APPROVED ON
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INFARMED

SUMMARY OF MEDICINAL 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]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 6.25 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.39 mg of ivabradine hydrochloride).
[Each film-coated tablet contains 6.25 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg of ivabradine hydrochloride]
[Each film-coated tablet contains 12.5 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.39 mg of ivabradine hydrochloride]
[Each film-coated tablet contains 12.5 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg of ivabradine 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.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Carivalan 6.25/ 5 mg:White, hexagonal, film-coated tablet engraved with  on one face and CI2 on the other face.
Carivalan 6.25/7.5 mg: Yellow, hexagonal, film-coated tablet engraved with  on one face and CI3 on the other face.
Carivalan 12.5/5 mg: White, elliptic, film-coated tablet engraved with  on one face and CI4 on the other face.
Carivalan 12.5/7.5 mg: Yellow, elliptic, film-coated tablet engraved with  on one face and CI5 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 with ivabradine and carvedilol taken concomitantly at the same dosage levels for:
- symptomatic treatment of chronic stable angina pectoris in patients with coronary artery disease
- treatment of chronic heart failure (NYHA classes II-IV) with systolic dysfunction

4.2 Posology and method of administration

Posology

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

Carivalan should be used only in patients controlled with stable doses of the individual components administered simultaneously, when carvedilol and ivabradine are at their optimal dose.

The fixed-dose combination is not suitable for initiating therapy.

If it is necessary to change the posology, dosage adjustment should be done with the individual components carvedilol and ivabradine, ensuring the patient is kept at the optimal dose of carvedilol and ivabradine. It is recommended that the decision to adjust treatment be taken with the availability of a series of measurements of heart rate, ECG or 24-hour ambulatory monitoring.

If, during treatment, resting heart rate falls below 50 beats per minute or the patient displays symptoms related to bradycardia, such as dizziness, fatigue or hypotension, dosage reduction should be carried out with the individual components carvedilol and ivabradine, ensuring the patient is maintained at the optimal dose of these drugs. After dosage reduction, heart rate should be monitored (see section 4.4).
Treatment should be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dosage 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 therefore be used with caution in this patient population.

Monitoring of renal function is recommended in patients with chronic heart failure and 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 patients
Carivalan can be administered to 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 for ivabradine are shown in section 5.1.

Method of administration
Oral route.
Carivalan tablets should be taken twice daily during meals (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any other beta-blocker or to any of the excipients 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 dependency (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-lowering properties (see section 4.5);
- Combination with potent cytochrome P450 3A4 inhibitors, such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, oral erythromycin, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone (see sections 4.5 and 5.2);
- Pregnancy, lactation and women of child-bearing potential who are not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Special precautions

Absence of benefit on clinical outcomes in patients with symptomatic chronic stable angina pectoris.
Carivalan is indicated only in the symptomatic treatment of chronic stable angina pectoris, as ivabradine has no benefits on cardiovascular outcomes (for example: myocardial infarction or cardiovascular death) (see section 5.1).

Measurement of heart rate
As heart rate may fluctuate considerably over time, a series of measurements of heart rate, ECG or 24-hour ambulatory monitoring should be considered to determine resting heart rate in patients on treatment with ivabradine when titration is considered. This recommendation also applies to patients with a low heart rate, in particular when heart rate falls below 50 bpm, or after dosage reduction (see section 4.2).

Cardiac arrhythmias
Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and probably loses its efficacy when a tachyarrhythmia occurs (e.g. ventricular or supraventricular tachycardia). Carivalan is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.

The risk of developing atrial fibrillation increases in patients treated with ivabradine (see section 4.8). Atrial fibrillation has been more common in patients concomitantly using amiodarone or potent class I anti-arrhythmics. Regular clinical monitoring of patients treated with ivabradine for the occurrence of atrial fibrillation (sustained or paroxysmal) is recommended; this should also include ECG monitoring if clinically indicated (i.e. in case of aggravated angina, palpitations, irregular pulse).

Patients should be informed of the signs and symptoms of atrial fibrillation and advised to contact their physician if they occur. If atrial fibrillation develops during treatment, the relationship between the benefits and risks of continuing treatment with Carivalan should be carefully reconsidered.

Chronic heart failure patients with intraventricular conduction defects (left bundle branch block, right bundle branch block) and ventricular dyssynchrony should be carefully monitored.

Use in patients with low heart rate
Carivalan cannot be initiated in patients with a resting heart rate below 50 beats per minute (see section 4.3).
If, during treatment with Carivalan, resting heart rate persistently drops below 50 bpm or the patient displays symptoms related to bradycardia, such as dizziness, fatigue or hypotension, dosage reduction should be carried out with the individual components, ensuring that the patient is kept at the optimal dose of carvedilol and ivabradine or that treatment is 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 issues have arisen related to 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 treatment with Carivalan. Carivalan is not recommended in heart failure patients with NYHA functional classification IV because of the limited amount of data with ivabradine in this population.
Carivalan should be used with caution when combined with digitalis glycosides as these products, like carvedilol, may slow AV conduction (see section 4.5).

Stroke
The use of Carivalan is not recommended immediately after a stroke because there is no available data on ivabradine in these situations.

Visual function
Ivabradine influences retinal function. There is no evidence of a toxic effect on the retina with long-term ivabradine treatment (see section 5.1). Withdrawal of treatment should be considered if any unexpected deterioration of visual function occurs. Precautions should be taken in patients with retinitis pigmentosa.

