichen planus-like reactions and allergic exanthema are reported less frequent.

Nervous system disorders:

Commonly fatigue and headache have been reported.

Dizziness is very commonly reported.

Sleep disturbances, depressed mood and paraesthesia are reported less frequent.

Reproductive system and breast disorders:

Sexual impotence has been reported in less frequently.

Metabolism and nutrition disorders:

Weight increase is commonly reported.

Other:

Dryness of the mouth and has been reported in less frequent cases.

**Precautions:**

If patients experience dizziness or related symptoms, they should be advised not to operate any machinery or drive.

### Congestive Heart failure:

When symptoms of worsening cardiac effects or fluid retention occur during dosage increase, the diuretic dose should be increased. CARVETREND dose should not be increased until the symptoms have been stabilised. It may be necessary to reduce the dose of CARVETREND or temporarily discontinue its use.

As both CARVETREND and digitalis slow AV conduction, CARVETREND should be used with caution in patients who are controlled with digitalis, diuretics and/or ACE-inhibitor treatment.

### Bradycardia:

CARVETREND may cause bradycardia. If the pulse rate is below 55 beats per minute, CARVETREND dosage should be decreased.

### Ischaemic heart disease:

In these patients, treatment should not be abruptly discontinued but should instead be over a period of 7 to 14 days.

### Renal insufficiency:

As CARVETREND is metabolised mainly by the hepatic route, no dosage adjustments is necessary.

However, in patients with congestive heart failure (CHF) having low blood pressure (systolic < 100 mmHg), diffuse vascular disease, ischaemic heart disease and/or an underlying renal insufficiency, reversible deterioration of renal function has been observed.

Given these risk factors in patients with congestive heart failure, monitoring of renal function during dosage adjustment is advised. If worsening of renal function occurs, CARVETREND treatment should be discontinued or the dosage reduced.

### Diabetes mellitus:

CARVETREND should be used with care in diabetes mellitus patients as the early warning symptoms and signs of acute hypoglycaemia could be enhanced or masked.

In diabetics with CHF, worsening control of blood glucose may be accompanied with CARVETREND.

Therefore when CARVETREND therapy is initiated or even during dosage adjustment, regular monitoring of blood glucose is essential and hypoglycaemia treated accordingly.

### Pulmonary:

In patients with chronic obstructive pulmonary disease (COPD) with a bronchospastic element, CARVETREND treatment is not recommended.

Where the benefit outweighs the risk in patients not requiring oral or inhaled treatment for their bronchospastic disease, CARVETREND has been initiated.

However, when CARVETREND therapy is initiated or even during dosage adjustment, the patient should be closely monitored. Treatment should be discontinued or even reduced if bronchospasm is observed.

Thyrotoxicosis: Symptoms may be masked by CARVETREND.

Raynaud's phenomenon: Symptoms may be exacerbated.

Contact lens wearers: The possibility of reduced lacrimation should be borne in mind.

Phaeochromocytoma: Treatment should be initiated with alpha-blocking agents before using any beta-blocking agent. There is currently no documented evidence with CARVETREND use in this condition, despite CARVETREND displaying pharmacological properties of alpha- and beta-blockers.

Peripheral vascular disease: As beta-blockers can accelerate or exacerbate arterial insufficiency symptoms, CARVETREND should be used with caution.

Prinzmetal's angina: Medicines having non-selective beta-blocking activity can aggravate chest pains in patients with Prinzmetal's variant angina. Caution should be exercised when initiating CARVETREND treatment in patients suspected of having Prinzmetal's angina as there is no documented evidence of its use in this condition.

Other: Intravenous administration of 1 - 2 mg atropine can be used for protection against vagal influences.

#### **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

Symptoms may include bradycardia, severe hypotension, heart failure, cardiogenic shock and cardiac arrest. Vomiting, bronchospasm, respiratory problems, disturbed consciousness and generalized seizures have also been observed.

Treatment of overdose:

The patient must be kept under observation preferably under intensive care conditions where necessary.

The patient should be made to lie down, to improve brain blood supply. The stomach may be emptied by emesis or lavage shortly after the medicine is ingested.

