SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Implicor 25mg/5mg film-coated tablets
[Implicor 50mg/5mg film-coated tablets]
[Implicor 25mg/7.5mg film-coated tablets]
[Implicor 50mg/7.5mg film-coated tablets]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25mg of metoprolol tartrate and 5mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
[Each film-coated tablet contains 50 mg of metoprolol tartrate and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).]
[Each film-coated tablet contains 25 mg of metoprolol tartrate and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).]
[Each film-coated tablet contains 50 mg of metoprolol tartrate and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).]

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, film-coated tablet (25/5 mg) of 7.3mm diameter engraved with 1 on one face and on the other.
[White, round, film-coated tablet (50/5mg) of 8.5 mm diameter engraved with 2 on one face and  on the other.]
[White, oblong film-coated tablet (25/7.5 mg) of 9.3 mm long and 5.8 mm wide engraved with 3 on one face and  on the other.]
[White, oblong film-coated tablet (50/7.5mg) of 10.8 mm long and 6.7 mm wide, engraved with 4 on one face and  on the other.]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Implicor is indicated for the symptomatic treatment of chronic stable angina pectoris as substitution therapy in adult patients with normal sinus rhythm already controlled by metoprolol and ivabradine taken concomitantly at the same dose level.

4.2 Posology and method of administration

Posology

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

Implicor should only be used in patients controlled on stable doses of the monocomponents given concurrently when metoprolol is at the optimal dose.

It is recommended that the decision to titrate treatment takes place with the availability of serial heart measurements, ECG or ambulatory 24-hour monitoring and titration should be done with the individual components metoprolol and ivabradine, ensuring the patient is maintained at an optimal dose of metoprolol and ivabradine. 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 monocomponents metoprolol and ivabradine, ensuring the patient is maintained at an optimal dose of metoprolol. 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.

Patients with renal impairment
No dosage adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min (see section 5.2).

Implicor should be used with precaution in patients with creatinine clearance below 15 ml/min.

Patients with hepatic impairment
Implicor can be administered in patients with mild hepatic impairment.
Caution should be exercised when administering in patients with moderate hepatic impairment.
Implicor is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

Older people
Implicor can be administered in elderly patients with caution (see section 4.4).

Paediatric population
The safety and efficacy of Implicor in children and adolescents have not been established. No data are available.

Method of administration

Implicor should be taken orally twice daily during meals. The exposure of metoprolol is increased when administered with food (see section 5.2). This should be considered in patients who currently take metoprolol in a fasting state and switch to Implicor.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or to other beta-blockers (cross sensitivity between beta blockers may occur)
- Symptomatic bradycardia
- Cardiogenic shock
- Sick sinus syndrome (including Sino-atrial block)
- AV-block of 2nd and 3rd degree
- Acute myocardial infarction or patients with suspected acute myocardial infarction complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100mmHg) and/or severe heart failure.
- Severe (< 90/50 mmHg) or symptomatic hypotension
- Unstable or acute heart failure
- Patients undergoing intermittent inotropic therapy with beta-receptor agonist
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- Unstable angina
- Severe peripheral vascular disease
- Untreated phaeochromocytoma
- Severe hepatic insufficiency
- Metabolic acidosis

- 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)
- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties (see section 4.5)
- 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
Implicor 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 (e.g. ventricular or supraventricular tachycardia). Implicor 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 Implicor 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 ivabradine 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
Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 70 beats per minutes.
If, during treatment with Implicor, 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 monocomponents ensuring the patient is maintained at an optimal dose of metoprolol or treatment discontinued (see section 4.2).

Combination with calcium channel blockers
Concomitant use of Implicor 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 ivabradine treatment. Implicor should be used with caution in heart failure patients with NYHA functional classification IV due to limited amount of data in this population.

Stroke
The use of Implicor is not recommended immediately after a stroke since no data is available in these situations with ivabradine.