Precautions for use

Stopping treatment
If necessary, administration of ivabradine may be interrupted; however, abrupt withdrawal of therapy with a beta-blocker should be avoided, especially in patients with ischaemic disease. The end of treatment with Carivalan should be followed immediately by administration of an individual carvedilol tablet in order to ensure that the patient is kept at an optimal dose of carvedilol. Individual carvedilol posology should be decreased gradually, for example by reducing the daily dose by half every three days. If necessary, replacement therapy should be initiated simultaneously to prevent exacerbation of angina pectoris. If the patient develops symptoms, the dose should be reduced more slowly.

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

Patients with hypotension
Existing data in patients with mild to moderate hypotension are limited, and ivabradine should therefore be used with caution in these patients. Carivalan is contraindicated 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 any risk of (excessive) bradycardia on return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. However, in the absence of further data, non-urgent electrical 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 is necessary, careful 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 modification of blood pressure treatment, were transient, and did not affect the treatment effect of ivabradine. When changes are made to the treatment of patients with chronic heart failure treated with ivabradine, blood pressure should be monitored at appropriate intervals (see section 4.8).

Diabetic patients
Carvedilol may mask the symptoms and signs of acute hypoglycaemia. Impaired blood glucose control may occasionally occur in patients with diabetes mellitus and heart failure, associated with the use of carvedilol. Therefore, careful monitoring of diabetic patients medicated with Carivalan is required, by means of regular blood glucose measurements and adjustment of blood sugar-lowering medication as necessary (see section 4.5).

Peripheral vascular disease
Carivalan should be used with caution in patients with peripheral vascular disease, as beta-blockers may precipitate or aggravate symptoms of disease. The same applies to patients 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 increase. Precautions should therefore be taken when certain anaesthetics are used because of synergy of the negative inotropic effects of carvedilol and the anaesthetics (see section 4.5).

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

Contact lenses
Contact lens users medicated with Carivalan should be warned of the possibility of reduced tear production due to the carvedilol component.

Hypersensitivity
Carivalan should be administered with caution in patients with a history of serious hypersensitivity reactions and in patients undergoing desensitisation therapy, as beta-blockers, such as carvedilol, may increase sensitivity to allergens and the severity of anaphylactic reactions.

Psoriasis
In patients with a personal or family history of psoriasis associated with beta-blocker therapy, Carivalan should be prescribed only after a careful assessment of the risks and benefits, given that beta-blockers may aggravate skin reactions.

Phaeochromocytoma
In patients with phaeochromocytoma, treatment with an alpha-blocker should be initiated prior to use of a beta-blocker. Although carvedilol has alpha- and beta-blocking pharmacological activity, there is no data on the use of carvedilol in this condition. Therefore, in patients in whom phaeochromocytoma is suspected, Carivalan should be administered with caution.

Other precautions
Because there is insufficient clinical data, carvedilol should not be administered to patients with labile or secondary hypertension, orthostatic hypotension, acute myocarditis, haemodynamically relevant stenosis of the heart valves or ventricular outflow tract, or end-stage peripheral arterial disease, or who are medicated concomitantly with an alpha 1-receptor antagonist or an alpha 2-receptor agonist.

Excipients
As the tablets contain lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Carivalan contains less than 1 mmol sodium (23 mg) per tablet, i.e. it is virtually ‘sodium-free’.

Athletes:
This medicine contains the active substance carvedilol which may give rise to a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between carvedilol and ivabradine were observed in an interaction study conducted in healthy volunteers. Known information on interactions with other medicinal products for each of the individual active substances is provided below.

Ivabradine is metabolised by CYP3A4 only and is a very weak inhibitor of this cytochrome. Ivabradine has been shown not to influence the metabolism and plasma concentrations of other

CYP3A4 substrates (weak, moderate and strong inhibitors). CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant degree. Drug interaction studies have established that CYP3A4 inhibitors increase plasma ivabradine concentrations, while inducers decrease them. Increased plasma concentrations of ivabradine may be associated with a 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 drugs transported by P-glycoprotein will increase with concomitant administration of carvedilol. 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 decrease or increase the plasma concentration of R- and S-carvedilol (see section 5.2).
Some of the interactions that have been observed in patients or healthy individuals are described below. However, this list is not exhaustive.

Concomitant use contraindicated (see section 4.3):

Known interaction with the medicinal product	Component	Interaction with other medicinal products
Potent CYP3A4 inhibitors (azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, oral erythromycin, 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 contraindicated. Potent CYP3A4 inhibitors, such as ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased mean plasma exposure to ivabradine 7- to 8-fold (see section 4.3).
	Carvedilol Concomitant use with precautions	Patients medicated with inhibitors of cytochrome P450 enzymes (e.g. cimetidine, fluoxetine, verapamil, ketoconazole, haloperidol, erythromycin) should be carefully 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 (see section 4.3).

Known interaction with the medicinal product	Component	Interaction with other medicinal products
	Carvedilol Concomitant use with precautions	Isolated cases of conduction disturbances (rarely with haemodynamic implications) have been observed when carvedilol has been administered with diltiazem or verapamil. As with other beta-blockers, if carvedilol is to be administered concomitantly with verapamil- or diltiazem-type calcium channel blockers, it is recommended to monitor ECG and blood pressure, as such concomitant administration may increase the risk of AV conduction disturbances.

