

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carivalan 6.25 mg/5 mg film-coated tablets
[Carivalan 6.25 mg/7.5 mg film-coated tablets]
[Carivalan 12.5 mg/5 mg film-coated tablets]
[Carivalan 12.5 mg/7.5 mg film-coated tablets]
[Carivalan 25 mg/5 mg film-coated tablets]
[Carivalan 25 mg/7.5 mg film-coated tablets]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 6.25 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).

[Each film-coated tablet contains 6.25 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride)]

[Each film-coated tablet contains 12.5 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride)]

[Each film-coated tablet contains 12.5 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride)]

[Each film-coated tablet contains 25 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride)]


[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 (68.055 mg for Carivalan 6.25/5 mg, 65.360 mg for Carivalan 6.25/7.5 mg, 78.710 mg for Carivalan 12.5/5 mg, 76.015 mg for Carivalan 12.5/7.5 mg, 85.530 mg for Carivalan 25/5 mg and 82.835 mg for Carivalan 25/7.5 mg).


For the full list of excipients, see section 6.1.


3. PHARMACEUTICAL FORM


Film-coated tablet.


White, hexagonal, film-coated tablet (6.25/5 mg) (longest diagonal 7.3 mm) engraved with CI2 on one face and  on the other face.

[Yellow, hexagonal, film-coated tablet (6.25/7.5 mg) (longest diagonal 7.3 mm) engraved with CI3 on one face and  on the other face.]

[White, elliptic, film-coated tablet (12.5/5 mg) (10.6 mm x 5.3 mm) engraved with CI4 on one face and  on the other face.]

[Yellow, elliptic, film-coated tablet (12.5/7.5 mg) (10.6 mm x 5.3 mm) engraved with CI5 on one face and  on the other face.]

[White, octagonal, film-coated tablet (25/5 mg) (diameter 7.8 mm) engraved with CI6 on one face and  on the other face.]

[Yellow, octagonal, film-coated tablet (25/7.5 mg) (diameter 7.8 mm) engraved with CI7 on one face and  on the other face.]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Carivalan is indicated as substitution therapy in adult patients with normal sinus rhythm already controlled by ivabradine and carvedilol taken concomitantly at the same doses level 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

4.2 Posology and method of administration

Posology

The recommended dose of Carivalan is one tablet twice daily, once in the morning and once in the evening.

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 (see section 4.4). 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 (see section 5.2) and SBP >100 mmHg.

No data are available in patients with creatinine clearance below 15 mL/min. 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 (see sections 4.4 and 5.2).

Carivalan is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

Elderly

Carivalan can be administered in elderly patients with caution (see section 5.2).

Paediatric population

The safety and efficacy of Carivalan in children and adolescents have not been established. No data are available with Carivalan. The data with ivabradine is presented in section 5.1.

Method of administration

Oral use.

Carivalan tablet should be taken twice daily during a meal (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any other beta-blockers or to any of the excipients of this medicinal product listed in section 6.1;
- 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 phaeochromocytoma;
- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties (see section 4.5);
- 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 (see sections 4.5 and 5.2);
- Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Special warnings

Lack of benefit on clinical outcomes in patients with symptomatic chronic stable angina pectoris

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) (see section 5.1).

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 (see section 4.2).

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). 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 (see section 4.8). 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 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

Carivalan must not be initiated in patients with a pre-treatment resting heart rate below 50 beats per minute (see section 4.3).

If, during treatment with 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 (see section 4.2).

Combination with calcium channel blockers

Concomitant use of Carivalan with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated (see sections 4.3 and 4.5). 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 (see section 5.1).

Chronic heart failure

Heart failure must be stable before considering Carivalan treatment. Carivalan is not recommended in heart failure patients with NYHA functional classification IV due to limited amount of data with ivabradine in this population.

Carivalan should be used with caution in combination with digitalis glycosides since these products, as well as carvedilol, may slow the AV conduction (see section 4.5).

Stroke

The use of 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 (see section 5.1). 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 ischaemic heart disease. The cessation of 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), ischaemic 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. Carivalan is contra-indicated in patients with severe hypotension (systolic arterial blood pressure <90 mmHg, diastolic arterial blood pressure <50 mmHg) (see section 4.3).

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 Carivalan.

