PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

This medicine can be sold with a doctor's prescription only

Iclusig 15 mg coated tablets
Iclusig 30 mg coated tablets
Iclusig 45 mg coated tablets

Each 15 mg Iclusig tablet contains 15 mg of ponatinib (as hydrochloride).
Each 30 mg Iclusig tablet contains 30 mg of ponatinib (as hydrochloride).
Each 45 mg Iclusig tablet contains 45 mg of ponatinib (as hydrochloride).

Warning: vascular occlusion, heart failure and hepatotoxicity.

Vascular occlusion: blood clots in the arteries and veins, and vascular occlusion occurred in approximately 27% of patients treated with Iclusig, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease and the need for urgent revascularization procedures.
Patients with and without cardiac risk factors, including those under 50 years of age, have experienced these symptoms.

Heart failure, including cases that caused death, occurred in 8% of patients treated with Iclusig.

Hepatotoxicity, liver failure and death occurred in patients treated with Iclusig.

Excipients and allergens: see section 2 under 'Important information about some of this medicine's ingredients' and section 6 'Additional information'.

Read this entire leaflet carefully before you start taking this medicine. This leaflet contains concise information about the medicine. If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for your illness. Do not pass it on to others. It may harm them even if you think that their illness is the same as yours.
This medicine is intended for use in adults above age 18 only.

1. What is the medicine intended for?

This medicine is intended to treat adults with the following **leukemia** types**,** when other treatments are no longer effective or who have a genetic alteration known as a T315I mutation:

- Chronic myeloid leukemia (CML)
- Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL)

Therapeutic Group: Iclusig belongs to the group of tyrosine kinase inhibitors.

How does Iclusig work?
Iclusig is a tyrosine kinase enzyme inhibitor. In patients with chronic myeloid leukemia (CML) and Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL), changes in DNA trigger a signal that encourages the body to produce abnormal white blood cells. Iclusig blocks this signal, thereby stopping the production of the abnormal cells.

2. Before you take the medicine

Do not take this medicine if:

You are sensitive (allergic) to the active ingredient ponatinib or to any of the other ingredients in this medicine, as listed in section 6 of this leaflet. You are pregnant, breastfeeding or planning pregnancy.

Special warnings regarding the use of this medicine
Before treatment with Iclusig tell the doctor if:

- you suffer from a liver or pancreas disorder or reduced kidney function
- you have a history of alcohol abuse
- you have previously had a heart attack or stroke
- you have previously had blood clots in blood vessels
- you have previously suffered from renal artery stenosis in one or both kidneys
- you suffer from heart problems including heart failure, irregular heartbeats and QT interval prolongation
- you have high blood pressure
- or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall
- you have a history of bleeding
- you have previously suffered from viral hepatitis B or if you suspect that you may currently be suffering from this disease. Iclusig can reactivate viral hepatitis B, which can lead to death in some cases. Your doctor will examine you in order to diagnose the symptoms of the disease before beginning treatment with Iclusig.

In these cases your doctor will check:

- your heart function and blood vessels condition, will perform a complete blood count every two weeks for the first 3 months, and monthly afterwards or according to the doctor's decision.
- lipase level every two weeks for the first two months, and periodically afterwards. If the lipase level increases, the doctor may stop the treatment or decrease the dose.
- liver function. Liver function tests should be performed periodically, according to the doctor's decision.

A brain condition called posterior reversible encephalopathy syndrome (PRES) was reported in patients who used the medicine. The symptoms may include a sudden onset of severe headaches, confusion, convulsions and vision changes. Report to the doctor immediately if you experience any of these symptoms during the treatment period with the medicine because this condition can be dangerous.

Children and adolescents
This medicine is intended only for adults above the age of 18 years. There is no information about the safety and efficacy of this medicine when used in children and adolescents.

Tests and Follow-Up
Before and while taking this medicine, your doctor will refer you for the following tests:

- heart function evaluation and blood vessel condition, will perform a complete blood count every two weeks for the first 3 months, and monthly afterwards or as decided by the doctor.
- lipase level every two weeks for the first two months, then from time to time. If the lipase level increases, the doctor may stop the treatment or decrease the dose.
- liver function. Liver function tests should be performed periodically, as decided by your doctor.

Interactions/drug interactions:
Tell the doctor or pharmacist if you are taking or have recently taken any other medicines, including non-prescription drugs and nutrition supplements.
Especially if you are taking medicines of the following groups:

- medicines to treat fungal infections - ketoconazole, itraconazole, voriconazole
- medicines to treat HIV - indinavir, nelfinavir, ritonavir, saquinavir
- medicines to treat bacterial infections - clarithromycin, telithromycin, troleandomycin
- nefazodone - a medicine to treat depression
- St. John's wort - a herbal product used to treat depression
- carbamazepine – a medicine to treat epilepsy, euphoric/depressive stages and certain pain conditions
- phenobarbital, phenytoin - for the treatment of epilepsy
- rifabutin, rifampicin – for the treatment of tuberculosis or other infections
- digoxin – for the treatment of heart problems
- dabigatran - a medicine to prevent blood clots
- colchicine – for the treatment of gout attacks
- medicines to lower cholesterol levels - pravastatin, rosuvastatin
- methotrexate – for the treatment of severe joint inflammation, cancer and psoriasis
- sulfasalazine - for the treatment of severe bowel and rheumatic joint inflammation

In all of these cases the treatment with Iclusig may affect the treatment with other medicines or be affected by them.

