

## **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.

#### *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.

#### *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).

*Elderly* 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 2<sup>nd</sup> and 3<sup>rd</sup> 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 retinal function. There is no evidence of a toxic effect of long-term ivabradine treatment on the retina (see section 5.1). 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  $\beta$  2-receptors, for example, such as terbutaline, are prescribed. If the patient is already using a  $\beta$  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.

*Elderly* 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. pimozone, 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 I 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 neuromuscular 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1000$  to  $< 1/100$ ); rare ( $\geq 1/10000$  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  |

|  |  |           |           |
|--|--|-----------|-----------|
| <b>Cardiac disorders</b>                               | 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  |           |
| <b>Vascular disorders</b>                              | 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  |
| <b>Respiratory, thoracic and mediastinal disorders</b> | Dyspnoea   | Uncommon  | -         |
|  | Bronchospasm (also in patients without obstructive pulmonary disease)                      | -         | Uncommon  |
|  | Rhinitis   | -         | Rare      |
|  | Dyspnoea exertional  | -         | Common    |
| <b>Gastrointestinal disorders</b>                      | Nausea   | Uncommon  | Common    |
|  | Constipation   | Uncommon  | Common    |
|  | Diarrhoea  | Uncommon  | Common    |
|  | Abdominal pain   | Uncommon* | Common    |
|  | Vomiting   | -         | Common    |
|  | Dry mouth  | -         | Rare      |
|  | Dysgeusia  | -         | Rare      |
|  | Retroperitoneal fibrosis   | -         | Very rare |
| <b>Hepatobiliary disorders</b>                         | Hepatitis  | -         | Very rare |
|  | Abnormal liver function test   | -         | Rare      |
|  | Hepatic function abnormal  | -         | Rare      |
| <b>Skin and subcutaneous tissue disorders</b>          | 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  |
| <b>Musculoskeletal and connective tissue disorders</b> | Muscle spasms  | Uncommon  | Rare      |
|  | Arthralgia   | -         | Very rare |
|  | Muscle weakness  | -         | Rare      |
|  | Muscle cramps  | -         | Uncommon  |

|   |  |           |             |
|---|--|-----------|-------------|
| <b>General disorders and administration site conditions</b> | Asthenia (possibly related to bradycardia) | Uncommon* | -           |
|   | Fatigue                                    | Uncommon* | Very common |
|   | Malaise (possibly related to bradycardia)  | Rare*     | -           |
|   | Oedema                                     | -         | Uncommon    |
|   | Weight increase                            | -         | Uncommon    |
| <b>Investigations</b>                                       | Blood creatinine increased                 | Uncommon  | -           |
|   | ECG prolonged QT interval                  | Uncommon  | -           |
|   | Transaminases increased                    | -         | Rare        |
| <b>Reproductive system and breast disorders</b>             | 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  $I_h$  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  $I_h$  by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field (see section 4.8).

##### Pharmacodynamic effects

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20 mg twice daily indicates a trend towards a plateau effect which is consistent with a reduced risk of severe bradycardia below 40 bpm (see section 4.8). At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:

- in clinical electrophysiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals;
- in patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any deleterious influence on LVEF.

##### Clinical efficacy and safety

The 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.

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

## 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 for 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*

- Elderly: no pharmacokinetic differences (AUC and C<sub>max</sub>) 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*

- Elderly: 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 ectrodactyilia in the rabbit.

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

#### 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:  
 36 months

#### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

#### **6.5 Nature and contents of container**

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

Not all pack sizes may be marketed

#### **6.6 Special precautions for disposal**

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

### **7. MARKETING AUTHORISATION HOLDER**

<[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}>

**LABELLING AND PACKAGE LEAFLET**

## **LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON/BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Implicor 25 mg/5 mg film-coated tablets  
metoprolol tartrate / ivabradine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One film-coated tablet contains 25 mg of metoprolol tartrate and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).

**3. LIST OF EXCIPIENTS**

<To be completed nationally>

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets.