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products

The use of Carivalan in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided (see section 4.5). 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 may mask symptoms and signs of acute hypoglycaemia. 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 Carivalan is required by means of regular blood glucose measurements and adjustment of anti-diabetic medication as necessary (see section 4.5).

Peripheral vascular disease

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. Carivalan is contraindicated in case of severe peripheral vascular disease (see section 4.3).

Anaesthesia and major surgery

Beta-blockers reduce the risk of arrhythmias under anaesthesia, but the risk of hypotension may be increased. Caution should therefore be applied when using certain anaesthetics due to the negative synergic, inotropic effects of carvedilol and anaesthetic products (see section 4.5).

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 Carivalan should be advised of the possible reduction of lachrymal secretion due to the carvedilol component.

Hypersensitivity

Carivalan should be used with caution in patients with a history of serious hypersensitivity reactions and in those undergoing desensitisation 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, Carivalan should only be prescribed after a careful weighing of risks and benefits as beta-blockers may worsen the skin reactions.

Phaeochromocytoma

In patients with phaeochromocytoma, 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 Carivalan to patients suspected of having phaeochromocytoma.

Further precautions

Due to insufficient clinical data, carvedilol should not be administered to patients with labile or secondary hypertension, orthostatic hypotension, acute myocarditis, a haemodynamically relevant stenosis of the heart valves or ventricular outflow tract, end-stage peripheral arterial disease or who are concomitantly receiving an α 1-receptor antagonist or α 2-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.

4.5 Interaction with other medicinal products and other forms of interaction

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 metabolised 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 (see section 4.4).

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 (see section 5.2).

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 (see section 4.3):

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 <i>Concomitant use contraindicated</i>	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. (see section 4.3)
	Carvedilol <i>Concomitant use with precaution</i>	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 <i>Concomitant use contraindicated</i>	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 (see section 4.3).
	Carvedilol <i>Concomitant use with precaution</i>	Isolated cases of conduction disturbances (rarely with haemodynamic 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 (see section 4.4):

Known interaction with the product	Component	Interaction with other medicinal product
QT prolonging medicinal products <u>Cardiovascular QT prolonging medicinal products</u> (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone). <u>Non-cardiovascular QT prolonging medicinal products</u> (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).	Ivabradine <i>Concomitant use not recommended</i>	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 (see section 4.4).
	Carvedilol <i>Concomitant use with precautions with amiodarone</i>	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

Known interaction with the product	Component	Interaction with other medicinal product
		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 haemodynamic 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 <i>Concomitant use not recommended</i>	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 <i>Concomitant use not recommended</i>	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 <i>Concomitant use with precaution</i>	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 <i>Concomitant use with precaution</i>	CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, <i>Hypericum perforatum</i> [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 <i>Concomitant use with precaution with rifampicin</i>	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

Known interaction with the product	Component	Interaction with other medicinal product
		antihypertensive effect.
Cimetidine	Carvedilol <i>Concomitant use with precaution</i>	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 <i>Concomitant use with precaution</i>	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 <i>Concomitant use with precaution</i>	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 <i>Concomitant use with precaution</i>	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 hypoglycaemics	Carvedilol <i>Concomitant use with precaution</i>	Medicines with beta-blocking effects may enhance the blood glucose-lowering effects of insulin and oral anti-diabetic medicines. Hypoglycaemic symptoms (especially tachycardia and palpitations) may be

Known interaction with the product	Component	Interaction with other medicinal product
		masked or attenuated. Therefore, blood glucose levels must be closely monitored in patients receiving insulin or oral antidiabetic medicines.
Catecholamine-depleting agents	Carvedilol <i>Concomitant use with precaution</i>	Patients taking both a beta-blocker (such as carvedilol) and a medicinal product that can deplete catecholamines (e.g. reserpine, guanethidine, methyl dopa, guanfacine and monoamine oxidase inhibitors (except for MAO-B inhibitors)) should be carefully observed for signs of hypotension and/or severe bradycardia
Clonidine	Carvedilol <i>Concomitant use with precaution</i>	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 <i>Concomitant use with precaution</i>	Concomitant administration of dihydropyridines and carvedilol should be closely monitored as there have been reports of heart failure and severe hypotension in this situation.
Anaesthetics	Carvedilol <i>Concomitant use with precaution</i>	Careful monitoring of vital signs is recommended during anaesthesia due to the synergistic, negative, inotropic and hypotensive effects of carvedilol and anaesthetic drugs.
Beta-agonist bronchodilators	Carvedilol <i>Concomitant use with precaution</i>	Non-cardioselective beta-blockers antagonise the bronchodilatory effects of beta-receptor agonists. These patients must be monitored closely.
Potassium-depleting diuretics (thiazide diuretics and loop diuretics)	Ivabradine <i>Concomitant use with precaution</i>	Hypokalaemia can increase the risk of arrhythmia. As ivabradine may cause bradycardia, the resulting combination of hypokalaemia 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