Intravenous injection of atropine up to 3 mg should be used to treat the bradycardia immediately. Sympathomimetics such as dobutamine, isoprenaline, adrenaline or orciprenaline, based on body mass and effect, may be used. When further measures are deemed necessary, it is recommended that noradrenaline be preferred to isoprenaline in order to restore circulation. The recommended initial dose of noradrenaline is intravenous 5 µg to 10 µg and repeated accordingly to the patient's response; alternatively use an IV infusion at 5 µg/minute till a satisfactory clinical response is achieved. Glucagon may be preferred in severe overdose. The recommended

starting dose is 1 mg – 10 mg intravenously followed by a 2 mg - 2,5 mg per hour as a long-term infusion to sustain heart function.

Norfenephrine or noradrenaline may be administered while continuously evaluating the circulatory conditions in cases where intoxication is dominated by peripheral vasodilation.

When bradycardia is resistant to therapy, therapy with a pacemaker should be considered.

Beta-sympathomimetics (IV and/or aerosol) should be used for bronchospasm.

IV injection of clonazepam or diazepam is recommended for seizures.

In cases where there are symptoms of shock during severe intoxication, antidote treatment should be continued for a relatively long period due to the elimination of carvedilol from its binding sites.

**IDENTIFICATION:**

CARVETREND 6,25 mg: A white, round, slightly biconvex, bevelled edge tablet

CARVETREND 12,5 mg: A white, round, slightly biconvex, bevelled edge tablet, with a dividing cross on one side.

CARVETREND 25 mg: A white, round, slightly biconvex tablets, bevel-edged, one side scored.

**PRESENTATION:**

CARVETREND 6,25 mg is available in red PVC/PVDC and Aluminium foil blister packs of 30 tablets

CARVETREND 12,5 mg is available in red PVC/PVDC and Aluminium foil blister packs of 30 tablets.

CARVETREND 25 mg in available in red PVC/PVDC and Aluminium foil blister packs of 30 tablets.

**STORAGE INSTRUCTIONS:**

Store in a cool (below 25°C), dry place.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBERS:**

CARVETREND 6,25 mg: 37/7.1.3/0276

CARVETREND 12,5 mg: 37/7.1.3/0277

CARVETREND 25 mg: 37/7.1.3/0278

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

Pharma Dynamics (Pty) Ltd.

F02 Grapevine House

Steenberg Office Park

WESTLAKE

7945



**Carvetrend 6,25 mg**

**Carvetrend 12,5 mg**

**Carvetrend 25 mg**

**SKEDULERINGSSTATUS:**

S3

**EIENDOMSNAAM EN DOSEERVORM:**

Carvetrend 6,25 mg tablet

Carvetrend 12,5 mg tablet

Carvetrend 25 mg tablet.

**SAMESTELLING:**

Elke Carvetrend 6,25 mg tablet bevat 6,25 mg karvedilol.

Elke Carvetrend 12,5 mg tablet bevat 12,50 mg karvedilol.

Elke Carvetrend 25 mg tablet bevat 25,00 mg karvedilol.

**FARMAKOLOGIESE KLASSIFIKASIE:**

A:7.1.3 Ander hipotensie middels.

**FARMAKOLOGIESE WERKING:**

In dieselfde dosisreikwydte toon karvedilol beide nie-selektiewe beta-blokkerende eienskappe en tree dit op as 'n **antihipertensie** middel wat vasodilatasie eienskappe besit.

Karvedilol is 'n kompeterende, nie-selektiewe antagonist van beta<sub>1</sub>- en beta<sub>2</sub>-adrenoreseptore; soos gedemonstreer in beide *in vitro* en *in vivo* dierestudies.

Die middel se beta-blokkerende aktiwiteit lei tot 'n verlaging van perifere vaskulêre weerstand deur onderdrukking van die renien-angiotensien-aldosteroonsisteem en vasodilatasie. Selektiewe blokkade van alfa<sub>1</sub>-adrenoreseptore is hoofsaaklik verantwoordelik vir vasodilatasie.

Karvedilol besit geen intrinsieke simpatomimetiese aktiwiteit nie.

Die farmakologiese werking van karvedilol in **kongestiewe hartversaking** is nie vasgestel nie.

Sien INDIKASIES vir besonderhede.

**Farmakokinetika:**

Karvedilol ondergaan ekstensiewe presistemiese hepatiese metabolisme wat 'n lae en wisselende absolute biobesikbaarheid van 25% tot gevolg het. Metabolisme is hoofsaaklik hepaties. Liniêre korrelasie tussen dosis en serumkonsentrasie is waargeneem.