14 film-coated tablets  
28 film-coated tablets  
56 film-coated tablets  
98 film-coated tablets  
112 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

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

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Batch {number}

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Implicor 25 mg/5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

**1. NAME OF THE MEDICINAL PRODUCT**

Implicor 25 mg/5 mg film-coated tablets  
metoprolol tartrate / ivabradine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

For RMS (the Netherlands):  
Les Laboratoires Servier

**3. EXPIRY DATE**

EXP {MM/YYYY}

**4. BATCH NUMBER**

Batch {number}

**5. OTHER**

**Abbreviations for days of the week**

MON  
TUE  
WED  
THU  
FRI  
SAT  
SUN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON/BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Implicor 50 mg/5 mg film-coated tablets  
metoprolol tartrate / ivabradine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One film-coated tablet contains 50 mg of metoprolol tartrate and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).

**3. LIST OF EXCIPIENTS**

<To be completed nationally>

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets.

14 film-coated tablets  
28 film-coated tablets  
56 film-coated tablets  
98 film-coated tablets  
112 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

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

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Batch {number}

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Implicor 50 mg/5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

**1. NAME OF THE MEDICINAL PRODUCT**

Implicor 50 mg/5 mg film-coated tablets  
metoprolol tartrate / ivabradine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

For RMS (the Netherlands):  
Les Laboratoires Servier

**3. EXPIRY DATE**

EXP {MM/YYYY}

**4. BATCH NUMBER<, DONATION AND PRODUCT CODES>**

Batch {number}

**5. OTHER**

**Abbreviations for days of the week**

MON  
TUE  
WED  
THU  
FRI  
SAT  
SUN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON/BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Implicor 25 mg/7.5 mg film-coated tablets  
metoprolol tartrate / ivabradine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One film-coated tablet contains 25 mg of metoprolol tartrate and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).

**3. LIST OF EXCIPIENTS**

<To be completed nationally>

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets.

14 film-coated tablets  
28 film-coated tablets  
56 film-coated tablets  
98 film-coated tablets  
112 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

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

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Batch {number}

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Implicor 25 mg/7.5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

**1. NAME OF THE MEDICINAL PRODUCT**

Implicor 25 mg/7.5 mg film-coated tablets  
metoprolol tartrate / ivabradine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

For RMS (the Netherlands):  
Les Laboratoires Servier

**3. EXPIRY DATE**

EXP {MM/YYYY}

**4. BATCH NUMBER**

Batch {number}

**5. OTHER**

**Abbreviations for days of the week**

MON  
TUE  
WED  
THU  
FRI  
SAT  
SUN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON/BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Implicor 50 mg/7.5 mg film-coated tablets  
metoprolol tartrate / ivabradine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One film-coated tablet contains 50 mg of metoprolol tartrate and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).

**3. LIST OF EXCIPIENTS**

<To be completed nationally>

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets.

14 film-coated tablets  
28 film-coated tablets  
56 film-coated tablets  
98 film-coated tablets  
112 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

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

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Batch {number}

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Implicor 50 mg/7.5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

**1. NAME OF THE MEDICINAL PRODUCT**

Implicor 50 mg/7.5 mg film-coated tablets  
metoprolol tartrate / ivabradine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

For RMS (the Netherlands):  
Les Laboratoires Servier

**3. EXPIRY DATE**

EXP {MM/YYYY}

**4. BATCH NUMBER**

Batch {number}

**5. OTHER**

**Abbreviations for days of the week**

MON  
TUE  
WED  
THU  
FRI  
SAT  
SUN

**PACKAGE LEAFLET**

## Package leaflet: Information for the patient

**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**

Metoprolol tartrate /ivabradine

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### What is in this leaflet

1. What Implicor is and what it is used for
2. What you need to know before you take Implicor
3. How to take Implicor
4. Possible side effects
5. How to store Implicor
6. Contents of the pack and other information

#### 1. What Implicor is and what it is used for

Implicor is used to treat symptomatic stable angina pectoris in adults (which causes chest pain). Instead of taking ivabradine and metoprolol as separate tablets you will receive one tablet of Implicor which contains both ingredients in the same strength.