Visual function
Ivabradine influences on retinal function (see section 5.1). To date, there is no evidence of a toxic effect of ivabradine on the retina, but the effects of long-term ivabradine treatment beyond one year on retinal function are currently not known. Cessation of Implicor 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
Abrupt cessation of therapy with a beta-blocker should be avoided, especially in patients with ischaemic heart disease. The cessation of the therapy should immediately be followed by the intake of metoprolol mono-component ensuring the patient is maintained at an optimal dose of metoprolol. Ivabradine intake can be interrupted if necessary. Posology of metoprolol mono-component should be decreased gradually; ideally over a period of at least two weeks while at the same time starting the replacement therapy if necessary. If the patient develops any symptoms the dose should be reduced more slowly.

Patients with hypotension
Limited data are available in patients with mild to moderate hypotension treated with ivabradine, and Implicor should therefore be used with caution in these patients. Implicor is contra-indicated in patients with severe hypotension (blood pressure < 90/50 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 ivabradine.

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products
The use of Implicor 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 on ivabradine. When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval.

Bronchial asthma and chronic obstructive pulmonary diseases
Although metoprolol is a cardioselective betablocker, caution is advised in patients with bronchial asthma and chronic obstructive pulmonary diseases.
If necessary, simultaneously bronchodilator drugs, that selectively stimulate the β 2-receptors, for example, such as terbutaline, are prescribed. If the patient is already using a β 2-receptor stimulant, it may sometimes be necessary to adjust the dosage.

Severe peripheral arterial disease
In patients suffering from peripheral arterial disorders (Raynaud's disease or syndrome, arteritis or chronic occlusive arterial disease of the lower limbs), beta-blockers can aggravate the condition. In these cases, stop treatment with Implicor and titrate with the individual monocomponents. A cardioselective beta-blocker with partial agonist activity is preferable and should be administered with caution.

Phaeochromocytoma
When known or suspected to have phaeochromocytoma, beta-blockers should always be given in combination with an alpha blocker.

Diabetic patients
Caution is advised when Implicor is used in patients with diabetes mellitus, especially those who are using insulin or oral antidiabetic drugs. It is recommended to inform diabetic patients that beta-blockers may mask the hypoglycaemic tachycardia; however, other signs of hypoglycaemia such as drowsiness and sweating may not necessarily be suppressed and increased sweating may occur.

Prinzmetal angina
Beta-blockers may increase the number and duration of attacks in patients with Prinzmetal angina. The use of a cardioselective beta-1 blocker is possible in minor and associated forms, provided it is administered with a vasodilator.

Psoriasis.Exacerbation of psoriasis has been reported with beta-blockers. Patients with psoriasis or with a history of psoriasis should only be given beta-blockers after carefully balancing the benefits against the risks.

Thyrotoxicosis
Beta-blockers can mask the symptoms of thyrotoxicosis.

General anaesthesia
Long-term treatment with beta-blockers should not be routinely withdrawn prior to major surgery. The reduced ability of the heart to respond to adrenergic stimulation can increase the risks of general anaesthesia and surgical procedures. Before any surgery requiring general anaesthesia, the anaesthetist should be informed that the patient is being treated with a beta-blocker. If it is thought necessary to withdraw the beta-blocker before surgery, this should be done gradually and completed about 48 hours before general anaesthesia.

Older people
Elderly patients must be closely monitored since an excessive decrease in blood pressure or heart rate may lead to an insufficient blood supply to vital organs with beta-blockers.

Allergic reactions
Caution is advised in patients with a history of severe hypersensitivity reactions and patients undergoing desensitisation therapy as there is a risk of more severe anaphylactic reactions.
Metoprolol can increase the sensitivity to allergens and the severity of anaphylactic reactions. Therapy with adrenaline does not always have the desired therapeutic effect in individual patients treated with beta-receptor blockers (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between metoprolol 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.

Contra-indication of concomitant use

Linked to ivabradine

The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone is contra-indicated (see section 4.3). 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.