Concomitant use not recommended (see section 4.4):

Known interaction with the medicinal product	Component	Interaction with other medicinal products
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 and intravenous erythromycin).	Ivabradine Concomitant use not recommended	Concomitant use of cardiovascular and non-cardiovascular QT-prolonging medicinal products and ivabradine should be avoided, as QT prolongation may be exacerbated by heart rate reduction. If the combination is necessary, careful cardiac monitoring is required (see section 4.4).
	Carvedilol Concomitant use with precautions with amiodarone	In patients with heart failure, amiodarone reduced the clearance of S-carvedilol, very probably by inhibiting CYP2C9. Mean plasma concentration of R-carvedilol remained unchanged. Consequently, there is a 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 implications) have been observed when carvedilol has been administered with amiodarone. Concomitant administration of carvedilol and (oral) amiodarone should be carefully monitored as cases of bradycardia, cardiac arrest and ventricular fibrillation have been reported shortly after the initiation of concomitant treatment.
Intravenous antiarrhythmic drugs (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 drugs and carvedilol. Concomitant use of beta-blockers with drugs of this type should be carefully monitored
Grapefruit juice	Ivabradine Concomitant use not recommended	Ivabradine exposure was increased 2-fold after concomitant administration with grapefruit juice. Consumption of grapefruit juice with ivabradine should therefore be avoided.

Concomitant use with precautions:

Known interaction with the medicinal product	Component	Interaction with other medicinal products
Moderate CYP3A4 inhibitors (other than diltiazem, verapamil) e.g. fluconazole	Ivabradine Concomitant use with precautions	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 enzyme inducers	Ivabradine Concomitant use with precautions	CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, Hypericum perforatum [St John's Wort]) may decrease ivabradine exposure and activity. Concomitant use of CYP3A4-inducing medicinal products may require an adjustment of ivabradine dosage. The combination of ivabradine 10 mg twice daily with St John's Wort has been shown to reduce ivabradine AUC by half. Intake of St John's Wort should be restricted during treatment with ivabradine.
	Carvedilol Concomitant use with precautions with rifampicin	In a study of 12 healthy subjects, administration of rifampicin with carvedilol reduced plasma concentrations of carvedilol by around 70%, very probably by inducing P-glycoprotein, which caused a decrease in intestinal absorption of carvedilol and an antihypertensive effect.
Cimetidine	Carvedilol Concomitant use with precautions	Cimetidine increased the AUC of carvedilol by about 30% without causing any changes in C_{max}. It may be necessary to take care with patients medicated with inhibitors of mixed function oxidases (e.g. cimetidine), as they may increase serum carvedilol levels. However, based on cimetidine's relatively small effect on carvedilol levels, the likelihood of significant clinical interactions is minimal.
Fluoxetine	Carvedilol Concomitant use with precaution	In a randomised, cross-over study in 10 patients with heart failure, concomitant administration of carvedilol and fluoxetine, a strong inhibitor of CYP2D6, resulted in stereoselective inhibition of carvedilol metabolism with a 77% increase in the mean AUC of the R(+) enantiomer. However, no differences in adverse events, arterial blood pressure or heart rate were observed between treatment groups.
Cardiac glycosides (digoxin, digitoxin)	Carvedilol Concomitant use with precautions	Digoxin and digitoxin concentrations increase when digoxin and carvedilol are administered concomitantly. Digoxin, digitoxin and carvedilol all prolong AV conduction time and increased monitoring of digoxin levels is therefore recommended when initiating, adjusting or discontinuing treatment with Carivalan.
Ciclosporin	Carvedilol Concomitant use with precautions	Two studies in kidney and heart transplant patients medicated with oral ciclosporin showed an increase in plasma ciclosporin concentration following initiation of treatment with carvedilol. Carvedilol appears to increase absorption of orally administered ciclosporin,

Known interaction with the medicinal product	Component	Interaction with other medicinal products
		by inhibiting P-glycoprotein activity in the intestine. In order to maintain therapeutic levels, it was necessary to reduce ciclosporin dosage in approximately 30% of patients, while others required no dosage adjustment. On average, the dose in these patients was reduced by approximately 20%. Because of high inter-individual dose variability, it is recommended that ciclosporin concentrations be monitored carefully after initiation of Carivalan and that the dose of ciclosporin be adjusted appropriately. No interaction is expected between carvedilol and ciclosporin administered intravenously.
Insulin or oral hypoglycaemics	Carvedilol Concomitant use with precautions	Beta-blockers may increase the blood sugar-lowering effects of insulin and oral hypoglycaemic medicines. Symptoms of hypoglycaemia (especially tachycardia and palpitations) may be masked or attenuated. Blood glucose levels should therefore be carefully monitored in patients medicated with insulin or oral hypoglycaemic agents.
Catecholamine-depleting drugs	Carvedilol Concomitant use with precautions	Patients medicated concomitantly with beta-blockers (such as carvedilol) and catecholamine-depleting drugs (e.g. reserpine, guanethidine, methyldopa, guanfacine and monoamine oxidase inhibitors (except MAO-B inhibitors)) should be carefully observed for signs of severe bradycardia and/or hypotension
Clonidine	Carvedilol Concomitant use with precautions	Concomitant administration of clonidine and beta-blockers (such as carvedilol) may potentiate blood pressure-lowering and heart rate-lowering effects. In the event of withdrawal of concomitant treatment with beta-blockers and clonidine, the beta-blocker should be discontinued first. Treatment with clonidine may be discontinued a few days later, by gradually decreasing the dosage
Dihydropyridine	Carvedilol Concomitant use with precautions	Concomitant administration of dihydropyridines and carvedilol should be carefully monitored as there have been reports of heart failure and severe hypotension in this situation.
Anaesthetics	Carvedilol Concomitant use with precautions	Careful monitoring of vital signs is recommended during anaesthesia due to synergy of the hypotensive and negative inotropic effects of carvedilol and anaesthetics.
Beta-agonist bronchodilators	Carvedilol Concomitant use with precautions	Non-cardioselective beta-blockers antagonise the bronchodilatory effects of beta-agonist bronchodilators. Careful monitoring of these patients is recommended.
Potassium-depleting diuretics (thiazide diuretics and loop diuretics)	Ivabradine Concomitant use with precautions	Hypokalaemia may increase the risk of arrhythmias. As ivabradine may cause bradycardia, the resulting combination of hypokalaemia and bradycardia is a

Known interaction with the medicinal product	Component	Interaction with other medicinal products
		predisposing factor for the onset of severe arrhythmias, especially in patients with long QT syndrome, whether of congenital origin or substance-induced.

