Carvedilol + Ivabradine

CARIVALAN®

6.25 mg/5 mg 6.25 mg/7.5 mg
12.5 mg/5 mg 12.5 mg/7.5 mg
25 mg/5 mg 25 mg/7.5 mg

Film-coated tablets

Beta Blocking Agent, Other Combination

DESCRIPTION:
6.25/5 mg: White, hexagonal, film-coated tablet (longest diagonal 7.3 mm) engraved with C12 on one face and on the other face.
6.25/7.5 mg: Yellow, hexagonal, film-coated tablet (longest diagonal 7.3 mm) engraved with C13 on one face and on the other face.
12.5/5 mg: White, elliptic, film-coated tablet (10.6 mm x 5.3 mm) engraved with C14 on one face and on the other face.
12.5/7.5 mg: Yellow, elliptic, film-coated tablet (10.6 mm x 5.3 mm) engraved with C15 on one face and on the other face.
25/5 mg: White, octagonal, film-coated tablet (diameter 7.8 mm) engraved with C16 on one face and on the other face.
25/7.5 mg: Yellow, octagonal, film-coated tablet (diameter 7.8 mm) engraved with C17 on one face and on the other face.

FORMULATION:
6.25/5 mg: Each film-coated tablet contains 6.25 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
Excipient with known effect: Lactose monohydrate 68.055 mg.
6.25/7.5 mg: Each film-coated tablet contains 6.25 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).
Excipient with known effect: Lactose monohydrate 65.360 mg.
12.5/5 mg: Each film-coated tablet contains 12.5 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
Excipient with known effect: Lactose monohydrate 78.710 mg.
12.5/7.5 mg: Each film-coated tablet contains 12.5 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).
Excipient with known effect: Lactose monohydrate 76.015 mg.
25/5 mg: Each film-coated tablet contains 25 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
Excipient with known effect: Lactose monohydrate 85.530 mg.
25/7.5 mg: Each film-coated tablet contains 25 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).
Excipient with known effect: Lactose monohydrate 82.835 mg.

PHARMACODYNAMICS AND PHARMACOKINETICS:
Pharmacodynamics:
Carvedilol
Carvedilol is a vasodilating non-selective beta-blocker, which reduces the peripheral vascular resistance by selective alpha 1-receptor blockade and suppresses the renin-angiotensin system through non-selective beta-blockade.
Plasma renin activity is reduced and fluid retention is rare.
Carvedilol has no intrinsic sympathomimetic activity. Like propranolol, it has membrane-stabilizing properties.
Carvedilol is a racemate of two stereoisomers. Both enantiomers were found to have alpha-adrenergic blocking characteristics in animal experiments. Non-selective beta1- and beta2- adrenoceptor blockade is attributed mainly to the S(-) enantiomer.
The antioxidant properties of carvedilol and its metabolites have been demonstrated in *in vitro* and *in vivo* animal studies and *in vitro* in a number of human cell types.
In hypertensive patients, a reduction in blood pressure is not associated with a concomitant increase in peripheral resistance, as observed with pure beta-blockers. The heart rate is slightly decreased. Stroke volume remains unchanged. Renal blood flow and renal function remain normal, as does peripheral blood flow. Therefore, cold extremities, which often occur with beta-blockers, are rarely seen. In hypertensive patients, carvedilol increases the plasma norepinephrine concentration.
In prolonged treatment of patients with angina pectoris, carvedilol has been seen to have an anti-ischemic effect and to alleviate pain. Hemodynamic studies have demonstrated that carvedilol reduces ventricular pre- and after-load.
In patients with left ventricular dysfunction or congestive heart failure, carvedilol has a favorable effect on hemodynamics and the left ventricular ejection fraction and its dimensions. Carvedilol reduces mortality and the need for cardiovascular hospitalization in patients with heart failure.
Carvedilol has no negative effect on the serum lipid profile or electrolytes. The ratio of high-density lipoproteins and low-density lipoproteins remains normal.

Ivabradine
Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarization in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarization.
Ivabradine can interact also with the retinal current I_h which closely resembles cardiac I_f. It participates in the temporal resolution of the visual system, by curtailing the retinal response to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of I_h by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field.
The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20 mg twice daily indicates a trend towards a plateau effect, which is consistent with a reduced risk of severe bradycardia below 40 bpm.
At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarization:
- in clinical electrophysiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals;
- in patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any deleterious influence on LVEF.

Pharmacokinetics:
The rate and extent of absorption of ivabradine and carvedilol from Carivalan are not significantly different, respectively, from the rate and extent of absorption of ivabradine and carvedilol when taken alone as monotherapy.