Linked to ivabradine and metoprolol

- Moderate CYP3A4 inhibitors: 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. The concomitant use of ivabradine with these medicinal products is contraindicated (see section 4.3).
- Calcium channel blockers such as Verapamil or Diltiazem administered intravenously may enhance the depressant effect of beta-blockers on blood pressure, heart rate, myocardial contractility and atrioventricular conduction. An increase in negative inotropic and chronotropic effects can occur, therefore these medicinal products should not be administered intravenously to patients who are being treated with beta blockers (see section 4.3).

Concomitant use not recommended

Linked to ivabradine

- QT prolonging medicinal products
  - Cardiovascular QT prolonging medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).
  - Non cardiovascular QT prolonging medicinal products (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).

  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).
- Grapefruit juice: ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be avoided.

Linked to metoprolol

The following combinations with metoprolol should be avoided:
- Barbituric acid derivatives: Barbiturates (studied for pentobarbital) induce the metabolism of metoprolol through enzyme induction. Decreased plasma concentrations of metoprolol with decreased clinical effects (faster hepatic metabolism) has been observed with phenobarbital.
- Centrally acting antihypertensive agents (e.g. clonidine)
- Significant increase in blood pressure may occur if treatment with the centrally acting antihypertensive agent is stopped suddenly. Avoid stopping the centrally acting antihypertensive agent abruptly. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”.
- The concomitant use of clonidine with a non-selective beta blocker, and possibly also with a selective beta blocker, increases the risk of rebound hypertension. If clonidine is administered concomitantly, the administration of the clonidine medication needs to be continued for some time after beta-blocker therapy is discontinued.
- Class 1 antiarrhythmic agents (e.g. quinidine, tocainide, procainamide, aimaline, amiodarone, flecainide and disopyramide)

Beta-blockers may increase the negative inotropic effect of antiarrhythmic drugs and their effect on atrial conduction time. In particular, in patients with pre-existing sinus node dysfunction, concomitant administration of amiodarone may cause additional electrophysiological effects including bradycardia, sinus arrest and atrioventricular block. Amiodarone has an extremely long half-life (approximately 50 days), which means that interactions can occur a long time after discontinuation of the preparation. Antiarrhythmics such as quinidine, tocainide, procainamide, aimaline, amiodarone, flecainide and disopyramide may potentiate the effect of metoprolol on heart rate and atrioventricular conduction.

Concomitant use with precaution

Linked to ivabradine

- Potassium-depleting diuretics (thiazide diuretics and loop diuretics): 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.
- Moderate CYP3A4 inhibitors: 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.
- CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, Hypericum perforatum [St John's Wort]) may decrease ivabradine exposure and activity. The concomitant use of CYP3A4 inducing medicinal products may require an adjustment of the dose of ivabradine. The combination of ivabradine 10 mg twice daily with St John's Wort was shown to reduce ivabradine AUC by half. The intake of St John's Wort should be restricted during the treatment with ivabradine.

Linked to metoprolol

Metoprolol serves as a substrate for CYP2D6, a cytochrome P 450 isoenzyme.

Enzyme inducing and enzyme inhibiting substances can influence the plasma concentration of metoprolol.
- Rifampicin lowers the plasma concentration of metoprolol.
- Cimetidine, alcohol and hydralazine can increase the plasma concentration of metoprolol. Metoprolol is mainly, but not exclusively, metabolised via the hepatic enzyme cytochrome CYP 2D6 (see also section 5.2).
- Substances that have an inhibitory effect on CYP 2D6, as e.g. selective serotonin-reuptake inhibitors like paroxetine, fluoxetine and sertraline as well as diphenhydramine, hydroxychloroquine, celecoxib, terbinafine, neuroleptics (e.g. chlorpromazine, triflupromazine, chlorprothixene) and possibly propafenon can increase the plasma concentration of metoprolol.

An inhibitory effect on CYP 2D6 has also been reported for amiodarone and quinidine (antiarrhythmics).

Metoprolol can reduce the elimination of other medicinal products (e.g. lidocaine).