Concomitant use to be taken into consideration (because of carvedilol):

Known interaction with the medicinal product	Interaction with other medicinal product
Antihypertensive drugs	As with other drugs with beta-blocking activity, carvedilol may potentiate the effect of other concomitantly administered drugs with an antihypertensive effect (e.g. alpha 1-receptor antagonists) or that have hypotension as part of their adverse effect profile.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Concomitant administration of NSAIDs and beta-blockers may lead to an increase in blood pressure and decrease the ability to control blood pressure. The antihypertensive effect of carvedilol decreases 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 stabilised blood pressure medicated with other drugs, such as oestrogens or corticosteroids.
Nitrates	Nitrates increase hypotensive effects.
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	Increased vasoconstriction.
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 representing a specific risk for excessive bradycardia.
Barbiturates	Concomitant administration of carvedilol with barbiturates may result in a decrease in the efficacy of carvedilol due to enzyme induction.

Specific drug interaction studies have shown no clinically significant effect of the following medicinal products on the 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 and warfarin and on the pharmacodynamics of aspirin.

In the principal phase III clinical trials, the following medicinal products were routinely combined with ivabradine with no evidence of safety problems: angiotensin-converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, aldosterone antagonists, short- and long-acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetic agents, aspirin and other anti-platelet medicinal products.

Paediatric population
Interaction studies have been performed only 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
On the basis of existing data on the individual components, the use of Carivalan is contraindicated 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 to humans is unknown. Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death and immature and premature births. In addition, adverse effects (especially hypoglycaemia and bradycardia, hypotension, respiratory depression and hypothermia) may occur in the foetus and newborn. There may be an increased risk of cardiac and pulmonary complications in the newborn during the postnatal period.
Data on the use of ivabradine in pregnant women are limited or non-existent.

Animal studies with ivabradine have shown reproductive toxicity. These studies showed embryotoxic and teratogenic effects (see section 5.3). The potential risk to humans is unknown.

Breast-feeding
Carivalan is contraindicated during breast-feeding (see section 4.3).
Animal studies have shown that carvedilol or its metabolites are excreted in breast milk. It is not known whether carvedilol is excreted in breast milk in humans.
Animal studies show that ivabradine is excreted in milk. Women who need to take ivabradine should stop breast-feeding and have recourse to another method of feeding their children.

Fertility
There are no clinical data on the use of Carivalan as regards fertility.
Studies with carvedilol have shown impaired fertility in adult female rats. Studies in rats with ivabradine have shown no effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of existing data with the individual components, use of Carivalan may affect the ability to drive or use machinery.

Due to the variety of specific reactions of each individual medicated with 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 alcoholic drinks are consumed.

Ivabradine may affect the patient’s ability to drive. Patients should be warned that ivabradine may cause transient luminous phenomena that consist mainly of phosphenes. Luminous phenomena may occur in situations when there are sudden variations in light intensity, particularly 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 safety profile

In the case of carvedilol, the frequency of undesirable effects is not dose-dependent, except in the case of dizziness, visual disturbances and bradycardia.

For ivabradine, the most common adverse reactions were luminous phenomena (phosphenes) and bradycardia, which are dose-dependent and related to the pharmacological effect of the medicinal product.

Table with list of adverse reactions:

The following adverse reactions were observed during treatment with carvedilol and ivabradine administered separately and grouped by MedDRA classification, according to organ system class and 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 calculated from the available data).

MedDRA system organ class	Adverse reaction	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 of 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	Luminous phenomena (phosphenes)	-	Very common
	Visual impairment	Common	Uncommon
	Irritation of the eye	Common	-
	Blurred vision	-	Common
	Reduced lacrimation	Common	-
	Diplopia	-	Uncommon
Ear and labyrinth disorders	Vertigo	-	Uncommon

MedDRA	Adverse reaction	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	-
	1st degree AV block (prolonged PQ interval on ECG)	-	Common
	Ventricular extrasystoles	-	Common
	Atrial fibrillation	-	Common
	Angina pectoris	Uncommon	-
	Palpitations	-	Uncommon
	Supraventricular extrasystoles	-	Uncommon
	AV block	Uncommon	-
	2nd degree AV block	-	Very rare
	3rd degree AV block	-	Very rare
	Sick sinus syndrome	-	Very rare
Vascular disorders	Hypotension	Very common	Uncommon (probably related to bradycardia)
	Postural hypotension	Common	-
	Disturbances of peripheral circulation (cold extremities, PVD, exacerbation of intermittent claudication and Raynaud's 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
	Diarrhoea	Common	Uncommon
	Abdominal pain	Common	Uncommon*
	Vomiting	Common	-
	Dyspepsia	Common	-
	Constipation	Uncommon	Uncommon
	Dry mouth	Rare	-
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 (which may occur several weeks up to years after the start of treatment). Existing lesions may worsen.	Uncommon	-
	Alopecia	Uncommon	-
	Angioedema	-	Uncommon
	Exanthema	-	Uncommon
	Erythema	-	Rare
	Pruritus	-	Rare