Karvedilol word ekstensief (ongeveer 98%) gebind aan plasmaproteïen (primêr alfa-suurglikoproteïene en ook albumien).

Die gemiddelde eliminasië halfleeftyd is 6 tot 10 uur.

Die tempo van absorpsie (tyd totdat maksimum serumkonsentrasie bereik word), maar nie die mate van absorpsie (biobeskikbaarheid), word deur voedsel verlaag.

Eliminasië is hoofsaaklik biliêr.

Dosisaanpassing in pasiënte met nierinkorting is nie nodig nie.

Piek plasmakonsentrasies van karvedilol en biobeskikbaarheid is beduidend verhoog in pasiënte met ernstige lewerinkorting, en dit word dus nie in hierdie pasiënte aanbeveel nie (sien KONTRA-INDIKASIES).

### **INDIKASIES:**

Carvetrend word aangedui vir die behandeling van:

- ❖ Essensieel ligte tot matige hipertensie.
- ❖ Ligte tot matige stabiele simptomaties kongestiewe hartversaking wat óf deur kardiomiopatie, óf iskemie veroorsaak word. Gebruik as 'n byvoeging tot standaard terapie. Die middel is al gebruik in pasiënte wat nie vir AOE (angiotensien-omsettingsensiem)-inhibeerders tolerant is nie. Dit is ook al gebruik in pasiënte wat op digitalis terapie is, al dan nie.

### **KONTRA-INDIKASIES:**

Hipersensitiwiteit teenoor enigeen van die bestanddele.

Brongiale asma, chroniese obstruktiwepulmonale siekte, ernstige bradikardie (< 50 spm), siek-sinus-sindroom insluitend sino-arteriële blok, tweede of derde graad atrioventrikulêre blok, onstabiele hartversaking, gedekompenseerde hartversaking (Nieu York Hart Assosiasie (NYHA) klas IV wat intraveneuse inotropiese ondersteuning noodsaak), kardiogeniese skok, lewerinkorting wat klinies manifesteer, en ernstige hipotensie (sistoliese BD <85 mmHg.)

*Kinders:* Veiligheid is nie vasgestel nie.

### **WAARSKUWINGS:**

Gebruik met uiterste versigtigheid in pasiënte met kongestiewe hartversaking wat in die verlede toereikende kliniese beheer bereik het.

Feochromositoom pasiënte moet eers met alfa-blokkeerders beheer word alvorens CARVETREND-behandeling ingestel word.

Gebruik versigtig in pasiënte met nierinkorting.

Moenie in pasiënte met obstruktiwepulmonale siektes, brongospasma, of allergiese toestande wat die lugweë betrek (byvoorbeeld, glottis edeem, allergiese rinitis) gebruik nie.

Moenie in pasiënte met metaboliese asidose, gedeeltelike hartblok, of sinus bradikardie gebruik

nie.

## **INTERAKSIES:**

Gelyktydige toediening van karvedilol:

- Mag potensiëring van die effek veroorsaak wanneer dit saam met ander antihipertensie middels of medisyne wat hipotensie as 'n nuwe-effek veroorsaak, gebruik word.
- Mag 'n verhoging van ongeveer 16% in ewewigstoestand digoksien trog-konsentrasies in hipertensiewe pasiënte veroorsaak. Digoksienvlakke behoort gemoniteer te word wanneer karvedilolterapie begin, aangepas of gestaak word.
- Mag 'n verhoging van sistemiese biobeskikbaarheid (ongeveer 30%) van karvedilol veroorsaak sonder om  $K_{maks}$  te beïnvloed nie, wanneer dit saam met simetidien toegedien word.
- Mag verminderde sistemiese beskikbaarheid van karvedilol veroorsaak wanneer dit met rifampisien toegedien word.
- Met insulien of orale hipoglisemiese middels mag dit hulle uitwerkings verhoog. Gereelde monitering van bloedglukose word aanbeveel omdat hipoglisemiese tekens en simptome of versluier of vererger word.
- Mag lei tot 'n verhoging in die plasmavlakke van karvedilol wanneer dit saam met hidralasien en alkohol toegedien word, aangesien hierdie middels deur die lewer gemetaboliseer word.
- Mag sinergisme van uitwerkings veroorsaak wanneer dit saam met diltiasem toegedien word.
- Met medisyne wat tot uitputting van katesjolinamien lei, bv. reserpien, of blokkeerders van adrenergiese neurone, soos kwanetidien of betanidien, kan dit tot hipotensie en/of ernstige bradikardie lei. Hierdie pasiënte moet word vir hierdie tekens en simptome versigtig gemoniteer word.
- Met beta-adrenoreseptor-stimulerende middels, bv. isoprenalien, kan dit lei tot verminderde karvediloluitwerkings.
- Met alfa-adrenoreseptor-stimulerende middels soos noradrenalin of middels met beide alfa- en beta-adrenoreseptor-stimulerende eienskappe soos adrenalin, kan dit lei tot verhoogde perifere vasokonstriksie effekte en omkering van die hipotensiewe uitwerkings van karvedilol; bradikardie kan moontlik voorkom.

