

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}>