MedDRA	Adverse reaction	Frequency	
	Urticaria	-	Rare
	Severe skin reactions (such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)	Very rare	-
Musculoskeletal and connective tissue disorders	Pain in extremities	Common	-
	Gout	Common	-
	Muscle spasms	-	Uncommon
Renal and urinary disorders	Renal failure and changes in renal function 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
	Prolonged QT interval on ECG	-	Uncommon
	Increase in the transaminases ALT, AST and GGT	Very rare	-
Reproductive system and breast disorders	Impotence, erectile dysfunction	Uncommon	-

*Frequency calculated on the basis of adverse events detected by way of spontaneous reports in clinical trials

Description of selected adverse reactions

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

Heart 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).

Reversible deterioration in renal function has been observed during treatment with carvedilol in patients with chronic heart failure and low blood pressure, ischaemic heart disease and diffuse vascular disease and/or baseline renal insufficiency (see point 4.4).

Non-selective beta-blockers in particular may cause latent diabetes to become manifest, manifest diabetes to become worse and blood glucose control to deteriorate. Although it is not common, glucose balance may also be slightly altered during treatment with carvedilol.

In women, carvedilol may cause urinary incontinence, which resolves once treatment is discontinued.

Ivabradine
Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient increase in brightness in a limited area of the visual field. They are generally triggered by sudden variations in light intensity. Phosphenes may also be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), bright, coloured lights, or multiple images (retinal persistency). The onset of phosphenes is generally during 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 disappeared during or after treatment; the majority (77.5%) disappeared during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment on account of phosphenes.

Bradycardia was reported by 3.3% of patients, particularly during the first 2 to 3 months after the start of treatment. 0.5% of patients experienced severe bradycardia of 40 bpm or lower.

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

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important, as it enables continuous monitoring of the risk/benefit relationship of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly

4.9 Overdose

There is no information on overdose with Carivalan in man.

Symptoms:

Related to carvedilol
In the event of overdose, severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest may occur. Respiratory problems, bronchospasm, vomiting, altered consciousness and generalised seizures may also occur.

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

Treatment*:*
In addition to general procedures, vital signs should be monitored and corrected, if necessary in intensive care. For 4 hours after administration, absorption of carvedilol in the gastrointestinal tract can be reduced by gastric lavage, activated charcoal and induced vomiting.

Patients should be placed in the supine position. Intravenous (i.v.) atropine, at a dose of 0.5 mg to 2 mg, 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 administered in the event of severe bradycardia, which should be treated symptomatically by specialists. To support ventricular function, intravenous administration of glucagon or sympathomimetics (e.g. dobutamine, isoprenaline, orciprenaline or adrenaline, according to body weight and effect) is recommended. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment should be considered, in particular with intravenous beta-stimulating agents such as isoprenaline; temporary cardiac pacing may also be introduced, if necessary. Hypotension may be treated with administration of intravenous fluids.
If a positive inotropic effect is required, phosphodiesterase inhibitors such as milrinone may be considered. In the case of drug-resistant bradycardia, it may be necessary to implant a pacemaker. If peripheral vasodilation dominates in the toxicological profile then norfenefrine or noradrenaline should be administered, with continuous monitoring of the circulation (5 to 10 micrograms i.v., repeated according to arterial blood pressure response; or 5 micrograms per minute by infusion, titrated according to arterial blood pressure).

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

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 should be continued for a sufficiently long period, as prolongation of elimination half-life and redistribution of carvedilol from deeper compartments are to be expected. Consequently, supportive treatment should be continued until the patient is stabilised. Treatment duration depends on the severity of the overdose.

Carvedilol is not eliminated by dialysis, as the active substance cannot be dialysed, probably 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 peripheral vascular resistance by selectively blocking alpha 1 receptors and suppressing 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 racemic mixture of two stereoisomers. In animal models, both enantiomers showed alpha adrenergic-blocking characteristics. 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 human cells of various types.

Pharmacodynamic effects:

In hypertensive patients, decreased blood pressure is not associated with a concomitant increase in peripheral resistance, contrary to what is observed with pure beta-blockers. Heart rate is slightly decreased and systolic volume unchanged. Renal blood flow and renal function remain normal, as does peripheral blood flow; consequently, coldness of the extremities, which is common with beta-blockers, is rare. In hypertensive patients, carvedilol increases plasma norepinephrine concentration.

In prolonged treatment of patients with angina pectoris, carvedilol was seen to have an anti-ischaemic effect and to relieve pain. Haemodynamic studies have demonstrated that carvedilol reduces ventricular preload and afterload.

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

Carvedilol has no negative effect on serum electrolytes or lipid profile. 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, the 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; as a consequence the extremities get cold only in exceptional cases.
- A normal ratio between HDL and LDL is maintained.
- Serum electrolytes are not altered.
- Carvedilol does not stimulate the renin-angiotensin system; plasma renin actually decreases. Water retention is rare.
- In patients with heart failure, carvedilol showed favourable effects on haemodynamics and an improvement in left ventricular dimensions and ejection fraction. In patients with ischaemic heart disease, carvedilol showed anti-ischaemic and anti-anginal properties. Carvedilol reduces ventricular preload and afterload.