Known interaction with the product	Interaction with other medicinal product
	and reduced ability to control blood pressure. The antihypertensive effect of carvedilol is decreased due to water and sodium retention.
Oestrogens and corticosteroids	Carvedilol's antihypertensive activity may be reduced due to water and sodium retention in patients with a stabilised blood pressure who are receiving additional treatment such as oestrogens 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy

Based on existing data with the individual components, the use of Carivalan is contra-indicated during pregnancy (see section 4.3).

There are insufficient data on the use of carvedilol in pregnant women. Experimental animal studies have shown reproductive toxicity (see section 5.3). The potential risk use in humans is unknown. Beta-blockers reduce placental perfusion which may result in intrauterine foetal death and immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia, hypotension, respiratory depression and hypothermia) may occur in the foetus 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 (see section 5.3). The potential risk for humans is unknown.

Breast-feeding

Carivalan is contra-indicated during breast-feeding (see section 4.3).

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.

Fertility

There are no clinical data on fertility with the use of Carivalan.

Studies with carvedilol have shown impaired fertility in adult female rats. Studies in rats with ivabradine shown no effect on fertility in males and females (see section 5.3).

4.7 Effects on ability to drive and use machines

Based on existing data with the individual components, the use of 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.

4.8 Undesirable effects

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	Anaemia	Common	-
	Eosinophilia	-	Uncommon
	Thrombocytopenia	Rare	-
	Leukopenia	Very rare	-
Immune system disorders	Allergic reactions (hypersensitivity)	Very rare	-
Metabolism and nutrition disorders	Hypercholesterolaemia	Common	-
	Deterioration in glycaemic control (hyperglycaemia or hypoglycaemia) in patients with pre-existing diabetes	Common	-
	Diabetes mellitus	Common	-
	Hyperuricaemia	-	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	-
	Paraesthesia	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

MedDRA	Undesirable effects	Frequency	
Cardiac disorders	Heart failure	Very common	-
	Bradycardia	Common	Common
	Pulmonary oedema	Common	-
	Oedema (including generalised and peripheral oedema and swelling of the genital area and feet, hypervolaemia 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	Dyspnoea	Common	Uncommon
	Asthma in predisposed patients	Common	-
	Nasal congestion	Rare	-
	Wheezing	Rare	-
Gastrointestinal disorders	Nausea	Common	Uncommon
	Constipation	Uncommon	Uncommon
	Diarrhoea	Common	Uncommon
	Abdominal pain	Common	Uncommon*
	Vomiting	Common	-
	Dry mouth	Rare	-
	Dyspepsia	Common	-
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

MedDRA	Undesirable effects	Frequency	
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, ischaemic heart disease and diffuse vascular disease and/or basal renal insufficiency (see point 4.4).

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), coloured 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 suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

There is no information on overdose with 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 generalised seizures may also occur.

Linked to ivabradine

Overdose may lead to severe and prolonged bradycardia (see section 4.8).

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 specialised 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 haemodynamic 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 stabilised. The length of the treatment depends on the severity of the overdose.

Carvedilol is not eliminated by dialysis, since the active substance cannot be dialysed, presumably due to its high degree of plasma protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, other combinations, **ATC code:** C07FX06

Carvedilol

Mechanism of action:

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-stabilising 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.

Pharmacodynamic effects:

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-ischaemic effect and to alleviate pain. Haemodynamic studies have demonstrated that carvedilol reduces ventricular pre- and after-load.