Carvedilol
Absorption: The absolute bioavailability of carvedilol administered orally is approximately 25%. Maximum plasma concentration is achieved approximately 1 hour after administration. There is a linear relationship between dose and plasma concentrations. In patients with a slow debrisoquine hydroxylation, carvedilol's plasma concentration increased by a factor of 2 to 3, compared with rapid metabolizers of debrisoquine. Food intake does not affect bioavailability, although it takes longer to reach maximum plasma concentration.
Distribution: Carvedilol is highly lipophilic. Plasma protein binding is about 98 to 99%. The distribution volume is around 2 L/kg. The first-pass effect after oral administration is around 60 - 75%.
Biotransformation: Carvedilol is extensively metabolized to various metabolites which are excreted primarily via bile. The first pass metabolism after oral administration is about 60-75%. The enterohepatic circulation of the parent substance has been demonstrated in animals.
Carvedilol is metabolized in the liver, mainly through oxidation of the aromatic ring and glucuronidation. Demethylation and hydroxylation at the phenol ring produce three active metabolites with beta-blocking activity. These three active metabolites have a weak vasodilating effect, compared with carvedilol. According to preclinical studies, the beta-blocking activity of the metabolite 4-hydroxyphenol is approximately 13 times higher than that of carvedilol. However, the metabolite concentrations in humans are about 10 times lower than that of carvedilol. Two of the carbazole-hydroxy metabolites of carvedilol are extremely potent antioxidants, making them 30 - 80 times stronger than carvedilol.
The oxidative metabolism of carvedilol is stereoselective. R-enantiomer is primarily metabolized by CYP2D6 and CYP1A2, while S-enantiomer is primary metabolized by CYP2C9 and to a lesser extent by CYP2D6. Other CYP450 isoenzymes participating in carvedilol metabolism include CYP3A4, CYP2E1 and CYP2C19. Maximum plasma concentration of R-carvedilol in plasma is approximately twice the concentration of S-carvedilol. R-enantiomer is metabolized mainly via hydroxylation. In the slow metabolizers of CYP2D6, an increase of carvedilol concentration in plasma may occur, mainly of the R-enantiomer, leading to the increase of the alpha-blocking activity.
Elimination: The average half-life of elimination of carvedilol varies between 6 and 10 hours. The plasma clearance is approximately 590 mL/min. Elimination is mainly via bile. Excretion is mainly via feces. A minor part is eliminated renally in the form of metabolites.
Special populations:
Elderly: The pharmacokinetics of carvedilol is dependent on age. Plasma carvedilol levels are around 50% higher in the elderly than in young people.
Hepatic impairment: In a study involving patients with liver cirrhosis, the bioavailability of carvedilol was four times higher and the maximum plasma concentration five times higher and the distribution volume three times higher than in healthy subjects.
Renal impairment: In some hypertensive patients with moderate (creatinine clearance 20-30 mL/min) or severe (creatinine clearance <20 mL/min) renal impairment, an increase in plasma carvedilol concentrations of approximately 40-55% was seen compared to patients with normal renal function. However, there was a large variation in the results.

Ivabradine
Under physiological conditions, ivabradine is rapidly released from tablets and is highly water-soluble (>10 mg/mL). Ivabradine is the S-enantiomer with no bioconversion demonstrated in vivo. The N-desmethylated derivative of ivabradine has been identified as the main active metabolite in humans.
Absorption and bioavailability: Ivabradine is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 hour under fasting condition. The absolute bioavailability of the film-coated tablets is around 40%, due to first-pass effect in the gut and liver.
Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30%. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure.
Distribution: Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100 L in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/mL (CV=29%). The average plasma concentration is 10 ng/mL (CV=38%) at steady state.
Biotransformation: Ivabradine is extensively metabolized by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative (S 18982) with an exposure about 40% of that of the parent compound. The metabolism of this active metabolite also involves CYP3A4. Ivabradine has low affinity for CYP3A4, shows no clinically relevant CYP3A4 induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Inversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations.

Elimination: Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. The total clearance is about 400 mL/min and the renal clearance is about 70 mL/min. Excretion of metabolites occurs to a similar extent via feces and urine. About 4% of an oral dose is excreted unchanged in urine.
Linearity/non linearity: The kinetics of ivabradine is linear over an oral dose range of 0.5 – 24 mg.

Special populations:
Elderly: no pharmacokinetic differences (AUC and C_{max}) have been observed between elderly (≥ 65 years) or very elderly patients (≥75 years) and the overall population.
Renal impairment: the impact of renal impairment (creatinine clearance from 15 to 60 mL/min) on ivabradine pharmacokinetic is minimal, in relation with the low contribution of renal clearance (about 20 %) to total elimination for both ivabradine and its main metabolite S 18982.
Hepatic impairment: in patients with mild hepatic impairment (Child Pugh score up to 7) unbound AUC of ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. Data are insufficient to draw conclusions in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment.
Pediatric population: The pharmacokinetic profile of ivabradine in pediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the pharmacokinetics described in adults when a titration scheme based on age and weight is applied.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship:
PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing ivabradine and S 18982 plasma concentrations for doses of up to 15-20 mg twice daily. At higher doses, the decrease in heart rate is no longer proportional to ivabradine plasma concentrations and tends to reach a plateau. High exposures to ivabradine that may occur when ivabradine is given in combination with strong CYP3A4 inhibitors may result in an excessive decrease in heart rate although this risk is reduced with moderate CYP3A4 inhibitors. The PK/PD relationship of ivabradine in pediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the PK/PD relationship described in adults.

INDICATIONS:
Carvedilol + Ivabradine (Carivalan) is indicated as substitution therapy in adult patients with normal sinus rhythm already controlled by ivabradine and carvedilol taken concomitantly at the same dose levels for:
- the symptomatic treatment of chronic stable angina pectoris in coronary artery disease patients,
- the treatment of chronic heart failure (II-IV NYHA-class) with systolic dysfunction.

DOSAGE AND ADMINISTRATION:
The recommended dose of Carvedilol + Ivabradine (Carivalan) is one tablet twice daily, once in the morning and once in the evening.
Carvedilol + Ivabradine (Carivalan) should only be used in patients controlled on stable doses of the individual components given concurrently when carvedilol and ivabradine are at the optimal dose.
The fixed dose combination is not suitable for initiation therapy.
If a change of posology is required, titration should be done with the individual components carvedilol and ivabradine, ensuring the patient is maintained at an optimal dose of carvedilol and ivabradine. It is recommended that the decision to titrate treatment takes place with the availability of serial heart measurements, ECG or ambulatory 24-hour monitoring.
If during treatment, heart rate decreases below 50 beats per minute at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, down titration should be done with the individual components carvedilol and ivabradine, ensuring the patient is maintained at an optimal dose of carvedilol and ivabradine. After dose reduction, heart rate should be monitored.
Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.