Omsigtigheid moet uitgeoefen word as karvedilol toedien word met:

- Kalsiumantagonis, veral verapamiel. Hierdie spesifieke kombinasie is teenaangedui in pasiënte met versteurde hartfunksie.
- Middels wat die miokardium onderdruk, insluitend anti-aritmiese middels, soos kinidien, disopiramied, lignokaïen, prokaïenamied en fenitoïen, as gevolg van die waarskynlikheid van verhoogde AV-geleidingstyd en 'n negatiewe inotropiese uitwerking.

Ander:

- Die gebruik van karvedilol in pasiënte wat narkose ondergaan, is nie vasgestel nie. Dit word aanbeveel dat karvedilolterapie ten minste 48 uur voor narkose gestaak word.
- Wanneer klonidien-en karvedilolterapie gelyktydig gestaak word, word dit aanbeveel dat karvedilol eerste onttrek word, gevolg deur 'n geleidelike vermindering van die klonidiendosering 'n paar dae later.

## **SWANGERSKAP EN LAKTASIE**

*Swangerskap:* Veiligheid is nie vasgestel nie.

*Laktasie:* Omdat karvedilol in borsmelk uitgeskei word, behoort dit nie tydens borsvoeding toegedien te word nie.

## **DOSIS EN GEBRUIKSAANWYSINGS:**

Tablette behoort na maaltye geneem te word. Behandeling moet begin word met lae dosis en geleidelik opwaarts getitreer word totdat 'n optimale uitwerking verkry is.

### Essensiële Hipertensie:

*Volwassenes:* Die aanvanklike aanbevole dosis is 12,5 mg een keer per dag vir die eerste 2 dae. Dosering word daarna verhoog tot 25 mg per dag.

Kombinasie met 'n diuretikum mag help om die gewenste kliniese respons te verkry.

*Bejaardes:* Die aanvanklike aanbevole dosis is 12,5 mg een keer per dag. Indien die kliniese reaksie onvoldoende is, behoort die dosis met tussenposes van 14 dae na 25 mg een keer per dag of in verdeelde dosis, verhoog te word.

Die voorkoms van nuwe-effekte verhoog beduidend met dosis hoër as 25 mg terwyl doeltreffendheid slegs effens toeneem.

### Simptomatiese Kongestiewe Hartversaking:

CARVETREND moet met voedsel geneem word om die tempo van absorpsie te verlaag en die voorkoms van ortostatiese uitwerkings te verminder.

Tydens opwaartse titrasie moet dosering individueel toegepas, en versigtig gemoniteer word deur 'n mediese praktisyn wat ondervinding in die beheer van hartversaking het.

Pasiënte wat gelyktydig digitalis, diuretika en AOE-inhibeerders ontvang, behoort eers stabilisering van dosering vir hierdie medisyne te bereik alvorens behandeling met CARVETREND begin word.

Behandeling behoort met 3,125 mg twee keer per dag vir ten minste 14 dae begin te word; indien hierdie dosis verdra word, moet die dosering met intervalle van nie minder as 14 dae verhoog word tot 6,25 mg twee keer per dag, 12,5 mg twee keer per dag, en dan 25 mg twee keer per dag.

Die maksimum aanbevole dosis vir pasiënte wat:

- minder as 85 kg weeg, is 25 mg twee Keer per dag en
- meer as 85 kg weeg, is 50 mg twee keer per dag.