In patients with left ventricular dysfunction or congestive heart failure, carvedilol has a favourable effect on haemodynamics and the left ventricular ejection fraction and its dimensions. Carvedilol reduces mortality and the need for cardiovascular hospitalisation 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.

Clinical efficacy and safety:

Clinical studies have shown that a balance between vasodilation and the beta-blocking effect of carvedilol causes the following haemodynamic and metabolic effects:

- In hypertensive patients, a reduction in blood pressure is not accompanied by an increase in global peripheral resistance.
- Heart rate remains unchanged or may decrease slightly.
- Renal circulation and glomerular filtration are not altered.
- Carvedilol maintains peripheral circulation such that the extremities will only get cold in exceptional cases.
- A normal ratio is maintained between HDL and LDL.
- Serum electrolytes are not altered.
- Carvedilol does not stimulate the renin-angiotensin system; plasma renin actually diminishes. Water retention is rarely observed.
- In patients with heart failure, carvedilol showed favourable effects on haemodynamics and an improvement in left ventricular size and ejection fraction. In patients with ischaemic heart disease, carvedilol showed anti-ischaemic and antianginal properties. Carvedilol reduces ventricular preload and afterload.

In a large multi-centre, double-blind, placebo-controlled study on mortality (COPERNICUS), 2,289 patients presenting with severe, ischaemic or non-ischaemic, chronic stable heart failure on standard therapy were randomised, either on carvedilol (1,156 patients) or on placebo (1,133 patients). Patients had left ventricular systolic dysfunction with an average ejection fraction of less than 20%. All-cause mortality was reduced by 35% - 19.7% in the placebo group - to 12.8% in the carvedilol group (Cox proportional hazards, $P=0.00013$). The benefit of carvedilol on mortality was consistent in all sub-populations studied. Sudden death was reduced by 41% in the carvedilol group (4.2% versus 7.8%). The combined secondary assessment parameters in terms of mortality or hospitalisations due to heart failure, mortality or cardiovascular hospitalisations, and mortality or all-cause hospitalisations all improved significantly in the carvedilol group in relation to the placebo group (31%, 27% and 24% reductions respectively, $P=0.00004$). The incidence of severe secondary effects in the study was lower in the carvedilol group (39% versus 45.4%). At the start of treatment, the incidence of aggravated heart failure was similar in the two groups. The incidence of aggravated heart failure during the study was lower in the carvedilol group (14.5% versus 21.1%).

Ivabradine

Mechanism of action:

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 depolarisation 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 repolarisation.

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 (see section 4.8).

Pharmacodynamic effects:

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 (see section 4.8).

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 repolarisation:

- 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.

Clinical efficacy and safety:

The anti-anginal and anti-ischaemic efficacy of ivabradine was studied in five double-blind randomised trials (three versus placebo, and one each versus atenolol and amlodipine). These trials included a total of 4,111 patients with chronic stable angina pectoris, of whom 2,617 received ivabradine.

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment. Efficacy was confirmed with 7.5 mg twice daily. In particular, the additional benefit over 5 mg twice daily was established in a reference-controlled study versus atenolol: total exercise duration at trough was increased by about 1 minute after one month of treatment with 5 mg twice daily and further improved by almost 25 seconds after an additional 3-month period with forced titration to 7.5 mg twice daily. In this study, the anti-anginal and anti-ischaemic benefits of ivabradine were confirmed in patients aged 65 years or more. The efficacy of 5 and 7.5 mg twice daily was consistent across studies on exercise test parameters (total exercise duration, time to limiting angina, time to angina onset and time to 1 mm ST segment depression) and was associated with a decrease of about 70% in the rate of angina attacks. The twice-daily dosing regimen of ivabradine gave uniform efficacy over 24 hours.

In an 889-patients randomised placebo-controlled study, ivabradine given on top of atenolol 50 mg once daily showed additional efficacy on all ETT parameters at the trough of drug activity (12 hours after oral intake).

In a 725-patients randomised placebo-controlled study, ivabradine did not show additional efficacy on top of amlodipine at the trough of drug activity (12 hours after oral intake) while an additional efficacy was shown at peak (3-4 hours after oral intake).