In a large multicentre, double-blind, placebo-controlled study that evaluated mortality (COPERNICUS), 2,289 patients with severe, ischaemic or non-ischaemic, chronic, stable heart failure medicated with standard therapy were randomised to carvedilol (1,156 patients) or placebo (1,133 patients). Patients had left ventricular systolic dysfunction with mean ejection fraction of less than 20%. All-cause mortality was reduced by 35%: 19.7% in the placebo group versus 12.8% in the carvedilol group (Cox proportional hazards, p=0.00013). The benefit of carvedilol on mortality was consistent in all subpopulations studied. Sudden death was reduced by 41% in the carvedilol group (4.2% versus 7.8%). The set of secondary assessment parameters, in terms of mortality or hospitalisations due to heart failure, mortality or hospitalisations due to cardiovascular causes and all-cause mortality or 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 across 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 an agent that purely lowers the heart rate, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls 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, or on myocardial contractility or ventricular repolarisation.

Ivabradine can also interact with the retinal I_h current which closely resembles cardiac I_f. It participates in the temporal resolution of the visual system, by reducing the retinal response to bright light stimuli. In specific circumstances (such as sudden changes in luminosity), partial inhibition of I_h

by ivabradine explains the luminous phenomena that may occasionally be experienced by patients. Luminous phenomena (phosphenes) are described as a transient increase in brightness in a limited area of the visual field (see section 4.8).

Pharmacodynamic effects:

The main pharmacodynamic property of ivabradine in man 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 the doses usually recommended, heart rate reduction is approximately 10 bpm at rest and during exercise. This results in a decrease 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, one versus atenolol and one versus amlodipine). These trials included a total of 4,111 patients with stable angina pectoris, of whom 2,617 received ivabradine.

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters at the end of 3 to 4 weeks of treatment. Efficacy was confirmed with 7.5 mg twice daily. In particular, the additional benefit relative to 5 mg twice daily was established in a reference-controlled study versus atenolol: total exercise duration at trough 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 over. The efficacy of 5 and 7.5 mg twice daily was consistent across all the 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 ivabradine dosage regimen ensured uniform efficacy over 24 hours.

In a randomised, placebo-controlled study in 889 patients, ivabradine added to atenolol 50 mg once daily showed additional efficacy on all exercise test parameters at the trough of drug activity (12 hours after oral administration).

In a randomised, placebo-controlled study in 725 patients, ivabradine did not show additional efficacy over amlodipine 10 mg once daily at the trough of drug activity (12 hours after oral administration) while additional efficacy was shown at peak (3-4 hours after oral administration).

In a randomised placebo-controlled study in 1,277 patients, ivabradine, when added to amlodipine 5 mg once daily or nifedipine GITS 30 mg once daily over a 6-week treatment period, demonstrated a statistically significant additional efficacy (OR = 1.3, 95% CI [1.0–1.7]; p=0.012) at the trough of drug activity (12 hours after oral intake of ivabradine) 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 exercise test). Ivabradine did not show additional efficacy on secondary endpoints of exercise test parameters at the trough of drug activity while an additional efficacy was shown at the 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 or of rebound phenomena after abrupt discontinuation of treatment. 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 arterial blood pressure) at rest and during exercise. Effects on arterial pressure and peripheral vascular resistance were small and not clinically significant.

A sustained reduction in 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 maintained in diabetic patients (n=457) with a safety profile similar to that of the population in general.

A large study, BEAUTIFUL, was carried out in 10,917 patients with coronary artery disease and left ventricular dysfunction (LVEF <40%) already treated with the therapy deemed optimal, in which 86.9% of patients were receiving beta-blockers. The main efficacy criterion was the composite of cardiovascular death, hospitalisation for acute myocardial infarction or hospitalisation for new onset or worsening of heart failure. The study showed no difference in the frequency of the primary composite outcome in the ivabradine group in comparison with 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=1,507), no safety signal was identified in relation to cardiovascular death, hospitalisation for acute myocardial infarction or heart failure (ivabradine 12.0% versus placebo 15.5%, p=0.05). For this subgroup, a subsequent analysis in patients treated with carvedilol at the start of the study (n=254) showed similar results (ivabradine 8.4% versus placebo 17.9%, HR: 0.40, 95% CI [0.19; 0.83]).

A large study, SIGNIFY, was carried out in 19,102 patients with coronary artery disease and without clinical heart failure (LVEF >40%) already treated with the therapy deemed optimal. 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], titrated up to 10 mg twice daily). The main efficacy criterion was the composite outcome 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 in comparison with the placebo group (relative risk ivabradine/placebo 1.08, p=0.197). Bradycardia was reported in 17.9% of patients in the ivabradine group (2.1% in the placebo group). During the study, 7.1% of patients received verapamil, diltiazem or strong CYP 3A4 inhibitors.
A small, statistically significant, increase in the primary composite endpoint was observed in a pre-specified subgroup of patients with CCS class II angina or higher at baseline (n=12,049) (annual rate 3.4% versus 2.9%, relative risk ivabradine/placebo 1.18, p=0.018), but not in the subgroup of the total population with angina of CCS class ≥ I (n=14,286) (relative risk ivabradine/placebo 1.11, p=0.110).
The higher-than-approved dose used in the study does not fully explain these results.

The SHIFT study was a large, multicentre, international, randomised, double-blind, placebo-controlled study conducted in 6,505 adult patients with stable chronic heart failure (for ≥ 4 weeks), NYHA class II to IV, with reduced left ventricular ejection fraction (LVEF ≤ 35%) and resting heart rate ≥ 70 bpm. Patients received the standard treatment, 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. Median duration of follow-up 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 the ivabradine and placebo groups 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 reduction in relative risk of 18% in the rate of the primary composite endpoint including cardiovascular mortality and hospitalisations for worsening heart failure (hazard ratio: 0.82, 95% CI [0.75; 0.90] – p<0.0001), apparent 3 months after the start of treatment. The absolute risk reduction was 4.2%. The results for the primary endpoint were explained chiefly by the outcomes for heart failure, hospitalisation for worsening heart failure (absolute risk reduction of 4.7%) and death from heart failure (absolute risk reduced by 1.1%).