Die mediese praktisyn behoort die pasiënt vir simptome van agteruitgaande hartversaking of vasodilatasie te kontroleer voor die dosisinkremente. Die diuretikum behoort verhoog te word om die verbygaande agteruitgaande hartversaking of vloeistofretensie te behandel; in sommige gevalle mag verlaging van die dosis CARVETREND of tydelike staking van CARVETREND nodig blyk te wees. Wanneer behandeling met CARVETREND vir langer as 14 dae gestaak is, behoort die doseringsregimen van bogenoemde beginpunt ingestel te word. Vermindering van die diuretikumdosis mag help met die beheer van vasodilatasie simptome (soos duiseligheid, hoofpyn en posturale hipotensie). Die dosis AOE-inhibeerder kan verlaag word indien simptome aanhou. Indien nodig mag die CARVETREND-dosis verminder word. Die CARVETREND-dosis behoort nie verhoog te word totdat die simptome van agteruitgaande hartversaking of vasodilatasie gestabiliseer is nie.

#### Bejaardes:

Plasmavlakke van karvedilol is ongeveer 50% hoër in bejaarde persone as dit met jong persone vergelyk word; geskikte dosisaanpassing behoort gemaak te word.

#### Sirroose:

Plasmavlakke van karvedilol is 5 keer hoër in pasiënte met sirroose van die lewer as in gesonde persone; geskikte dosisaanpassing behoort gemaak te word.

#### **NEWE-EFFEKTE EN SPESIALE VOORSORGMATREËLS:**

Met die uitsondering van bradikardie, abnormale visie en duiseligheid, is die frekwensie van nadelige insidente nie dosisafhanklik nie. Hierdie uitwerkings is gewoonlik lig, kort van duur en kom dit gewoonlik aan die begin van behandeling voor.

#### Gastroïntestinale siektes:

Braking, naarheid, diarree, abdominale pyn, en hardlywigheid in seldsame gevalle, word algemeen aangemeld.

#### Vaskulêre siektes:

Edeem van die bene, afhanklike en genitale edeem, perifere, veralgemeende vloeistof-oorbelading en hipovolemie word algemeen aangemeld. Pyn in die ekstremitate word algemeen aangemeld.

#### Hartsiektes:

Hipotensie, bradikardie, posturale hipotensie word algemeen aangemeld. Laasgenoemde is meestal waargeneem toediening van die produk begin word, of wanneer die dosis verhoog word,

maar wanneer die produk soos aanbeveel gebruik word, is die voorkoms verlaag.

AV-blok, hartversaking tydens dosisverhoging, sinkopee, angina pectoris of progressie van hartversaking word minder dikwels aangemeld.

Daar word gerapporteer dat die frekwensie van nuwe-effekte in hipertensiewe pasiënte wat met CARVETREND behandel word, laer as in kongestiewe hartversaking is.

#### Siektes van die bloed en limfatiese sisteem:

Trombositopenie en hipercholesterolemie word algemeen aangemeld. Verminderde perifere sirkulasie, Raynaud-siekte of verergering van simptome van intermitterende kloudikasie word minder dikwels gerapporteer. Leukopenie en veranderinge in serumtransaminases is in geïsoleerde gevalle aangemeld.

#### Endokriene siektes:

Hiperglisemie (pasiënte met voorafbestaande diabetes mellitus) word algemeen aangemeld. Dit is moontlik dat latente diabetes mellitus te voorskyn sal tree en bestaande diabetes sal vererger word as gevolg van die beta-blokkerende eienskappe van CARVETREND.

#### Respiratories, torakaal en mediastinale siektes:

Asma en dispnee in vatbare pasiënte word algemeen aangemeld. Griep-agtige simptome, toe neus en hyg word minder dikwels gerapporteer.

#### Oogsiektes:

Visie abnormaliteite en verminderde traanafskieding word algemeen aangemeld. Oogirritasie, versteurde visie is minder dikwels gerapporteer.

#### Renale en urinêre siektes:

Renale abnormaliteite in pasiënte met diffuse vaskulêre siekte en/of ingekorte funksie, mikturisie versteurings en akute nierversaking word minder dikwels gerapporteer.

#### Siektes van die vel en subkutane weefsel:

Bestaande letsels kan vererger word, psoriatiese velletsels kan voorkom, geïsoleerde of minder frekwente velreaksies, bv. pruritus, urtikarie, lichen-planus-agtige reaksies en allergiese eksanteem word minder dikwels gerapporteer.

#### Siektes van die senusisteem:

Moegheid en hoofpyn is dikwels aangemeld.

Duiseligheid word baie algemeen gerapporteer.

Slaapsteurnisse, depressiewe luim en parestesie word minder dikwels aangemeld.