Implicor is a combination of two active ingredients, metoprolol tartrate and ivabradine. Metoprolol is a beta blocker. Beta-blockers slow the heart beat, lessen the force with which the heart muscle contracts and reduces the blood vessel contraction in the heart, brain and throughout the body. Ivabradine works mainly by reducing the heart rate by a few beats per minute. This lowers the heart's need for oxygen especially in the situations when an angina attack is more likely to happen. In this way, metoprolol and ivabradine help to control and reduce the number of angina attacks.

#### 2. What you need to know before you take Implicor

##### **Do not take Implicor:**

- if you are allergic to ivabradine, metoprolol or any of the other ingredients of this medicine (listed in section 6), or to other beta blockers.
- if you have a resting heart rate before treatment that is too slow if you feel weak, have decreased level of consciousness, shortness of breath, hypotension or chest pain (due to symptomatic bradycardia)
- if you are suffering from cardiogenic shock (a serious heart condition caused by very low blood pressure, treated in hospitals)
- if you suffer from a heart rhythm disorder (irregular heart beat)
- if you are having a heart attack or a suspected heart attack complicated by the following conditions: a very low heart rate; a slow or irregular heart beat; the upper value of your blood pressure is lower than 100 mmHg and/or severe heart failure
- if you have very low blood pressure
- if you have heart failure which has recently become worse

- if you have been receiving treatment with beta-receptor agonists such as dobutamine for heart failure
- if your heart beat is exclusively regulated by your pacemaker
- if you suffer from unstable angina (a severe form of angina in which chest pain occurs very frequently, with or without exercise)
- if you have severe blood vessel disorder
- if you have high blood pressure due to a tumour near the kidney (untreated phaeochromocytoma)
- if you suffer from severe liver problems
- if you have too much acid in your blood (metabolic acidosis)
- if you are taking medicines for treatment of fungal infections (such as ketoconazole, itraconazole), macrolide antibiotics (such as clarithromycin, erythromycin given orally, josamycin and telithromycin), HIV protease inhibitors (such as nelfinavir, ritonavir) and nefazodone (medicine to treat depression) or diltiazem, verapamil (used for high blood pressure or angina pectoris)
- if you are a woman able to have children and not using reliable contraception
- if you are pregnant or trying to become pregnant
- if you are breast-feeding.

### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Implicor.

You should inform your doctor if you have or have had any of the following conditions:

- if you suffer from heart rhythm disorders (such as irregular heartbeat, palpitations, increase in chest pain), sustained atrial fibrillation (a type of irregular heartbeat) or an abnormality of electrocardiogram (ECG) called 'long QT syndrome'
- if you have symptoms such as tiredness, dizziness or shortness of breath (this could mean that your heart rate is slowing down too much e.g. under 50 beats per minute)
- if you suffer from symptoms of atrial fibrillation (pulse rate at rest unusually high (over 110 beats per minute) or irregular, without any apparent reason, making it difficult to measure),
- if you have had a stroke recently (cerebral attack)
- if you suffer from chronic eye retinal disease or if your eyesight deteriorates
- if you suffer from low blood pressure or uncontrolled blood pressure, especially after a change in your antihypertensive treatment,
- if you are going to have a cardioversion (a medical procedure that can restore a fast or irregular heartbeat to a normal rhythm)
- if you suffer from severe heart failure or heart failure with abnormality of ECG called 'bundle branch block'
- if you suffer from asthma or have a significant narrowing of the airways called COPD (chronic obstructive pulmonary disease)
- if you have circulation problems (e.g. Raynaud's disease)
- if you have or are suspected to have a tumour on the adrenal glands (phaeochromocytoma)
- if you have diabetes
- if you suffer from Prinzmetal angina (chest pain in periods of rest)
- if you have psoriasis (severe skin rashes)
- if you have an overactive thyroid gland (the symptoms are tremors, a fast heart rate, sweating or weight loss)
- if you are going to have a surgery which requires a general anaesthesia
- if you are elderly
- if you suffer from severe kidney problems
- if you suffer from moderate liver problems
- if you have a history of hypersensitive reactions or are undergoing desensitisation therapy

Do not suddenly stop taking Implicor since this can cause severe changes in the rhythm or rate of the heart and increase the risk of a heart attack.