In a 1,277-patients randomised placebo-controlled study, ivabradine demonstrated a statistically significant additional efficacy on response to treatment (defined as a decrease of at least 3 angina attacks per week and/or an increase in the time to 1 mm ST segment depression of at least 60 seconds during a treadmill ETT) on top of amlodipine 5 mg once daily or nifedipine GITS 30 mg once daily, at the trough of drug activity (12 hours after oral ivabradine intake) over a 6-week treatment period (Odds ratio = 1.3, 95% CI [1.0–1.7]; $p=0.012$). Ivabradine did not show additional efficacy on secondary endpoints of ETT parameters at the trough of drug activity while an additional efficacy was shown at peak (3-4 hours after oral ivabradine intake).

Ivabradine efficacy was fully maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There was no evidence of pharmacological tolerance (loss of efficacy) developing during treatment nor of rebound phenomena after abrupt treatment discontinuation. The anti-anginal and anti-ischaemic effects of ivabradine were associated with dose-dependent reductions in heart rate and with a significant decrease in rate pressure product (heart rate x systolic blood pressure) at rest and during exercise. The effects on blood pressure and peripheral vascular resistance were minor and not clinically significant.

A sustained reduction of heart rate was demonstrated in patients treated with ivabradine for at least one year ($n=713$). No influence on glucose or lipid metabolism was observed.

The anti-anginal and anti-ischaemic efficacy of ivabradine was preserved in diabetic patients ($n=457$) with a similar safety profile as compared to the overall population.

A large outcome study, BEAUTIFUL, was performed in 10,917 patients with coronary artery disease and left ventricular dysfunction (LVEF <40%) on top of optimal background therapy with 86.9% of patients receiving beta-blockers. The main efficacy criterion was the composite of cardiovascular death, hospitalization for acute MI or hospitalization for new onset or worsening heart failure. The study showed no difference in the rate of the primary composite outcome in the ivabradine group by comparison to the placebo group (relative risk ivabradine:placebo 1.00, P=0.945).

In a post-hoc subgroup of patients with symptomatic angina at randomisation (n=1507), no safety signal was identified regarding cardiovascular death, hospitalization for acute myocardial infarction or heart failure (ivabradine 12.0% versus placebo 15.5%, P=0.05). From this subgroup, a post analysis in patients treated with carvedilol at baseline (n=254) showed similar results (ivabradine 8.4% versus placebo 17.9%, HR: 0.40, 95% CI [0.19;0.83]).

A large outcome study, SIGNIFY, was performed in 19,102 patients with coronary artery disease and without clinical heart failure (LVEF >40%), on top of optimal background therapy. A therapeutic scheme higher than the approved posology was used (starting dose 7.5 mg twice daily (5 mg twice daily, if age ≥75 years) and titration up to 10 mg twice daily). The main efficacy criterion was the composite of cardiovascular death or non-fatal myocardial infarction. The study showed no difference in the rate of the primary composite endpoint in the ivabradine group by comparison to the placebo group (relative risk ivabradine/placebo 1.08, P=0.197). Bradycardia was reported by 17.9 % of patients in the ivabradine group (2.1% in the placebo group). Verapamil, diltiazem or strong CYP 3A4 inhibitors were received by 7.1% of patients during the study.

A small statistically significant increase in the primary composite endpoint was observed in a pre-specified subgroup of patients with angina patients in CCS class II or higher at baseline (n=12,049) (annual rates 3.4% versus 2.9%, relative risk ivabradine/placebo 1.18, P=0.018), but not in the subgroup of the overall angina population in CCS class ≥ I (n=14,286) (relative risk ivabradine/placebo 1.11, P=0.110).

The higher than approved dose used in the study did not fully explain these findings.

The SHIFT study was a large multicentre, international, randomised double-blind placebo controlled outcome trial conducted in 6,505 adult patients with stable chronic heart failure (for ≥ 4 weeks), NYHA class II to IV, with a reduced left ventricular ejection fraction (LVEF ≤ 35%) and a resting heart rate ≥ 70 bpm.

Patients received standard care including beta-blockers (89%), ACE inhibitors and/or angiotensin II antagonists (91%), diuretics (83%), and anti-aldosterone agents (60%). In the ivabradine group, 67% of patients were treated with 7.5 mg twice a day. The median follow-up duration was 22.9 months. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm. The difference in heart rate between ivabradine and placebo arms was 10.8 bpm at 28 days, 9.1 bpm at 12 months and 8.3 bpm at 24 months.