Effect of treatment on the primary composite endpoint, its components and secondary endpoints

	Ivabradine (N=3241) n (%)	Placebo (N=3264) 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:				
- Cardiovascular 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 heart failure	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 cardiovascular reasons	977 (30.15)	1,122 (34.38)	0.85 [0.78; 0.92]	0.0002

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

A significant improvement in NYHA class was seen in the last recorded value: 887 (28%) of patients who received ivabradine improved, compared with 776 (24%) of patients who received placebo (p=0.001).

In the subgroup of patients with HR ≥75 bpm (n=4150), a more significant reduction of 24% was recorded in the primary composite endpoint (hazard ratio: 0.76, 95% CI [0.68; 0.85] – p<0.0001); this effect was also observed 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 was in line with that of the population in general.

A significant effect on the primary composite endpoint was observed in the group of patients who received treatment with beta-blockers (hazard ratio: 0.85, 95% CI [0.76; 0.94]). In the subgroup of patients with HR ≥75 bpm and with 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 the start of the study (n=2596), a significant reduction of relative risk was observed in the primary composite endpoint in the ivabradine group compared with the placebo group (hazard ratio: 0.80, 95% CI [0.68; 0.94]). In the subgroup of patients with HR ≥ 75bpm and receiving carvedilol at the start of the study (n=1654), a consistent trend was observed (HR: 0.79, 95% CI [0.65; 0.95]).

In a randomised, placebo-controlled study in 97 patients, the data collected during specific ophthalmologic investigations for the purpose of 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 randomized, double-blind, placebo-controlled study was conducted in 116 paediatric patients (17 aged between 6 and 12 months, 36 aged between 1 and 3 years and 63 aged between 3 and 18 years) with chronic heart failure and dilated cardiomyopathy, already treated with the therapy deemed optimal. Seventy-four patients received ivabradine (ratio 2:1).
The starting dose was 0.02 mg/kg twice daily in the subgroup aged 6-12 months; 0.05 mg/kg twice daily in the groups aged 1-3 years and 3-18 years weighing <40 kg; and 2.5 mg twice daily in the group aged 3-18 years and weighing ≥40 kg. The dose was adjusted depending on 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 in the form of oral solution or tablet twice daily. The absence of pharmacokinetic differences between the two formulations was shown in an open-label, randomized, two-period cross-over study in 24 healthy adult volunteers. A 20% reduction in heart rate, without bradycardia, was achieved in 69.9% of patients in the ivabradine group versus 12.2% in the placebo group during the titration period of 2 to 8 weeks (OR: E=17.24, 95% CI [5.91; 50.30]). The mean doses of ivabradine that enabled a 20% reduction in heart rate to be achieved 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 subgroups aged 1-3 years, aged 3-18 years and <40 kg, and aged 3-18 years and ≥40 kg, respectively.
Mean LVEF increased from 31.8% to 45.3% after 12 months in the ivabradine group versus 35.4% to 42.3% in the placebo group. There was an improvement in NYHA class in 37.7% of patients medicated with ivabradine versus 25.0% in the placebo group. These improvements were not statistically significant.
The safety profile, after one year, was similar to that described in adult patients with chronic heart failure.

The long-term effects of ivabradine on growth, puberty and general development, and the long-term efficacy of ivabradine therapy 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 administered separately as monotherapy.

Carvedilol
Absorption
The absolute bioavailability of carvedilol administered orally is approximately 25%. Peak plasma concentration is achieved approximately 1 hour after administration. There is a linear relationship between dose and plasma concentrations. In patients with slow debrisoquine hydroxylation, plasma carvedilol concentrations increased 2- to 3-fold, compared with rapid debrisoquine metabolisers. Food does not affect bioavailability but the time necessary to reach peak plasma concentration is longer.

Distribution
Carvedilol is highly lipophilic. Plasma protein binding is about 98 to 99%. Volume of distribution is approximately 2 L/kg. After oral administration, the first-pass effect is approximately 60-75%.

Biotransformation
Carvedilol is extensively metabolised to various metabolites that are mostly excreted in the bile. First-pass metabolism after oral administration is approximately 60-75%. Enterohepatic circulation of the initial substance has been demonstrated in animals.
Carvedilol is metabolised in the liver, mainly by oxidation and glucuronidation of the aromatic ring. 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 4-hydroxyphenol metabolite is approximately 13 times higher than that of carvedilol. However, metabolite concentrations in humans are about 10 times lower than those of carvedilol. Two of the hydroxy-carbazole metabolites of carvedilol are extremely potent antioxidants, which makes them 30-80 times stronger than carvedilol.

The oxidative metabolism of carvedilol is stereoselective. The R-enantiomer is chiefly metabolised by CYP2D6 and CYP1A2, while the S-enantiomer is chiefly metabolised by CYP2C9 and, to a lesser degree, by CYP2D6. Other CYP450 isoenzymes that participate in carvedilol metabolism include CYP3A4, CYP2E1 and CYP2C19. Peak plasma concentration of R-carvedilol in plasma is approximately twice the concentration of S-carvedilol. The R-enantiomer is metabolised mainly by hydroxylation. In slow metabolisers of CYP2D6, an increase in plasma carvedilol concentration, chiefly of the R-enantiomer, may occur, causing an increase in alpha-blocking activity.