Renal impairment:
No dosage adjustment is required in patients with renal insufficiency and creatinine clearance above 15 mL/min and SBP >100 mmHg.
No data are available in patients with creatinine clearance below 15 mL/min. Carvedilol + Ivabradine (Carivalan) should be used with precaution in patients with creatinine clearance below 15 mL/min.
Monitoring of renal function is recommended in chronic heart failure patients with SBP <100 mmHg.

Hepatic impairment:
It may be necessary to adjust the dose in patients with mild to moderate hepatic impairment. Caution should be exercised in patients with moderate hepatic impairment.
Carvedilol + Ivabradine (Carivalan) is contraindicated in patients with severe hepatic impairment.

Elderly:
Carvedilol + Ivabradine (Carivalan) can be administered in elderly patients with caution.

Pediatric population:
The safety and efficacy of Carvedilol + Ivabradine (Carivalan) in children and adolescents have not been established. No data are available with Carvedilol + Ivabradine (Carivalan). The data with ivabradine is presented in Pharmacodynamics section.

Method of administration:
Oral use.
Carvedilol + Ivabradine (Carivalan) tablet should be taken twice daily during a meal.

CONTRAINDICATIONS:
- Hypersensitivity to the active substances or to any other beta-blockers or to any of the excipients;
- Severe hepatic impairment;
- Acute or unstable/decompensated heart failure;
- Unstable angina;
- Prinzmetal's angina;
- AV-block of 2nd and 3rd degree;
- Sick sinus syndrome (including sino-atrial block);
- Symptomatic or severe bradycardia (<50 bpm);
- Acute myocardial infarction;
- Cardiogenic shock;
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker);
- Severe peripheral vascular disease (e.g. Raynaud's phenomenon);
- Severe hypotension (systolic arterial blood pressure <90 mmHg, diastolic arterial blood pressure <50 mmHg);
- Chronic obstructive pulmonary disease associated with bronchial obstruction;
- History of bronchospasm or asthma;
- Metabolic acidosis;
- Untreated pheochromocytoma;
- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties;
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os,* josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone;
- Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Special warnings
Lack of benefit on clinical outcomes in patients with symptomatic chronic stable angina pectoris
Carvedilol + Ivabradine (Carivalan) is indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death).

Measurement of heart rate
Given that the heart rate may fluctuate considerably over time, serial heart rate measurements, ECG or ambulatory 24-hour monitoring should be considered when determining resting heart rate in patients on treatment with ivabradine when titration is considered. This also applies to patients with a low heart rate, in particular when heart rate decreases below 50 bpm, or after dose reduction.

Cardiac arrhythmias
Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (eg. ventricular or supraventricular tachycardia). Carvedilol + Ivabradine (Carivalan) is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function. In patients treated with ivabradine, the risk of developing atrial fibrillation is increased. Atrial fibrillation has been more common in patients using concomitantly amiodarone or potent class I anti-arrhythmics. It is recommended to regularly clinically monitor ivabradine treated patients for the occurrence of atrial fibrillation (sustained or paroxysmal), which should also include ECG monitoring if clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse).
Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued Carvedilol + Ivabradine (Carivalan) treatment should be carefully reconsidered.
Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely.

Use in patients with a low heart rate
Carvedilol + Ivabradine (Carivalan) must not be initiated in patients with a pre-treatment resting heart rate below 50 beats per minute.
If, during treatment with Carvedilol + Ivabradine (Carivalan), resting heart rate decreases persistently below 50 bpm or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, down titration should be done with the individual components ensuring the patient is maintained at an optimal dose of carvedilol and ivabradine or treatment discontinued.

Combination with calcium channel blockers
Concomitant use of Carvedilol + Ivabradine (Carivalan) with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated. No safety issue has been raised on the combination of ivabradine with nitrates and dihydropyridine calcium channel blockers such as amlodipine. Additional efficacy of ivabradine in combination with dihydropyridine calcium channel blockers has not been established.

Chronic heart failure
Heart failure must be stable before considering Carvedilol + Ivabradine (Carivalan) treatment. Carvedilol + Ivabradine (Carivalan) is not recommended in heart failure patients with NYHA functional classification IV due to limited amount of data with ivabradine in this population. Carvedilol + Ivabradine (Carivalan) should be used with caution in combination with digitalis glycosides since these products, as well as carvedilol, may slow the AV conduction.

Stroke
The use of Carvedilol + Ivabradine (Carivalan) is not recommended immediately after a stroke since no data with ivabradine is available in these situations.

Visual function
Ivabradine influences retinal function. There is no evidence of a toxic effect of long-term ivabradine treatment on the retina. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Precautions for use
Stopping treatment
Ivabradine intake can be interrupted if necessary, however an abrupt cessation of therapy with a beta-blocker should be avoided, especially in patients with ischemic heart disease. The cessation of Carvedilol + Ivabradine (Carivalan) therapy should immediately be followed by the intake of carvedilol individual tablet ensuring the patient is maintained at an optimal dose of carvedilol. Posology of individual carvedilol should be decreased gradually; for example by reducing the daily dose by half every three days. If necessary, replacement therapy to prevent the exacerbation of angina pectoris should be initiated simultaneously. If the patient develops any symptoms, the dose should be reduced more slowly.