#### Siektes van die voortplantingsisteem en bors:

Seksuele impotensie is minder dikwels aangemeld.

#### Metaboliese en voedingsiektes:

Gewigstoename word algemeen gerapporteer.

#### Ander:

Droë mond is in seldsame gevalle aangemeld.

### **Voorsorgmaatreëls:**

Indien pasiënte duiseligheid of verwante simptome ondervind, moet hulle aangeraai word om nie masjiene te gebruik of motor te bestuur nie.

Kongestiewe Hartversaking:

Wanneer simptome van agteruitgaande kardiaale uitwerkings of vloeistofretensie tydens dosisverhogings voorkom, behoort die diuretikumdosis verhoog te word. Die dosis CARVETREND moet nie verhoog word totdat die simptome gestabiliseer is nie. Dit mag nodig wees om die dosis CARVETREND te verminder of om die gebruik daarvan tydelik te staak.

Omdat beide CARVETREND en digitalis AV-geleiding vertraag, behoort CARVETREND met omsigtigheid gebruik te word in pasiënte wat met digitalis, diuretika en/of AOE-inhibeerders beheer word.

Bradikardie:

CARVETREND mag bradikardie veroorsaak. Indien die polsslag laer as 55 slae per minuut is, moet die dosis CARVETREND verminder word.

Iskemiese hartsiekte:

In hierdie pasiënte behoort behandeling nie plotseling gestaak te word nie, maar moet in plaas daarvan moet dit oor 'n tydperk van 7 tot 14 dae gestaak word.

Nierontoereikendheid:

Omdat CARVETREND hoofsaaklik deur die hepatiese roete gemetaboliseer word, is geen dosisaanpassings nodig nie.

In pasiënte met kongestiewe hartversaking (KHV) met lae bloeddruk (sistolies <100 mmHg), diffuse vaskulêre siekte, iskemiese hartsiekte en/of onderliggende nierontoereikendheid, is omkeerbare verslegting van nierfunksie egter waargeneem.

In die lig van hierdie risikofaktore in pasiënte met kongestiewe hartversaking, word monitering van nierfunksie tydens dosisaanpassing aanbeveel. Indien nierfunksie sou versleg, behoort CARVETREND-behandeling gestaak, of die dosis verlaag te word.

Diabetes mellitus:

CARVETREND moet met omsigtigheid gebruik word in pasiënte met diabetes mellitus aangesien die vroeë waarskuwingssimptome en -tekens moontlik versterk of versluier mag word.

In diabete met KHV kan verergering van bloedglukose met CARVETREND voorkom.

Dus is gereelde monitering van bloedglukose essensieel wanneer CARVETREND-terapie begin word, of selfs tydens dosisaanpassing, en hipoglisemie moet dienooreenkomstige behandel word.

Pulmonaal:

CARVETREND-behandeling in pasiënte met chroniese obstruktiwe pulmonale siekte (COPS) met 'n brongospasma-element, word nie aanbeveel nie.

Waar die voordele die risiko oortref in pasiënte wat geen orale of ingeasemde behandeling vir hulle brongospastiese siekte benodig nie, is CARVETREND egter al gebruik.

Die pasiënt moet egter versigtig gemoniteer word wanneer CARVETREND-terapie begin word, en selfs as dosisaanpassing plaasvind. Behandeling moet gestaak of selfs verminder word indien brongospasma waargeneem word.

Tirotoksikose: Simptome mag deur CARVETREND versluier word.

Raynaud-siekte: Simptome mag vererger word.

Draers van kontaklense: Die moontlikheid van verminderde traanafskieding moet in gedagte gehou word.

Feochromositoom: Behandeling met alfa-blokkeerders behoort ingestel te word voordat enige beta-blokkeerder gebruik word. Daar bestaan teenswoordig geen gedokumenteerde inligting oor die gebruik van CARVETREND in hierdie toestand nie, ten spyte van die feit dat CARVETREND farmakologiese eienskappe van alfa- en beta-blokkeerders openbaar.

Perifere vaskulêre siekte: Omdat beta-blokkeerders die simptome van arteriële ontoereikendheid kan versnel of vererger, moet CARVETREND met omsigtigheid gebruik word.