The study demonstrated a clinically and statistically significant relative risk reduction of 18% in the rate of the primary composite endpoint of cardiovascular mortality and hospitalisation for worsening heart failure (hazard ratio: 0.82, 95% CI [0.75;0.90] – P<0.0001) apparent within 3 months of initiation of treatment. The absolute risk reduction was 4.2%. The results on the primary endpoint are mainly driven by the heart failure endpoints, hospitalisation for worsening heart failure (absolute risk reduced by 4.7%) and deaths from heart failure (absolute risk reduced by 1.1%).

Treatment effect on the primary composite endpoint, its components and secondary endpoints

	Ivabradine (N=3,241) n (%)	Placebo (N=3,264) n (%)	Hazard ratio [95% CI]	P-value
Primary composite endpoint	793 (24.47)	937 (28.71)	0.82 [0.75; 0.90]	<0.0001
Components of the composite:				
- CV death	449 (13.85)	491 (15.04)	0.91 [0.80; 1.03]	0.128
- Hospitalisation for worsening HF	514 (15.86)	672 (20.59)	0.74 [0.66; 0.83]	<0.0001
Other secondary endpoints:				
- All cause death	503 (15.52)	552 (16.91)	0.90 [0.80; 1.02]	0.092
- Death from HF	113 (3.49)	151 (4.63)	0.74 [0.58;0.94]	0.014
- Hospitalisation for any cause	1,231 (37.98)	1,356 (41.54)	0.89 [0.82;0.96]	0.003
- Hospitalisation for CV reason	977 (30.15)	1,122 (34.38)	0.85 [0.78; 0.92]	0.0002

The reduction in the primary endpoint was observed consistently irrespective of gender, NYHA class, ischaemic or non-ischaemic heart failure aetiology and of background history of diabetes or hypertension.

There was a significant improvement in NYHA class at last recorded value, 887 (28%) of patients on ivabradine improved versus 776 (24%) of patients on placebo (P=0.001).

In the subgroup of patients with heart rate ≥ 75 bpm (n=4,150), a greater reduction was observed in the primary composite endpoint of 24% (hazard ratio: 0.76, 95% CI [0.68;0.85] – P<0.0001) and for other secondary endpoints, including all cause death (hazard ratio: 0.83, 95% CI [0.72;0.96] – P=0.0109) and cardiovascular death (hazard ratio: 0.83, 95% CI [0.71;0.97] – P=0.0166). In this subgroup of patients, the safety profile of ivabradine is in line with the one of the overall population.

A significant effect was observed on the primary composite endpoint in the overall group of patients receiving beta blocker therapy (hazard ratio: 0.85, 95% CI [0.76;0.94]). In the subgroup of patients with heart rate ≥ 75 bpm and on the recommended target dose of beta-blocker, no statistically significant benefit was observed on the primary composite endpoint (hazard ratio: 0.97, 95% CI [0.74;1.28]) and other secondary endpoints, including hospitalisation for worsening heart failure (hazard ratio: 0.79, 95% CI [0.56;1.10]) or death from heart failure (hazard ratio: 0.69, 95% CI [0.31;1.53]).

In the subgroup of patients receiving carvedilol at baseline (n=2596), a significant relative risk reduction was observed on the primary composite endpoint in the ivabradine group as compared to the placebo group (HR: 0.80, 95% CI [0.68;0.94]). In the subgroup of patients with HR ≥ 75 bpm and receiving carvedilol at baseline (n=1654), a consistent trend was observed (HR: 0.79, 95% CI [0.65;0.95]).

In a 97-patient randomised placebo-controlled study, the data collected during specific ophthalmologic investigations, aiming at documenting the function of the cone and rod systems and the ascending visual pathway (*i.e.* electroretinogram, static and kinetic visual fields, colour vision, visual acuity), in patients treated with ivabradine for chronic stable angina pectoris over 3 years, did not show any retinal toxicity.

Paediatric population

Ivabradine

A randomised, double-blind, placebo-controlled study was performed in 116 paediatric patients (17 aged [6-12[months, 36 aged [1-3[years and 63 aged [3-18[years) with chronic heart failure and dilated cardiomyopathy on top of optimal background treatment. 74 received ivabradine (ratio 2:1).