Renal function in congestive heart failure
Reversible deterioration of renal function has been observed with carvedilol therapy in chronic heart failure patients with low arterial blood pressure (SBP < 100 mmHg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency.

Patients with hypotension
Limited data are available in patients with mild to moderate hypotension, and ivabradine should therefore be used with caution in these patients. Carvedilol + Ivabradine (Carivalan) is contra-indicated in patients with severe hypotension (systolic arterial blood pressure <90 mmHg, diastolic arterial blood pressure <50 mmHg).

Atrial fibrillation - Cardiac arrhythmias
There is no evidence of risk of (excessive) bradycardia on return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. However, in the absence of extensive data, non-urgent DC-cardioversion should be considered 24 hours after the last dose of Carvedilol + Ivabradine (Carivalan).

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products
The use of Carvedilol + Ivabradine (Carivalan) in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided. If the combination appears necessary, close cardiac monitoring is needed. Heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation, which may give rise to severe arrhythmias, in particular *Torsade de pointes.*

Hypertensive patients requiring blood pressure treatment modifications.
In the SHIFT trial, more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine. When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval.

Diabetic patients
Carvedilol + Ivabradine (Carivalan) may mask symptoms and signs of acute hypoglycemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure in connection with the use of carvedilol. Therefore, close monitoring of diabetic patients receiving Carvedilol + Ivabradine (Carivalan) is required by means of regular blood glucose measurements and adjustment of anti-diabetic medication as necessary.

Peripheral vascular disease
Carvedilol + Ivabradine (Carivalan) should be used with caution in patients with peripheral vascular diseases, as beta-blockers may precipitate or aggravate symptoms of the disease. The same also applies to those with Raynaud's syndrome, as there may be exacerbation or aggravation of symptoms. Carvedilol + Ivabradine (Carivalan) is contraindicated in case of severe peripheral vascular disease.

Anesthesia and major surgery
Beta-blockers reduce the risk of arrhythmias under anesthesia, but the risk of hypotension may be increased. Caution should therefore be applied when using certain anesthetics due to the negative synergic, inotropic effects of carvedilol and anesthetic products.

Thyrotoxicosis/hyperthyroidism
Beta-blockers, such as carvedilol, may mask the signs of hyperthyroidism and the symptoms of thyrotoxicosis.

Contact lenses
Patients who wear contact lenses and are treated with Carvedilol + Ivabradine (Carivalan) should be advised of the possible reduction of lachrymal secretion due to the carvedilol component.

Hypersensitivity
Carvedilol + Ivabradine (Carivalan) should be used with caution in patients with a history of serious hypersensitivity reactions and in those undergoing desensitization therapy as beta-blockers, such as carvedilol, may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Psoriasis
In patients with a personal or family history of psoriasis associated with beta-blocker therapy, Carvedilol + Ivabradine (Carivalan) should only be prescribed after a careful weighing of risks and benefits as beta-blockers may worsen the skin reactions.

Pheochromocytoma
In patients with pheochromocytoma, a treatment with alpha-blocking agent should be initiated prior to the use of any beta-blocking agent. Although carvedilol has both alpha- and beta- blocking pharmacological activity, there is no data regarding the use of carvedilol in this condition. Therefore, caution should be considered when in the administration of Carvedilol + Ivabradine (Carivalan) to patients suspected of having pheochromocytoma.

Further precautions
Due to insufficient clinical data, carvedilol should not be administered to patients with labile or secondary hypertension, orthostatic hypotension, acute myocarditis, a hemodynamically relevant stenosis of the heart valves or ventricular outflow tract, end-stage peripheral arterial disease or who are concomitantly receiving an α1-receptor antagonist or α2-receptor agonist.

Excipients
Since tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Effects on ability to drive and use machines
Based on existing data with the individual components, the use of Carvedilol + Ivabradine (Carivalan) may affect the ability to drive or use machinery.
Due to variability of individual reactions on carvedilol (such as dizziness, fatigue or decreased alertness), the ability to drive or operate machinery may be impaired. This is particularly true at the start of treatment, when the dose is increased, during the switch to a new preparation, or when taken together with alcohol.
Ivabradine may affect the patient's ability to drive. Patients should be warned that ivabradine may cause transient luminous phenomena (consisting mainly of phosphenes). Luminous phenomena may occur in situations when there are sudden variations in light intensity, especially when driving at night. Ivabradine has no influence on the ability to use machines. However, in post-marketing experience, cases of impaired driving ability due to visual symptoms have been reported.

PREGNANCY AND LACTATION:
Women of child-bearing potential:
Women of child-bearing potential should use appropriate contraceptive measures during treatment.

Pregnancy:
Based on existing data with the individual components, the use of Carvedilol + Ivabradine (Carivalan) is contra-indicated during pregnancy.
There are insufficient data on the use of carvedilol in pregnant women. Experimental animal studies have shown reproductive toxicity. The potential risk use in humans is unknown. Beta-blockers reduce placental perfusion which may result in intrauterine fetal death and immature and premature deliveries. In addition, adverse effects (especially hypoglycemia and bradycardia, hypotension, respiratory depression and hypothermia) may occur in the fetus and neonate. There may be an increased risk of cardiac and pulmonary complications in the neonate during the postnatal period.
There are no or limited amount of data from the use of ivabradine in pregnant women. Animal studies with ivabradine have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects. The potential risk for humans is unknown.