If any of the above applies to you, talk straight away to your doctor before or while taking Implicor.

### **Children and adolescents**

Implicor is not intended for use in children and adolescents younger than 18.

### **Other medicines and Implicor**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Treatment with Implicor can be affected by other medicines. Make sure to tell your doctor if you are taking any of the following medicines as special care may be required for:

- fluconazole and terbinafine (medicines used for fungal infections)
- rifampicin (medicine used for infections)
- barbiturates (medicine used to treat epilepsy or difficult sleeping)
- phenytoin (medicine used for epilepsy)
- *hypericum perforatum* or St John's Wort (herbal treatment used for depression)
- QT prolonging medicines to treat either heart rhythm disorders or other conditions:
  - o quinidine, disopyramide, ibutilide, sotalol, amiodarone (medicines used to treat heart rhythm problems)
  - o bepridil (medicine used to treat angina pectoris)
  - o pimozide, ziprasidone, sertindole (medicines used to treat anxiety, schizophrenia or other psychoses)
  - o mefloquine and halofantrine (medicines used to treat malaria)
  - o intravenous erythromycin (an antibiotic)
  - o pentamidine (medicine used to treat parasitic infection)
  - o cisapride (medicine used to treat digestion problems)
- furosemide, hydrochlorothiazide, indapamide (types of diuretics used to treat oedema and high blood pressure, which may decrease blood potassium levels)
- hydralazine, clonidine (medicine used to treat high blood pressure)
- flecainide, propafenone, tocainide, procainamide, aimaline (medicines used to heart rhythm problems)
- nitrates (medicines used to treat angina)
- digoxin (medicine used for heart problems)
- paroxetine, fluoxetine, sertraline, tricyclic antidepressants, neuroleptics (e.g. chlorpromazine, triflupromazine, chlorprothixene), and pentobarbital (medicines used to treat mental disorders such as depression or schizophrenia)
- celecoxib, indomethacin and floctafenine (Non-steroidal anti-inflammatory/antirheumatic agents (NSAID's) used to reduce inflammation, fever and pain)
- diphenhydramine (medicine used to treat allergies)
- hydroxychloroquine (medicine used to reduce inflammation in people with autoimmune diseases)
- other beta- blockers (e.g. eye drops)
- monoamine oxidase (MAO) inhibitors (medicines used to treat depression and Parkinson's disease)
- cimetidine (medicine used for heartburn or peptic ulcers)
- insulin and oral antidiabetic agents
- lidocaine (a local anaesthetic)
- inhalation of anaesthetics
- adrenaline (medicine used for emergency treatment of allergic reactions)
- parasympathomimetics medicines used to treat conditions such as Alzheimer's disease or glaucoma
- dipyridamole (medicine used to study the blood flow in heart)
- alfuzosin, doxazosin, prazosin, tamsulosin and terazosin (medicines used to treat urinary retention)
- ergotamine (medicine used to treat migraine)
- skeletal muscle relaxant
- antacid (medicine used for stomach upsets)

### **Implicor with food and drink**

Avoid grapefruit juice during treatment with Implicor. You should minimise your alcohol intake when taking this medicine as it may increase the effect of metoprolol.

Food may increase the effect of metoprolol.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

This medicine is not recommended during pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible.

Do not take Implicor if you are able to become pregnant unless you use reliable contraceptive measures (see “Do not take Implicor”).

You must not take Implicor if you are breast-feeding. Talk to your doctor if you are breast-feeding or intending to breast-feed as breastfeeding should be discontinued if you take Implicor.

### **Driving and using machines**

Implicor may cause temporary luminous visual phenomena (a temporary brightness in the field of vision), (see “Possible side effects”). If this happens to you, be careful when driving or using machines at times when there could be sudden changes in light intensity, especially when driving at night.

You should also be careful when taking Implicor together with alcohol or changing to another medicine since this may affect your ability to drive or use machines.

If the tablets make you feel dizzy or tired or give you a headache, do not drive or use machinery.