In patients using beta-receptor blockers the bradycardic effect is enhanced by inhalation anaesthetics.

When initiating treatment with these medicinal products in patients treated with metoprolol, the dose of metoprolol may need to be reduced:
- Nitrates may enhance the hypotensive effect of metoprolol
- Digitalis glucosides (digoxin)
  Digitalis glycosides in combination with beta-receptor blockers may increase the atrioventricular conduction time and induce bradycardia.
- Beta-receptor blockers (e.g. eye drops) or MAO-inhibitors
  Patients concomitantly treated with metoprolol and other beta-receptor blockers (e.g. eye drops) or MAO-inhibitors should be closely monitored. Concomitant administration with beta-blockers may result in bradycardia and an enhanced hypotensive effect.

- Adrenaline: if, under certain circumstances, adrenaline is administered to patients who take beta-receptor blockers, cardioselective beta-receptor blockers have a markedly lower impact on blood pressure control than non-selective beta-receptor blockers (see also section 4.4).
- Parasympathomimetic drugs
  The concomitant use of parasympathomimetics may cause long-term bradycardia.
- Non-steroidal anti-inflammatory/antirheumatic agents (NSAID's)
  The concomitant use of non-steroidal anti-inflammatory drugs such as indomethacin may reduce the antihypertensive effect of metoprolol.
- Insulin and oral antidiabetic agents
  Metoprolol may increase their hypoglycemic effect and symptoms of hypoglycaemia may be masked. In this case, the dosage of the oral blood glucose-reducing drug must be adjusted.

Combinations use to be taken into consideration
Linked to ivabradine

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.

Cytochrome P450 3A4 (CYP3A4)
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).

Linked to metoprolol

Tricyclic antidepressants and neuroleptics: Increased antihypertensive effect and risk of orthostatic hypotension (additive effect).

Mefloquine: Risk of excessive bradycardia (additive bradycardiac effects).

Dipyridamole (IV): Increased antihypertensive effect.

Urology alpha-blockers (alfuzosin, doxazosin, prazosin, tamsulosin, terazosin): Increased hypotensive effect. Greater risk of orthostatic hypotension.

Ergotamine: Increase of the vasoconstrictive effect.

Skeletal muscle relaxant: Curare-type muscle relaxant (enhancement of the neuromusular block).

Floctafenine : Beta blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.

Antacid: An increase in the plasma concentrations of metoprolol has been observed when the drug was coadministered with an antacid.

Paediatric population

Linked to ivabradine
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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

Pregnancy
Based on existing data with the monocomponents, the use of Implicor is contra-indicated during pregnancy (see section 4.3).
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. Therefore, ivabradine is contra-indicated during pregnancy.
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of metoprolol in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity with metoprolol (see section 5.3). Metoprolol should only be administered during pregnancy where absolutely necessary. Beta blockers reduce placental perfusion, which may result in intrauterine foetal death, miscarriage or premature delivery. In addition, foetuses and newborns may be affected by adverse effects such as hypoglycaemia, bradycardia, hypotension and breathing difficulties. The risk of cardiac and pulmonary complications is higher during the post-natal period. In the event of treatment during pregnancy, close foetal monitoring must be carried out, and continue for a few days after delivery.

Breast-feeding
Implicor is contra-indicated during breast-feeding (see section 4.3).
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. Metoprolol is concentrated in breast milk in a quantity that corresponds to three times the amount found in the mother’s plasma.

Fertility
There are no clinical data on fertility with the use of Implicor.
Studies in rats with ivabradine and metoprolol have 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 monocomponents the use of Implicor may affect the ability to drive or use machinery.

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.

Metoprolol may affect patients' ability to drive and operate machinery. Patients should be warned that headaches, dizziness or fatigue may occur. These effects may possibly be enhanced in the case of concomitant ingestion of alcohol or after changing to another medicinal product.

4.8 Undesirable effects

The safety profile of Implicor presented below is based on the known safety profile of the individual components.