The starting dose was 0.02 mg/kg twice daily in age-subset [6-12[months, 0.05 mg/kg twice daily in [1-3[years and [3-18[years <40 kg, and 2.5 mg twice daily in [3-18[years and ≥ 40 kg. The dose was adapted depending on the therapeutic response with maximum doses of 0.2 mg/kg twice daily, 0.3 mg/kg twice daily and 15 mg twice daily respectively. In this study, ivabradine was administered as oral liquid formulation or

tablet twice daily. The absence of pharmacokinetic difference between the 2 formulations was shown in an open-label randomised two-period cross-over study in 24 adult healthy volunteers. A 20% heart rate reduction, without bradycardia, was achieved by 69.9% of patients in the ivabradine group versus 12.2% in the placebo group during the titration period of 2 to 8 weeks (Odds ratio: E=17.24, 95% CI [5.91 ; 50.30]).

The mean ivabradine doses allowing to achieve a 20% heart rate reduction were 0.13 ± 0.04 mg/kg twice daily, 0.10 ± 0.04 mg/kg twice daily and 4.1 ± 2.2 mg twice daily in the age subsets [1-3]years, [3-18]years and <40 kg and [3-18]years and ≥ 40 kg, respectively.

Mean LVEF increased from 31.8% to 45.3% at M012 in ivabradine group versus 35.4% to 42.3% in the placebo group. There was an improvement in NYHA class in 37.7% of ivabradine patients versus 25.0% in the placebo group. These improvements were not statistically significant.

The safety profile, over one year, was similar to the one described in adult CHF patients.

The long-term effects of ivabradine on growth, puberty and general development as well as the long-term efficacy of therapy with ivabradine in childhood to reduce cardiovascular morbidity and mortality have not been studied.

5.2 Pharmacokinetic properties

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 metabolisers 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 metabolised 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 metabolised 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 metabolised by CYP2D6 and CYP1A2, while S-enantiomer is primarily metabolised 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 metabolised mainly via hydroxylation. In the slow metabolisers 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 faeces. 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 (see section 4.2).

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 metabolised 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 (see section 4.5).

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 faeces 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 (see section 4.2).
- 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 (see section 4.2).
- 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 (see sections 4.2 and 4.3).
- Paediatric population: The pharmacokinetic profile of ivabradine in paediatric 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 (see sections 4.3, 4.4 and 4.5). The PK/PD relationship of ivabradine in paediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the PK/PD relationship described in adults.

5.3 Preclinical safety data

No preclinical studies have been performed with the Carivalan.

Carvedilol:

Non-clinical studies on safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity revealed no special hazard for humans. In reproductive toxicity studies, impaired fertility, embryotoxicity (increased post-implantation loss, decreased fetal body weight and delayed skeletal development) and increased neonatal mortality at one week post-partum were observed at high doses.

Ivabradine:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Reproductive toxicity studies showed no effect of ivabradine on fertility in male and female rats. When pregnant animals were treated during organogenesis at exposures close to therapeutic doses, there was a higher incidence of foetuses with cardiac defects in the rat and a small number of foetuses with ectrodactylia in the rabbit.

In dogs given ivabradine (doses of 2, 7 or 24 mg/kg/day) for one year, reversible changes in retinal function were observed but were not associated with any damage to ocular structures. These data are consistent with the pharmacological effect of ivabradine related to its interaction with hyperpolarisation-activated I_h currents in the retina, which share extensive homology with the cardiac pacemaker I_f current. Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Starch, Pregelatinised (maize)

Lactose, monohydrate

Cellulose, microcrystalline (E460)

Croscarmellose, sodium (E468)

Maltodextrin
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Tablet film-coating:

Glycerol (E422)
Hypromellose (E464)
Magnesium stearate (E470b)
Titanium dioxide (E171)
Iron oxide yellow (E172) (for 6,25/7,5 mg, 12,5/7,5 mg and 25/7,5 mg)
Macrogol 6000 (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/aluminum blister packed in cardboard cartons:
Calendar packs containing 14, 28, 56, 98 or 112 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

For RMS (The Netherlands):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<{DD/MM/YYYY}>

<{DD month YYYY}>

<[To be completed nationally]>

<Detailed information on this medicinal product is available on the website of {name of MS/Agency}>