Breast-feeding:
Carvedilol + Ivabradine (Carivalan) is contra-indicated during breast-feeding.
Animal studies have shown that carvedilol or its metabolites are excreted in the breast milk. It is not known whether carvedilol is excreted in the human breast milk.
Animal studies indicate that ivabradine is excreted in milk. Women that need treatment with ivabradine should stop breast-feeding and choose for another way of feeding their child.

INTERACTIONS:
No interactions between carvedilol and ivabradine have been observed in an interaction study conducted in healthy volunteers. Information on interactions with other products that are known for the individual active substances is provided below.
Ivabradine is metabolized by CYP3A4 only and it is a very weak inhibitor of this cytochrome. Ivabradine was shown not to influence the metabolism and plasma concentrations of other CYP3A4 substrates (mild, moderate and strong inhibitors). CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. Drug-drug interaction studies have established that CYP3A4 inhibitors increase ivabradine plasma concentrations, while inducers decrease them. Increased plasma concentrations of ivabradine may be associated with the risk of excessive bradycardia.
Carvedilol is both a substrate and an inhibitor of P-glycoprotein. It is therefore possible that the bioavailability of medicines which are transported by P-glycoprotein will be increased if carvedilol is administered concomitantly. In addition, the bioavailability of carvedilol may be altered by inducers or inhibitors of P-glycoprotein.
Both inhibitors and inducers of the CYP2D6 and CYP2C9 isoenzymes may alter the systemic and presystemic metabolism of carvedilol in a stereoselective manner, which may reduce or elevate the plasma concentration of R- and S-carvedilol.
Some of these types of interactions which have been observed in patients or healthy subjects are listed below. However, this list is not exhaustive.

Concomitant use contraindicated:

Known interaction with the product	**Component**	**Interaction with other medicinal product**
Potent CYP3A4 inhibitors (azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone)	Ivabradine *Concomitant use contraindicated*	Pharmacokinetic interaction: The concomitant use of ivabradine with potent CYP3A4 inhibitors is contra-indicated. The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased ivabradine mean plasma exposure by 7 to 8 fold.
	Carvedilol *Concomitant use with precaution*	Patients receiving medications that inhibit cytochrome P450 enzymes (e.g. cimetidine, fluoxetine, verapamil, ketoconazole, haloperidol, erythromycin) should be closely monitored during concomitant treatment with carvedilol.
Moderate CYP3A4 inhibitors (diltiazem, verapamil)	Ivabradine *Concomitant use contraindicated*	Pharmacokinetic and pharmacodynamic interaction: Specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with the heart rate reducing agents diltiazem or verapamil resulted in an increase in ivabradine exposure (2- to 3-fold increase in AUC) and an additional heart rate reduction of 5 bpm.
	Carvedilol *Concomitant use with precaution*	Isolated cases of conduction disturbances (rarely with hemodynamic effect) have been observed when carvedilol has been administered with diltiazem, verapamil. Similar to other beta-blockers, if carvedilol is to be concomitantly orally administered with calcium channel blockers of the verapamil- or diltiazem-type, it is recommended to monitor ECG and blood pressure as concomitant administration of carvedilol with these substances may increase the risk AV conduction disturbances.

Concomitant use not recommended:

Known interaction with the product	Component	Interaction with other medicinal product
QT prolonging medicinal products Cardiovascular QT prolonging medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone). Non-cardiovascular QT prolonging medicinal products (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).	Ivabradine *Concomitant use not recommended*	The concomitant use of cardiovascular and non-cardiovascular QT prolonging medicinal products with ivabradine should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed.
	Carvedilol *Concomitant use with precautions with amiodarone*	In patients presenting with heart failure, amiodarone reduced the clearance of S-carvedilol, most probably by inhibiting CYP2C9. The average plasma concentration of R-carvedilol remained unchanged. As a result, there is the potential risk of increased beta-blockade caused by an increase in the plasma concentration of S-carvedilol. Isolated cases of conduction disturbances (rarely with hemodynamic effect) have been observed when carvedilol has been administered with amioradone. Concomitant administration with carvedilol and amiodarone (oral) must be carefully monitored as bradycardia, cardiac arrest and ventricular fibrillation have been reported shortly after the initiation of treatment following the concomitant use of beta-blockers (such as carvedilol) with amiodarone.
Intravenous antiarrhythmic agent (other than verapamil, diltiazem)	Carvedilol *Concomitant use not recommended*	There is a risk of heart failure in the event of concomitant intravenous administration of class Ia or Ic antiarrhythmic agents with carvedilol. The concomitant use of beta-blockers with this type of agents should be carefully monitored
Grapefruit juice	Ivabradine *Concomitant use not recommended*	Ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice with ivabradine should be avoided.

Concomitant use with precaution:

Known interaction with the product	Component	Interaction with other medicinal product
Moderate CYP3A4 inhibitors (other than diltiazem, verapamil) e.g. fluconazole	Ivabradine *Concomitant use with precaution*	The concomitant use of ivabradine with other moderate CYP3A4 inhibitors (e.g. fluconazole) may be considered at the starting dose of 2.5 mg twice daily and if resting heart rate is above 70 bpm, with monitoring of heart rate.
Cytochrome P450 enzymes inducers	Ivabradine *Concomitant use with precaution*	CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, *Hypericum perforatum* [St John's Wort]) may decrease ivabradine exposure and activity. The concomitant use of CYP3A4 inducing medicinal products may require an adjustment of the dose of ivabradine. The combination of ivabradine 10 mg twice daily with St John's Wort was shown to reduce ivabradine AUC by half. The intake of St John's Wort should be restricted during the treatment with ivabradine.
	Carvedilol *Concomitant use with precaution with rifampicin*	In a study of 12 healthy subjects, administering rifampicin with carvedilol reduced plasma concentrations of carvedilol by around 70%, most probably by inducing P-glycoprotein. This caused a decrease in intestinal absorption of carvedilol and antihypertensive effect.
Cimetidine	Carvedilol *Concomitant use with precaution*	Cimetidine increased carvedilol AUC by about 30% but causes no change in C_{max}. Care may be required for patients receiving inhibitors of mixed function oxidase, e.g. cimetidine, as serum levels of carvedilol may be increased. However, based on the relatively small effect of cimetidine on carvedilol drug levels, the likelihood of any clinically important interaction is minimal.
Fluoxetine	Carvedilol *Concomitant use with precaution*	In a randomized, cross-over study in 10 patients with heart failure, co-administration of carvedilol with fluoxetine, a strong inhibitor of CYP2D6, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in mean R(+) enantiomer AUC. However, no difference in adverse events, arterial blood pressure or heart rate were noted between treatment groups.
Cardiac glycosides (digoxin, digitoxin)	Carvedilol *Concomitant use with precaution*	Digoxin and digitoxin concentrations are increased when digoxin and carvedilol are administered concomitantly. Digoxin, digitoxin and carvedilol all prolong the AV conduction time and therefore increased monitoring of digoxin levels is recommended when initiating, adjusting or discontinuing Carivalan treatment.
Cyclosporin	Carvedilol *Concomitant use with precaution*	Two studies in renal and cardiac transplant patients receiving oral cyclosporine have shown an increase in cyclosporine plasma concentration following the initiation of carvedilol. Carvedilol appears to increase absorption of orally administered cyclosporine by inhibiting activity of P-glycoprotein in the intestine. In order to maintain therapeutic levels, in approximately 30% of patients a reduction of cyclosporine dose was necessary, while other patients required no dose adjustment. On average, the dose in these patients was reduced by approximately 20%. Due to wide individual variability of the dose among the patients, it is recommended that cyclosporine concentrations are monitored closely after initiation of Carivalan and that the dose of cyclosporine be appropriately adjusted. No interaction with carvedilol is expected with intravenous administration of cyclosporine
Insulin or oral hypoglycemics	Carvedilol *Concomitant use with precaution*	Medicines with beta-blocking effects may enhance the blood glucose-lowering effects of insulin and oral anti-diabetic medicines. Hypoglycemic symptoms (especially tachycardia and palpitations) may be masked or attenuated. Therefore, blood glucose levels must be closely monitored in patients receiving insulin or oral antidiabetic medicines.
Catecholamine-depleting agents	Carvedilol *Concomitant use with precaution*	Patients taking both a beta-blocker (such as carvedilol) and a medicinal product that can deplete catacholamines (e.g. reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (except for MAO-B inhibitors)) should be carefully observed for signs of hypotension and/or severe bradycardia
Clonidine	Carvedilol *Concomitant use with precaution*	Concomitant administration of clonidine with beta-blockers (such as carvedilol) may potentiate blood pressure and heart rate lowering effects. When concomitant treatment with beta-blockers and clonidine is to be terminated, the beta-blocker should be discontinued first. Clonidine therapy may be discontinued several days later by gradually decreasing the dosage
Dihydropyridine	Carvedilol *Concomitant use with precaution*	Concomitant administration of dihydropyridines and carvedilol should be closely monitored as there have been reports of heart failure and severe hypotension in this situation.
Anesthetics	Carvedilol *Concomitant use with precaution*	Careful monitoring of vital signs is recommended during anesthesia due to the synergistic, negative, inotropic and hypotensive effects of carvedilol and anesthetic drugs.
Beta-agonist bronchodilators	Carvedilol *Concomitant use with precaution*	Non-cardioselective beta-blockers antagonize the bronchodilatory effects of beta-receptor agonists. These patients must be monitored closely.
Potassium-depleting diuretics (thiazide diuretics and loop diuretics)	Ivabradine *Concomitant use with precaution*	Hypokalemia can increase the risk of arrhythmia. As ivabradine may cause bradycardia, the resulting combination of hypokalemia and bradycardia is a predisposing factor to the onset of severe arrhythmias, especially in patients with long QT syndrome, whether congenital or substance-induced.

Concomitant use to be taken into consideration (due to carvedilol):

Known interaction with the product	Interaction with other medicinal product
Antihypertensive medicines	As with other agents with beta-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs that have an antihypertensive effect (e.g. alpha1-receptor antagonists) or have hypotension as part of their adverse effect profile.
Non-steroidal anti-inflammatory drugs (NSAID)	Concomitant administration of NSAIDs and beta-blockers may lead to an increase in blood pressure and reduced ability to control blood pressure. The antihypertensive effect of carvedilol is decreased due to water and sodium retention.
Estrogens and corticosteroids	Carvedilol's antihypertensive activity may be reduced due to water and sodium retention in patients with a stabilized blood pressure who are receiving additional treatment such as estrogens or corticosteroids.
Nitrates	Nitrates increase hypotensive effect.
Sympathomimetics with alpha-mimetic and beta-mimetic effects	Sympathomimetics with alpha-mimetic and beta-mimetic effects increase the risk of hypotension and excessive bradycardia.
Ergotamine	Vasoconstriction increased.
Neuromuscular blocking agents	Increased neuromuscular block.
Beta-blockers in the form of eye drops	Concomitant use of carvedilol with other beta-blockers in the form of eye drops may cause an increase in adverse effects, with beta-blockers presenting a particular risk of excessive bradycardia.
Barbiturates	Concomitant administration of carvedilol with barbiturates can lead to a reduced efficacy of carvedilol due to enzyme induction.