Prinzmetal-angina: Medisyne wat nie-selektiewe beta-blokkerende aktiwiteit besit, kan borspyn in pasiënte met die Prinzmetal-angina variant veroorsaak. Omsigtigheid moet gebruik word wanneer CARVETREND-behandeling begin word in pasiënte wat vermoedelik Prinzmetal-angina het, omdat geen gedokumenteerde inligting oor hierdie middel se gebruik in hierdie toestand beskikbaar is nie.

Ander: Intraveneuse toediening van 1-2 mg atropien kan vir beskerming teen vagus-invloede gebruik word.

**BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:**

Simptome kan bradikardie, ernstige hipotensie, hartversaking, kardiogeniese skok en hartarres insluit. Braking, brongospasma, respiratoriese probleme, bewussynversteurings en veralgemeende aanvalle is ook al waargeneem.

**Behandeling van oordosering:**

Die pasiënt moet liefers onder intensiewe sorg toestande onder observasie gehou word, as dit nodig is.

Die pasiënt moet gaan lê om die bloedvoorsiening aan die brein te verbeter. Kort na inname van die medisyne kan die maag met emese of spoeling geledig word.

Intraveneuse inspuiting van atropien tot soveel as 3 mg, moet onmiddellik gebruik word om die

bradikardie te behandel. Simpatomimetika soos dobutamien, isoprenalien, adrenalien of orsiprenalien gegrond op liggaamsmassa en effek kan gebruik word. Wanneer addisionele maatreëls nodig geag word, word dit aanbeveel dat noradrenalinieëls liever as isoprenalien gebruik word om sirkulasie te herstel. Die aanbevole aanvangsdosis noradrenalinieëls is 5 µg tot 10 µg intraveneus wat volgens die pasiënt se reaksie herhaal word; as alternatief kan 'n IV-infusie van 5 µg/minuut gebruik word totdat 'n bevredigende kliniese respons bereik is. Glukagon mag in gevalle van ernstige oordosering verkies word. Die aanbevole aanvangsdosis is 1 mg -10 mg intraveneus, gevolg deur 2 mg - 2,5 mg per uur as 'n langtermyn infusie om hartfunksie te onderhou.

Nor-fenedrien of noradrenalinieëls kan toegedien word terwyl die sirkulatoriese toestande gedurig geëvalueer word in gevalle waar bedwelming deur perifere vasodilatasie oorheers word.

Wanneer bradikardie nie op terapie wil reageer nie, moet terapie met 'n pasaangeërd oorweeg word.

Beta-simpatomimetika (IV en/of aërosol) behoort vir brongospasma gebruik te word.

IV-inspuiting van klonasepam of diasepam word vir aanvalle aanbeveel.

In gevalle waar simptome van skok tydens ernstige bedwelming voorkom, moet behandeling met teenmiddel vir 'n relatief lang tydperk voortgesit word, omdat karvedilol van sy bindingsplekke verwyder word.

#### **IDENTIFIKASIE:**

CARVETREND 6,25 mg: 'n Wit, ronde, effens bikonvekse, afgeskuinste tablet

CARVETREND 12,5 mg: 'n Wit, ronde, effens bikonvekse, afgeskuinste tablet, met 'n skeidskruis aan die ander kant.

CARVETREND 25 mg: 'n Wit, ronde, effens bikonvekse tablet, met afgeskuinste kante, waarvan een kant gekeep is.

#### **AANBIEDING:**

CARVETREND 6,25 mg is beskikbaar in rooi PVC/PVDC en Aluminiumfoelie stulpverpakkings van 30 tablette.

CARVETREND 12,5 mg is beskikbaar in rooi PVC/PVDC en Aluminiumfoelie stulpverpakkings van 30 tablette.

CARVETREND 25 mg is beskikbaar in rooi PVC/PVDC en Aluminiumfoelie stulpverpakkings van 30 tablette.

#### **BERGINGSANWYSINGS:**

Bewaar op 'n koel (benede 25 °C), droë plek.

HOU BUITE BEREIK VAN KINDERS.

#### **REGISTRASIENOMMERS:**

CARVETREND 6,25 mg: 37/7.1.3/0276

CARVETREND 12,5 mg: 37/7.1.3/0277

CARVETREND 25 mg: 37/7.1.3/0278

**NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT:**

Pharma Dynamics (Edms) Bpk

F02 Grapevine House

Steenberg Office Park

WESTLAKE

7945

**DATUM VAN PUBLIKASIE VAN HIERDIE VOUJILJET:** 16 September 2004.