Use of this medicine and food
Avoid drinking grapefruit juice or eating grapefruit products during treatment with Iclusig.
The medicine can be taken with or without food.

Pregnancy and breastfeeding
This medicine must not be taken when pregnant and breastfeeding. Use effective contraception during treatment.

- **Women** of childbearing age should avoid becoming pregnant.
- **Men** treated with Iclusig are advised not to father children during treatment.

Breastfeeding - stop breastfeeding during treatment with Iclusig. It is unknown if Iclusig passes into breast milk.

Driving and using machines
Take special care when driving and operating dangerous machinery while using the medicine as you may experience visual disturbance, dizziness, tiredness or sleepiness.

Important information about some of the ingredients of this medicine
This product contains lactose – if you have been told by your doctor that you suffer from intolerance to sugars, consult the doctor before taking this medicine.

3. How to use this medicine?
Always use according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dosage or about how to take this medicine. The dosage and administration will be determined by the doctor only.
The usual recommended dosage is: 45 mg daily.
Do not exceed the recommended dose.

Swallow the tablet whole with a glass of water, with or without food. Do not crush and dissolve the tablets.
Do not swallow the desiccant canister contained in the bottle.

Duration of treatment: the treatment with Iclusig is long-term.
During treatment, your doctor may reduce the dose or temporarily stop the treatment if:
- the number of white blood cells (neutrophils) is reduced
- the number of platelets is reduced
- a severe side effect, not affecting the blood, occurs:
  - pancreas inflammation
  - increased levels of the serum proteins lipase or amylase
- you develop heart or blood vessel problems
- you suffer from liver disease

If you have accidentally taken a higher dosage
If you have taken an overdose or if a child has accidentally swallowed the medicine, proceed immediately to a doctor or a hospital emergency room and bring the package of the medicine with you.

If you forget to take this medicine at the set time, do not take a double dose. Take the next dose at the regular time and consult the doctor. Adhere to the treatment as recommended by your doctor.
Even if there is an improvement in your health, do not stop taking this medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.
If you have any further questions regarding the use of this medicine, consult the doctor or pharmacist.

4. Side effects
Like all medicines, the use of **Iclusig** may cause side effects in some users, especially those above 65 years of age. Do not be alarmed while reading the list of side effects, you may not suffer from any of them.

Seek medical attention immediately if you experience any of the following serious side effects:
If abnormal results from blood tests are received, inform the doctor immediately.

Serious side effects (common):
- Lung inflammation (may cause breathing difficulties)
- Pancreatic inflammation - inform your doctor immediately if this occurs. Symptoms include severe pain in the abdomen and back
- Fever, occasionally accompanied by other signs due to decreased number of white blood cells
- Heart attack (symptoms include: sudden feeling of increased heart rate, chest pain, shortness of breath)
- Changes in blood:
  - decreased number of red blood cells (symptoms include: weakness, dizziness and fatigue)
  - decreased number of blood platelets (symptoms include: increased tendency to bleed and bruise)
  - decreased number of neutrophil white blood cells (symptoms include: increased tendency for infection)
  - increased level of the serum protein lipase
- Heart rhythm disorder, abnormal pulse
- Heart failure (symptoms include: weakness, fatigue, swollen legs)
- Uncomfortable pressure, fullness, squeezing or pain in the center of the chest, (angina pectoris) and other chest pain with no connection to the heart.
- High blood pressure
- Stenosis of arterial vessels in the brain
- Problems of the blood vessels in the heart muscle
- Infection in the blood
- Swollen or red skin area that feels hot and sensitive (cellulitis)
- Dehydration
- Breathing difficulties
- Fluids in the thorax (may cause breathing difficulties)
- Diarrhoea
- Blood clot in a deep vein, sudden vein obstruction, blood clot in a blood vessel of the lung (symptoms include: flushing, hot flushes, redness of the face, breathing difficulties)
- Stroke (symptoms include: difficulty to speak or move, sleepiness, migraine, abnormal sensations)
- Blood circulation problems (symptoms include: pain in the legs or arms, coldness of the extremities of the feet and hands)
- Blood clot in the main arteries that carry blood to the head or the neck (carotid)
- Constipation
- Decreased levels of sodium in the blood.
- Increased tendency to bleed and bruise

Other side effects:
Very common side effects (may affect more than 1 in 10 people):
Upper airway infection (may cause breathing problems), decreased appetite, insomnia, headache, dizziness, cough, diarrhoea, vomiting, nausea, increased blood levels of the liver enzymes alanine aminotransferase and aspartate aminotransferase, dry skin, rash, itching, pain in bones, joints, pain in muscles, back, arms or legs, muscle spasms, fatigue, accumulation of fluid in arms and/or legs, fever, pain.