## **3. How to take Implicor**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The tablet must be taken twice daily, once in the morning and once in the evening during meals.

### **If you take more Implicor than you should**

If you take more tablets than prescribed, contact your nearest accident and emergency department or tell your doctor immediately. The most likely effects are dizziness, feeling faint, tired and difficulty in breathing due to your heart rate slowing down.

### **If you forget to take Implicor**

If you forget to take a dose of Implicor, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

### **If you stop taking Implicor**

Do not suddenly stop taking Implicor tablets since this can cause severe changes in the rhythm or rate of your heart and increase the risk of a heart attack. Only change the dose or stop the treatment in consultation with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common** (may affect more than 1 in 10 people):

- luminous visual phenomena (brief moment of increased brightness, most often caused by sudden changes in light intensity). They can also be described as a halo, coloured flashes, image decomposition or multiple images. They generally occur within the first two months of treatment after which they may occur repeatedly and resolve during or after treatment.
- feeling of tiredness.

**Common** (may affect up to 1 in 10 people):

- nightmares,
- headache,
- somnolence,
- trouble sleeping,
- dizziness,

- blurred vision (cloudy vision),
- modification in heart functioning (slow, irregular rapid contraction of the heart),
- cardiac extra beats
- abnormal perception of the heartbeat
- palpitations,
- uncontrolled blood pressure,
- low blood pressure when for example standing up,
- cold feet and hands,
- tingling and colour change (white, blue then red) in fingers and toes when exposed to the cold (Raynaud's disease),
- difficulty breathing when exercising,
- feeling sick (nausea),
- constipation,
- diarrhoea,
- vomiting,
- abdominal pain,
- libido disorder.

**Uncommon** (may affect up to 1 in 100 people):

- an excess of eosinophils (a type of white blood cells),
- exacerbation of psoriasis,
- high blood levels of uric acid ,
- low sugar (glucose) levels in the blood,
- depression,
- confusion,
- hallucinations,
- decreased alertness,
- fainting,
- pins and needles / tingling or numbness in the hands or feet,
- unresponsive to surroundings (stupor),
- impaired vision,
- dry eyes,
- eye irritation,
- double vision,
- spinning sensation (vertigo),
- worsening of symptoms of cardiac failure,
- a serious heart condition caused by very low blood pressure,
- a pain or uncomfortable feeling in the chest,
- low blood pressure due to slow heart beat,
- muscle pain in one or both legs that develops on walking,
- difficulty breathing (dyspnoea),
- wheezing and shortness of breath (bronchospasm),
- angioedema (such as swollen face, tongue or throat, difficulty in breathing or swallowing),
- skin rashes,
- skin rash with white, silvery coloured appearance (psoriasis)
- hives,
- increased sweating,
- muscle spasms,
- muscle cramps,
- feeling of weakness,
- swelling,
- increased weight,
- elevated creatinine in blood (a breakdown product of muscles),
- abnormal ECG heart tracing.

**Rare** (may affect up to 1 in 1 000 people):

- bleeding or bruising more easily than normal (low blood platelet count),
- nervousness,
- anxiety,
- inflammation of the eyes,
- tinnitus (buzzing, hissing, whistling, ringing or other persistent noise in the ears),
- runny/blocked nose,
- dry mouth,
- taste disturbances,
- change in liver function test,
- hepatic function abnormal,
- skin reddening,
- itching,
- hair loss,
- muscle weakness
- feeling unwell,
- elevation of certain liver enzymes,
- sexual dysfunction, impotence.

**Very rare** (may affect up to 1 in 10 000 people):

- lack of white blood cells,
- changes in personality,
- loss of memory
- decreased hearing,
- deafness,
- irregular heart beat
- aggravation of attacks in patients with angina pectoris,
- gangrene in cases of already poor existing blood supply to the limbs,
- retroperitoneal fibrosis (excess tissue in the compartment of the body below the chest),
- hepatitis (a liver disease),
- increased sensitivity of the skin to sun,
- swollen/painful joints (arthralgia),
- painful erection (Peyronie's disease).