Summary of the profile

The mostcommon adverse reactions with ivabradine . luminous phenomena (phosphenes) and bradycardia are dose dependent and related to the pharmacological effect of the medicinal product. The most commonly reported adverse reactions with metoprolol are bradycardia, nightmares, headache, somnolence, insomnia, dizziness, palpitations, orthostatic hypotension, peripheral coldness, Raynaud's disease, dyspnoea exertional, nausea, constipation, diarrhoea, abdominal pain, vomiting, fatigue and libido disorder.

Tabulated list of adverse reactions

The following undesirable effects have been observed during treatment with ivabradine and metoprolol given separately and ranked under the MedRA classification by body system, and under heading of frequency using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Undesirable effects**	**Frequency**	
		Ivabradine	**Metoprolol**
Blood and lymphatic system disorders	Eosinophilia	Uncommon	-
	Thrombocytopenia	-	Rare
	Leukopenia	-	Very rare
Immune system disorders	Exacerbation of psoriasis	-	Uncommon
Metabolism and nutrition disorders	Hyperuricaemia	Uncommon	-
	Hypoglycaemia		Uncommon
Psychiatric disorders	Depression	-	Uncommon
	Nightmares, abnormal dreams	-	Common
	Nervousness	-	Rare
	Anxiety	-	Rare
	Confusion	-	Uncommon
	Hallucination	-	Uncommon
	Depersonalisation	-	Very rare
Nervous system disorders	Headache	Common	Common
	Amnesia	-	Very rare
	Decreased alertness, consciousness	-	Uncommon
	Somnolence	-	Common
	Insomnia	-	Common
	Dizziness	Common	Common
	Syncope	Uncommon*	Rare
	Paraesthesia	-	Uncommon
	Stupor	-	Uncommon
Eye disorders	Luminous phenomena (phosphenes)	Very Common	-
	Blurred vision	Common	-
	Visual impairment	Uncommon*	Rare
	Xerophthalmia	-	Very rare
	Dry eyes	-	Uncommon
	Eye irritation	-	Uncommon
	Lacrimation reduced	-	Rare
	Diplopia	Uncommon*	-
	Conjunctivitis	-	Rare
Ear and labyrinth disorders	Vertigo	Uncommon	-
	Tinnitus	-	Rare
	Hearing impaired, hypoacusis	-	Very rare
	Deafness	-	Very rare

Cardiac disorders	Bradycardia	Common	Common
	AV 1st degree block (ECG prolonged PQ interval)	Common	-
	AV 1st degree block	-	Uncommon
	Ventricular extrasystoles	Common	-
	Palpitations	Uncommon	Common
	Supraventricular extrasystoles	Uncommon	-
	Atrial fibrillation	Common	-
	AV 2nd degree block	Very Rare	-
	AV 3rd degree block	Very Rare	-
	Sick sinus syndrome	Very Rare	-
	Cardiac failure	-	Uncommon
	Cardiogenic shock	-	Uncommon
	Aggravation of attacks in patient with angina pectoris	-	Very rare
	Arrhythmias	-	Rare
	Cardiac conduction disorder	-	Rare
	Chest Pain	-	Uncommon
Vascular disorders	Uncontrolled blood pressure	Common	-
	Hypotension (possibly related to bradycardia)	Uncommon*	-
	Orthostatic hypotension (with syncope)	-	Common
	Peripheral coldness	-	Common
	Raynaud's disease	-	Common
	Dry gangrene (in patients with a severe pre-existing impairment of peripheral circulation)	-	Very rare
	Intermittent claudication	-	Uncommon
	Blood pressure decreased	-	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Uncommon	-
	Bronchospasm (also in patients without obstructive pulmonary disease)	-	Uncommon
	Rhinitis	-	Rare
	Dyspnoea exertional	-	Common
Gastrointestinal disorders	Nausea	Uncommon	Common
	Constipation	Uncommon	Common
	Diarrhoea	Uncommon	Common
	Abdominal pain	Uncommon*	Common
	Vomiting	-	Common
	Dry mouth	-	Rare
	Dysgeusia	-	Rare
	Retroperitoneal fibrosis	-	Very rare
Hepatobiliary disorders	Hepatitis	-	Very rare
	Abnormal liver function test	-	Rare
	Hepatic function abnormal	-	Rare
Skin and subcutaneous tissue disorders	Angioedema	Uncommon*	-
	Rash	Uncommon*	Uncommon
	Dystrophic skin	-	Uncommon
	Erythema	Rare*	-
	Pruritus	Rare*	-
	Urticaria	Rare*	Uncommon
	Hyperhidrosis	-	Uncommon
	Alopecia	-	Rare
	Photosensitivity reaction	-	Very rare
	Psoriasis, rash psoriasiform	-	Uncommon
Musculoskeletal and connective tissue disorders	Muscle spasms	Uncommon	Rare
	Arthralgia	-	Very rare
	Muscle weakness	-	Rare
	Muscle cramps	-	Uncommon