Specific drug-drug interaction studies have shown no clinically significant effect of the following medicinal products on pharmacokinetics and pharmacodynamics of ivabradine: proton pump inhibitors (omeprazole, lansoprazole), sildenafil, HMG CoA reductase inhibitors (simvastatin), dihydropyridine calcium channel blockers (amlodipine, lacidipine), digoxin and warfarin. In addition, there was no clinically significant effect of ivabradine on the pharmacokinetics of simvastatin, amlodipine, lacidipine, on the pharmacokinetics and pharmacodynamics of digoxin, warfarin and on the pharmacodynamics of aspirin.
In pivotal phase III clinical trials, the following medicinal products were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone agents, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet medicinal products.

Pediatric population
Interaction studies have only been performed in adults.

ADVERSE DRUG REACTIONS:
Summary of the safety profile
For carvedilol, the frequency of undesirable effects is not dose-dependent, with the exception of dizziness, visual disturbances and bradycardia.
For ivabradine, the most common adverse reactions, luminous phenomena (phosphenes) and bradycardia are dose-dependent and related to the pharmacological effect of the medicinal product.

Tabulated list of adverse reactions
The following undesirable effects have been observed during treatment with carvedilol and ivabradine given separately and ranked under the MedDRA classification by body system and under heading of frequency using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable effects	Frequency	
		Carvedilol	Ivabradine
Infections and infestations	Bronchitis	Common	-
	Pneumonia	Common	-
	Upper respiratory tract infections	Common	-
	Urinary tract infections	Common	-
Blood and lymphatic system disorders	Anemia	Common	-
	Eosinophilia	-	Uncommon
	Thrombocytopenia	Rare	-
	Leukopenia	Very rare	-
Immune system disorders	Allergic reactions (hypersensitivity)	Very rare	-
Metabolism and nutrition disorders	Hypercholesterolemia	Common	-
	Deterioration in glycemic control (hyperglycemia or hypoglycemia) in patients with pre-existing diabetes	Common	-
	Diabetes mellitus	Common	-
	Hyperuricemia	-	Uncommon
Psychiatric disorders	Depressive mood, depression	Common	-
	Sleep disorders, nightmares	Uncommon	-
	Confusion	Uncommon	-
Nervous system disorders	Headache	Very common	Common
	Dizziness	Very common	Common
	Syncope	Uncommon	Uncommon
	Presyncope	Uncommon	-
	Paresthesia	Uncommon	-
Eye disorders	Reduced lacrimation	Common	-
	Luminous phenomena (phosphenes)	-	Very Common
	Visual impairment	Common	Uncommon
	Irritation of the eye	Common	-
	Blurred vision	-	Common
	Diplopia	-	Uncommon
Ear and labyrinth disorders	Vertigo	-	Uncommon
Cardiac disorders	Heart failure	Very common	-
	Bradycardia	Common	Common
	Pulmonary edema	Common	-
	Edema (including generalized and peripheral edema and swelling of the genital area and feet, hypervolemia and fluid retention)	Common	-
	AV-block	Uncommon	-
	AV 1st degree block (ECG prolonged PQ interval)	-	Common
	AV 2nd degree block	-	Very Rare
	AV 3rd degree block	-	Very Rare
	Ventricular extrasystoles	-	Common
	Atrial fibrillation	-	Common
	Angina pectoris	Uncommon	-
	Palpitations	-	Uncommon
	Supraventricular extrasystoles	-	Uncommon
	Sick sinus syndrome	-	Very Rare
Vascular disorders	Hypotension	Very common	Uncommon (possibly related to bradycardia)
	Postural hypotension	Common	-
	Disturbances of peripheral circulation (cold extremities, PVD, exacerbation of intermittent claudication and Raynauds phenomenon)	Common	-
	Uncontrolled blood pressure	-	Common
Respiratory, thoracic and mediastinal disorders	Dyspnea	Common	Uncommon
	Asthma in predisposed patients	Common	-
	Nasal congestion	Rare	-
	Wheezing	Rare	-
Gastrointestinal disorders	Nausea	Common	Uncommon
	Constipation	Uncommon	Uncommon
	Diarrhea	Common	Uncommon
	Abdominal pain	Common	Uncommon*
	Vomiting	Common	-
	Dry mouth	Rare	-
	Dyspepsia	Common	-

MedDRA System Organ Class	Undesirable effects	Frequency	
		Carvedilol	Ivabradine
Skin and subcutaneous tissue disorders	Skin reactions (such as allergic exanthema, dermatitis, urticaria, pruritus and increased sweating)	Uncommon	-
	Reactions similar to lichen planus, psoriasis or psoriasiform exanthema (occurring several weeks up to years after the start of treatment). Existing lesions may worsen.	Uncommon	-
	Alopecia	Uncommon	-
	Angioedema	-	Uncommon
	Rash	-	Uncommon
	Erythema	-	Rare
	Severe skin reactions (such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)	Very rare	-
	Pruritus	-	Rare
	Urticaria	-	Rare
Musculoskeletal and connective tissue disorders	Pain in extremities	Common	-
	Gout	Common	-
	Muscle cramps	-	Uncommon
Renal and urinary disorders	Renal failure and renal function abnormality in patients with diffuse vascular disease and/or underlying renal insufficiency	Common	-
	Micturition disorders	Common	-
	Urinary incontinence in women	Very rare	-
General disorders and administration site conditions	Asthenia, fatigue	Very common	Uncommon
	Pain	Common	-
	Malaise (possibly related to bradycardia)	-	Rare
Investigations	Weight gain	Common	-
	Blood creatinine increased	-	Uncommon
	ECG prolonged QT interval	-	Uncommon
	Increase in the transaminases ALT, AST and GGT	Very rare	-
Reproductive system and breast disorders	Impotence, erectile dysfunction	Uncommon	-

*Frequency calculated from clinical trials for adverse events detected from spontaneous report

Description of selected adverse reactions

Carvedilol

Dizziness, syncope, headache and debility are generally mild and are more likely to occur at the start of treatment.