Common side effects (may affect up to 1 in 10 people):
Inflammation of hair follicles, swollen, red area on or under the skin that feels hot and sensitive, decreased activity of the thyroid gland, fluid retention, low calcium, phosphate or potassium levels in the blood, increased blood sugar or uric acid levels in the blood, high blood triglycerides values, weight loss, mini stroke, nerve disorder in the arms and/or legs (often causes numbness and pain in the hands and feet), lethargy, migraine, increased or reduced sense of touch, abnormal sensation like tickling and itchiness, blurred vision, dry eye, eye infection, visual disturbances, tissue swelling in eyelid or around the eyes caused by build-up of fluid, palpitation, pain in one or both legs when walking or exercising, which disappears after some minutes of rest, flushing, hot flushes, nosebleeds, difficulty producing voice sounds, hypertension in the lungs, increased blood levels of the enzymes amylase, alkaline phosphatase and gamma-glutamyltransferase, heartburn caused by reflux of stomach juices, inflammation in the mouth, abdominal swelling or discomfort or indigestion, dry mouth, stomach bleeding (symptoms include: abdominal pain, vomiting blood), increased blood level of bilirubin (symptoms include: dark urine), pain in bones or neck, rash, peeling of the skin, abnormal thickening of the skin, redness, bruising, skin pain, changes in skin colour, hair loss, tissue swelling in face caused by excess fluid, night sweats, increased sweating, inability to develop or maintain an erection, chills, flu-like illness.

Uncommon side effects (may affect up to 1 in 100 people):
Metabolic disorders caused by the break-down products of dying cancer cells, bleeding in the brain, obstruction of the blood vessels in the eyes, heart problems, left sided chest pain, dysfunction of the left heart chamber, narrowing of the blood vessels, poor blood circulation, sudden increase in blood pressure, renal artery stenosis in one or both kidneys, circulatory problems in the spleen, liver damage, jaundice (manifested by yellowing of the skin and eyes), headaches, confusion, convulsions, vision loss – there may be symptoms of posterior reversible encephalopathy syndrome (PRES).

Rare side effects (may affect up to 1 in 1000 people):
Painful red lumps, skin pain, skin reddening (inflammation of fatty tissue under the skin).

Side effects of unknown frequency (the frequency cannot be defined by the available information):
Reactivation of viral hepatitis B if you have previously suffered from this disease. Bothersome skin rashes that include blisters or peeling of the skin that spreads throughout the body simultaneously with fatigue. Inform the doctor immediately if you experience these symptoms. An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

If a side effect appears, if any of the side effects worsens, or if you experience a side effect not mentioned in the leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

Iclusig is packed in a plastic bottle containing a plastic desiccant canister. Keep the canister in the bottle. Do not swallow the canister.
Avoid poisoning! This medicine and all other medicines must be stored in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by your doctor.
Do not use the medicine after the expiry date (exp. Date) stated on the package/bottle/carton/label. The expiry date refers to the last day of that month.
Storage conditions:
Store in the original package in order to protect from light at a temperature below 25°C.
Shelf life after first opening – use within 60 days.

6. Additional information

In addition to the active ingredient, this medicine also contains:

lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicone dioxide, magnesium stearate, talc, polyethylene glycol, polyvinyl alcohol, titanium dioxide

What the medicine looks like and what the package contains
Iclusig is presented as white, round, coated tablets and convex on the upper and lower side.
Iclusig 15 mg tablets - 6 mm in diameter with "A5" on one side.
Iclusig 30 mg tablets - 8 mm in diameter with "C7" on one side.
Iclusig 45 mg tablets - 9 mm in diameter with "AP4" on one side.

Iclusig is packed in a plastic bottle inside a cardboard box.
Each bottle contains a desiccant. Do not swallow it. Keep it in the bottle.
Bottles of Iclusig 15 mg contain 30 tablets.
Bottles of Iclusig 30 mg contain 30 tablets.
Bottles of Iclusig 45 mg contain 30tablets.
Not all pack sizes may be marketed.

Registration holder and address:
Medison Pharma Ltd., 10 Hashiloach St., P.O. Box 7090, Petach Tikva.

Manufacturer and address:
Incyte Biosciences Distribution B.V.
Paasheuvelweg 25, 1105 BP Amsterdam, Netherlands

Revised in May 2022 according to MOH guidelines.

Drug registration number at the National Medicines Registry of the Ministry of Health:
Iclusig 15 mg: 153-53-34243
Iclusig 30 mg: 159-07-35088
Iclusig 45 mg: 153-54-34244