General disorders and administration site conditions	Asthenia (possibly related to bradycardia)	Uncommon*	-
	Fatigue	Uncommon*	Very common
	Malaise (possibly related to bradycardia)	Rare*	-
	Oedema	-	Uncommon
	Weight increase	-	Uncommon
Investigations	Blood creatinine increased	Uncommon	-
	ECG prolonged QT interval	Uncommon	-
	Transaminases increased	-	Rare
Reproductive system and breast disorders	Sexual dysfunction/Impotence		Rare
	Libido disorder	-	Common
	Peyronie's disease	-	Very rare

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

Description of selected adverse reactions

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 Implicor in humans.

Symptoms

Linked to ivabradine

Overdose may lead to severe and prolonged bradycardia.

Linked to metoprolol

Poisoning due to an overdose of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting and cyanosis.

Symptoms may worsen, if using alcohol, blood pressure medicine, quinidines or barbiturates simultaneously.

The first manifestations usually appear 20 minutes to two hours after drug ingestion.

Management

In addition to general measures (e.g. gastric lavage which could be considered within 4 hours after ingestion and in case of serious intoxication, active charcoal) patients should be transferred to an intensive care setting, where vital parameters can be monitored and, if necessary, corrected.

Severe bradycardia should be treated symptomatically. 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. Potential antidotes to metoprolol include Orciprenaline (0.5 - 1 mg) i.v., Atropine 0.5 to 2mg i.v. and initially Glucagon 1 - 5 mg (max. 10 mg) i.v. In addition beta sympathomimetic agents may be given, with exact doses depending upon body weight and effect (e.g. Dobutamine, Isoprenaline, Orciprenaline, and Adrenaline). Dosage may need to be above recommended therapeutic levels.
Slow intravenous administration of Diazepam is advised in the event of seizures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, other combinations, ATC code: C07FX05.

Ivabradine

Mechanism of action
Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker If 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 Ih which closely resembles cardiac If. 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 Ih 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 antianginal 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 antianginal 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 1mm 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 a 889-patients randomised placebo-controlled study, ivabradine given on top of atenolol 50 mg o.d. 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 10 mg o.d. 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 1277-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 s during a treadmill ETT) on top of amlodipine 5 mg o.d. or nifedipine GITS 30 mg o.d. at the trough of drug activity (12 hours after oral ivabradine intake) over a 6-week treatment period (OR = 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 antianginal 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 antianginal 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 10917 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, hospitalisation for acute MI or hospitalisation 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, hospitalisation for acute MI or heart failure (ivabradine 12.0% versus placebo 15.5%, p=0.05).

A large outcome study, SIGNIFY, was performed in 19102 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 b.i.d. (5 mg b.i.d, if age ≥ 75 years) and titration up to 10 mg b.i.d). The main efficacy criterion was the composite of cardiovascular death or non-fatal MI. The study showed no difference in the rate of the primary composite endpoint (PCE) 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 PCE was observed in a pre-specified subgroup of patients with angina patients in CCS class II or higher at baseline (n=12049) (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=14286) (relative risk ivabradine/placebo 1.11, p=0.110).
The higher than approved dose used in the study did not fully explain these findings.