Cardiac failure is an event commonly reported both in patients treated with placebo and in patients treated with carvedilol (14.5% and 15.4% respectively, in patients with left ventricular dysfunction following acute myocardial infarction).

A reversible deterioration in renal function has been observed during treatment with carvedilol in patients with chronic cardiac insufficiency with low blood pressure, ischemic heart disease and diffuse vascular disease and/or basal renal insufficiency.

Non-selective beta-blockers in particular may cause latent diabetes to become manifest, manifest diabetes to be aggravated and blood glucose control to be impaired. The glucose balance may also be slightly upset during treatment with carvedilol, but this does not happen often.

Carvedilol may cause urinary incontinence in women. The problem is resolved once treatment is discontinued.

Ivabradine

Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. Phosphenes may also be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency). The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by 3.3% of patients particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm.

In the SIGNIFY study, atrial fibrillation was observed in 5.3% of patients taking ivabradine compared to 3.8% in the placebo group. In a pooled analysis of all the Phase II/III double blind controlled clinical trials with a duration of at least 3 months including more than 40,000 patients, the incidence of atrial fibrillation was 4.86% in ivabradine treated patients compared to 4.08% in controls, corresponding to a hazard ratio of 1.26, 95% CI [1.15-1.39].

REPORTING OF ADVERSE DRUG REACTION:

For suspected adverse dug reaction, report to the FDA at ***www.fda.gov.ph.***
Seek medical attention immediately at the first sign of any adverse drug reaction.

OVERDOSE AND TREATMENT:

There is no information on overdose with Carvedilol + Ivabradine (Carivalan) in humans.

Symptoms:

Linked to carvedilol

In case of an overdose, severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest may occur. Respiratory distress, bronchospasm, vomiting, altered consciousness and generalized seizures may also occur.

Linked to ivabradine

Overdose may lead to severe and prolonged bradycardia.

Management:

In addition to general procedures, vital signs must be monitored and corrected, if necessary under intensive care conditions. Within 4 hours after ingestion, the absorption of carvedilol in the gastrointestinal tract can be reduced through gastric lavage, activated charcoal and induced vomiting.

Patients should be placed in the supine position. Atropine, 0.5 mg to 2 mg intravenous (i.v.) and/or glucagon 1 to 10 mg i.v. (followed by a slow i.v. infusion of 2 to 5 mg/hour if necessary) may be given when severe bradycardia is present, which should be treated symptomatically in a specialized environment. To support ventricular function, intravenous administration of glucagon, or sympathomimetics (e.g. dobutamine, isoprenaline, orciprenaline, adrenaline and in accordance to body weight and effect) are recommended.

In the event of bradycardia with poor hemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicinal products such as isoprenaline may be considered temporary cardiac electrical pacing may be instituted if required. Extensive hypotension may be treated with administration of intravenous fluids.

If positive inotropic effect is required, phosphodiesterase inhibitors, e.g. milrone, should be considered. In the case of drug-resistant bradycardia, the initiation of pacemaker therapy may be required. If peripheral vasodilation dominates in the intoxication profile then norfenefrine or noradrenaline should be administered, with continuous monitoring of the circulation, either 5 to 10 micrograms i.v., repeated according to arterial blood pressure response, or 5 micrograms per minute by infusion titrated to arterial blood pressure.

For bronchospasm, β-sympathomimetics (as aerosol or intravenous) should be given, or aminophylline may be administered intravenously by slow injection or infusion.

In the event of seizures, slow intravenous injection of diazepam or clonazepam is recommended.

In cases of severe overdose with symptoms of shock, supportive treatment must be continued for a sufficiently long period, as a prolongation of elimination half-life and redistribution of carvedilol from deeper compartments are to be expected. Therefore, supportive treatment should be continued until the patient's condition has stabilized. The length of the treatment depends on the severity of the overdose.

Carvedilol + Ivabradine (Carivalan) is not eliminated by dialysis, since the active substance cannot be dialyzed, presumably due to its high degree of plasma protein binding.

CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

STORAGE CONDITION:

Store at temperatures not exceeding 30°C.

AVAILABILITY:

Carvedilol + Ivabradine (Carivalan) 6.25 mg/5 mg: PVC/PVDC/aluminum blister x 14's (Box of 56's)
Carvedilol + Ivabradine (Carivalan) 6.25 mg/7.5 mg: PVC/PVDC/aluminum blister x 14's (Box of 56's)
Carvedilol + Ivabradine (Carivalan) 12.5 mg/5 mg: PVC/PVDC/aluminum blister x 14's (Box of 56's)
Carvedilol + Ivabradine (Carivalan) 12.5 mg/7.5 mg: PVC/PVDC/aluminum blister x 14's (Box of 56's)
Carvedilol + Ivabradine (Carivalan) 25 mg/5 mg: PVC/PVDC/aluminum blister x 14's (Box of 56's)
Carvedilol + Ivabradine (Carivalan) 25 mg/7.5 mg: PVC/PVDC/aluminum blister x 14's (Box of 56's)

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