### **Reporting of side effects**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Implicor**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Implicor contains**

- The active substances are metoprolol tartrate and ivabradine (as hydrochloride).  
Implicor 25 mg/5 mg: each film-coated tablet contains 25 mg of metoprolol tartrate and 5 mg of ivabradine equivalent to 5.390 mg ivabradine as hydrochloride.

Implicor 50 mg/5 mg: each film-coated tablet contains 50 mg of metoprolol tartrate and 5 mg of ivabradine equivalent to 5.390 mg ivabradine as hydrochloride.

Implicor 25 mg/7.5 mg: each film-coated tablet contains 25 mg of metoprolol tartrate and 7.5 mg of ivabradine equivalent to 8.085 mg ivabradine as hydrochloride.

Implicor 50 mg/7.5 mg: each film-coated tablet contains 50 mg of metoprolol tartrate and 7.5 mg of ivabradine equivalent to 8.085 mg ivabradine as hydrochloride.

- The other ingredients are: in the core tablet: pregelatinised starch (*maize*), microcrystalline cellulose, maltodextrin, colloidal anhydrous silica (E551) and magnesium stearate (E470b) and in the tablet film-coating: glycerol (E422), hypromellose (E464), macrogol 6000, magnesium stearate (E470b) and titanium dioxide (E171).

### What Implicor looks like and contents of the pack

White, round, film-coated tablet (25/5 mg) of 7.3 mm diameter engraved with the number 1 on one face and this symbol  on the other.

White, round, film-coated tablet (50/5 mg) of 8.5 mm diameter engraved with the number 2 on one face and this symbol  on the other.

White, oblong film-coated tablet (25/7.5 mg) of 9.3 mm long and 5.8 mm wide engraved with the number 3 on one face and this symbol  on the other.

White, oblong film-coated tablet (50/7.5 mg) of 10.8 mm long and 6.7 mm wide, engraved with the number 4 on one face and this symbol  on the other.

The tablets are available in calendar packs (PVC/PVDC/aluminum blisters) of 14, 28, 56, 98 or 112 tablets. Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

#### Marketing Authorisation Holder

<[To be completed nationally]>

For RMS (Netherlands):

Les Laboratoires Servier

50, rue Carnot

92284 Suresnes cedex

France

#### Manufacturer

Les Laboratoires Servier Industrie

905, route de Saran

45520 Gidy

France

### This medicinal product is authorised in the Member States of the EEA under the following names:

|                |   |
|----------------|---|
| Austria        | IMPLICOR, Filmtabletten                       |
| Belgium        | Procadrax, comprimé pelliculé                 |
| Bulgaria       | IMPLICOR, филмирани таблетки                  |
| Croatia        | IMPLICOR, filmom obložene tablete             |
| Czech Republic | IMPLICOR, potahované tablety                  |
| Cyprus         | IMPLICOR, επικαλυμμένα με λεπτό υμένιο δισκία |
| Denmark        | IMPLICOR                                      |
| Estonia        | IMPLICOR                                      |
| Finland        | IMPLICOR, kalvopäällysteinen tabletti         |
| France         | IMPLICOR, comprimé pelliculé                  |
| Germany        | IMPLICOR, Filmtabletten                       |
| Greece         | IMPLICOR, επικαλυμμένα με λεπτό υμένιο δισκία |
| Hungary        | IMPLICOR, filmtabletták                       |

|             |                                    |
|-------------|------------------------------------|
| Italy       | IMPLICOR                           |
| Latvia      | IMPLICOR, apvalkotās tabletes      |
| Lithuania   | IMPLICOR, plėvele dengtos tabletės |
| Malta       | IMPLICOR, film-coated tablets      |
| Netherlands | IMPLICOR, filmomhulde tabletten    |
| Norway      | Implicor, tabletter filmdrasjerte  |
| Poland      | IMPLICOR                           |
| Romania     | IMPLICOR, comprimate filmate       |
| Slovakia    | INTUICOR, filmom obalené tablety   |
| Slovenia    | IMPLICOR, filmsko obložene tablete |
| Sweden      | Implicor, filmdragerade tabletter  |

**This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.**

Detailed information on this medicine is available on the web site of {MA/Agency}>