Metoprolol

Mechanism of action
Metoprolol is a cardioselective betablocker; it blocks beta1-adrenergic receptors (which are mainly located in the heart) at lower doses than those needed to block beta2-receptors, (which are mainly located in the bronchi and peripheral vessels). It has neither membrane-stabilising effect nor an intrinsic sympathomimetic activity (ISA).

Pharmacodynamic effects
Metoprolol reduces or inhibits the catecholamines effect on the heart, which leads to a decrease in the rhythm, contractility and cardiac output. Metoprolol has an antihypertensive effect, both in the orthostatic and supine position. It also reduces the rise in blood pressure due to exertion.

Clinical efficacy and safety
In patients with angina pectoris, metoprolol reduces the frequency and severity of ischaemic episodes and improves exertion tolerance. These positive effects may be due to decreased myocardial oxygen demand as a result of the reduced heart rate and myocardial contractility.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Implicor in all subsets of the paediatric population in the treatment of ischaemic coronary artery disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The rate and extent of absorption of ivabradine and metoprolol from Implicor are not significantly different, respectively, from the rate and extent of absorption of ivabradine and metoprolol when taken alone as monotherapy.

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
- Older people: no pharmacokinetic differences (AUC and Cmax) 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).

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).

Metoprolol
Absorption and distribution
Metoprolol is completely absorbed after an oral dose, peak plasma concentrations occurring 1.5 – 2 hours after dosing. Due to a pronounced first passage metabolism for metoprolol, the bioavailability of a single oral dose is approx. 50 %. Concomitant intake of food increases bioavailability by approximately 30-40%. Only a small fraction of metoprolol (approx. 5-10 %) binds to plasma proteins.

Biotransformation
Metoprolol is metabolised by hepatic oxidation. The three known main metabolites have been shown not to have a clinically significant beta blocking effect.
Metoprolol is metabolised primarily, but not solely, by the hepatic enzyme cytochrome (CYP) 2D6. Due to the polymorphy of the CYP 2D6 gene, the turnover rates vary with the individual. Individuals with poor metabolic capacity (approx. 7-8 %) exhibit higher plasma concentrations and slower elimination than individuals with good metabolic capacity.

Elimination
The plasma concentrations are stable and repeatable in the individuals, however more than 95 % of an oral dose is excreted in urine. Approximately 5 % of the dose is excreted in unchanged form; in single cases up to an entire 30 %. The elimination half-life of metoprolol in plasma is 3.5 hours on average (interval 1-9 hours). Total clearance is approximately 1 L/min.

Special populations
- Older people: The pharmacokinetics of metoprolol in the elderly is not significantly different from that in younger populations.
- Hepatic impairment: Increased bioavailability and decreased total clearance.
- Pregnancy: Metoprolol crosses into the placenta. The mean ratio of cord blood/maternal blood metoprolol concentration is 1.
- Lactation: Metoprolol is excreted in breast milk; the mean ratio of maternal milk/maternal blood metoprolol concentration is 3.7.

5.3 Preclinical safety data

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 Ih currents in the retina, which share extensive homology with the cardiac pacemaker If current. Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes.

Metoprolol
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development. In a 3-month dog study, prolongation of the QT-interval was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet
Starch, Pregelatinised (maize)
Cellulose, microcrystalline
Maltodextrin
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Film-coating
Glycerol (E422)
Hypromellose (E464)
Macrogol 6000
Magnesium stearate (E470b)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PVDC/aluminium blister packed in cardboard cartons:
30 months

High density polyethylene bottle equipped with a polypropylene stopper, containing a desiccant:
18 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
High density polyethylene bottle equipped with a polypropylene stopper, containing a desiccant:
Container of 100 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

<[To be completed nationally]>
For RMS (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}>