Elimination
The mean half-life of elimination of carvedilol varies between 6 and 10 hours. Plasma clearance is approximately 590 ml/min. Elimination is mainly via the biliary route and excretion mainly in the faeces. A smaller proportion is eliminated renally in the form of metabolites.

Special populations
- Elderly: The pharmacokinetics of carvedilol are age-dependent. Plasma carvedilol levels are approximately 50% higher in the elderly than in young individuals.
- Hepatic impairment: in a study that included patients with liver cirrhosis, the bioavailability of carvedilol was four times higher, peak plasma concentration five times higher and volume of distribution three times higher than in healthy individuals.
- 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. There was however wide variation in the results.

Ivabradine
Under physiological conditions, ivabradine is rapidly released and is highly 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 man.

Absorption and bioavailability
Ivabradine is rapidly and almost completely absorbed after oral administration with a plasma peak reached after about 1 hour under fasting conditions. The absolute bioavailability of the film-coated tablets is around 40%, due to the first-pass effect in the intestine and liver.
Food delayed absorption by approximately 1 hour and increased plasma exposure by approximately 20 to 30%. Administration of the tablet during meals is recommended in order to decrease intra-individual variability of exposure (see section 4.2).

Distribution
Ivabradine is approximately 70% plasma protein bound and steady state volume of distribution is

approximately 100 L in patients. Peak plasma concentration following chronic administration of the recommended dose of 5 mg twice daily is 22 ng/ml (CV=29%). Mean plasma concentration is 10 ng/mL (CV=38%) at steady state.

Biotransformation
Ivabradine is extensively metabolised by the liver and the intestine by oxidation, exclusively through cytochrome P450 3A4 (CYP3A4). The principal active metabolite is the N-desmethylated derivative (S 18982), with an exposure of about 40% of the parent compound. Metabolism of this active metabolite also involves CYP3A4. Ivabradine has low affinity for CYP3A4, shows no clinically relevant induction or inhibition of CYP3A4 and it is therefore unlikely that it modifies CYP3A4 substrate metabolism or plasma concentrations. Conversely, potent inhibitors and inducers may substantially affect plasma concentrations of ivabradine (see section 4.5).

Elimination
Ivabradine is eliminated with a principal half-life of 2 hours (70-75% of AUC) in plasma and an effective half-life of 11 hours. Total clearance is about 400 ml/min and renal clearance is about 70 ml/min. Excretion of metabolites occurs to a similar extent via the urinary and gastrointestinal routes. About 4% of an oral dose is excreted unchanged in the urine.

Linearity/non-linearity
The kinetics of ivabradine are linear over an oral dosage range of 0.5-24 mg.

Special populations
- Elderly: no pharmacokinetic differences (AUC and C_{max}) have been observed between elderly patients (≥ 65 years), very elderly patients (≥75 years) and the population in general (see section 4.2).
- Renal impairment: the impact of renal impairment (creatinine clearance from 15 to 60 ml/min) on the pharmacokinetics of ivabradine is minimal, which is related to the small contribution of renal clearance (about 20%) to total elimination, both for ivabradine and for its main metabolite S 18982 (see section 4.2).
- Hepatic impairment: in patients with mild hepatic impairment (Child-Pugh score up to 7) the AUC of unbound ivabradine and the main active metabolite were about 20% higher than in subjects with normal liver 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 patients (between 6 months and 18 years) with chronic heart failure is similar to the pharmacokinetics described in adults, when the dosage scheme based on age and weight is used.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship
PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing plasma concentrations of ivabradine and S 18982 for doses of up to 15-20 mg twice daily. At higher doses, the decrease in heart rate is no longer proportional to plasma concentrations of ivabradine and tends to reach a plateau. High exposures to ivabradine, which 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 patients aged between 6 months and 18 years with chronic heart failure is similar to the PK/PD relationship described in adults.

5.3 Preclinical safety data

No preclinical studies have been carried out with the Carivalan.

Carvedilol:

Non-clinical studies on safety pharmacology, repeat-dose toxicity, genotoxicity and carcinogenic potential revealed no special risks for humans. In reproductive toxicity studies, lower fertility, embryotoxicity (increased post-implantation loss, decreased foetal body weight and delayed skeletal development) and increased neonatal mortality in the first week post-partum were observed with high doses of the drug.

Ivabradine:
Non-clinical data reveal no special risks for humans, according to conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies showed no effect of ivabradine on the fertility of male and female rats. When pregnant females were treated during organogenesis with exposures close to therapeutic doses, a higher incidence of foetuses with heart defects was observed in rats and a small number of foetuses with ectrodactylia in rabbits.

In dogs that received ivabradine (doses of 2, 7 or 24 mg/kg/day) for one year, reversible changes in retinal function, not associated with any damage to ocular structures, were observed. 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

Core:
Pregelatinised starch, (maize starch)
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Maltodextrin
Colloidal anhydrous silica
Magnesium stearate

Film coating*:*
Glycerol
Hypromellose
Magnesium stearate
Titanium dioxide (E171)
Yellow iron oxide (E172) (for 6.25/7.5 mg, 12.5/7.5 mg)
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Carton box containing 1,2,3,or 4 colourless (PVC/PVDC/AL) blisters, each of 7 film coated tablets with insert leaflet

6.6 Special precautions for disposal and handling

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

7. LICENSE HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes
France

8. MANUFACTURER
Les Laboratoires Servier Industrie
905, route de Saran
F-45520 Gidy
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