

Package leaflet: Information for the patient

Iclusig 15 mg film-coated tablets Iclusig 45 mg film-coated tablets ponatinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

1. What Iclusig is and what it is used for

Iclusig is **used to treat** adults with the following **leukaemia** types who are no longer benefiting from treatment with other medicines, or have a certain genetic difference known as a T315I mutation:

- chronic myeloid leukaemia (CML): a blood cancer involving too many abnormal white blood cells in the blood and the bone marrow (where blood cells are formed).
- Philadelphia-chromosome positive acute lymphoblastic leukaemia (Ph+ ALL): a type of leukaemia involving too many immature white blood cells in the blood and blood forming bone marrow. In this kind of leukaemia, some of the DNA (genetic material) has become rearranged to form an abnormal chromosome, the Philadelphia chromosome.

Iclusig belongs to a group of medicines called tyrosine kinase inhibitors. In patients with CML and Ph+ ALL, changes in the DNA trigger a signal that tells the body to produce abnormal white blood cells. Iclusig blocks this signal, thereby stopping the production of these cells.

2. What you need to know before you take Iclusig

Do not take Iclusig

- if you are **allergic** to ponatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Iclusig if you have:

- a liver or pancreas disorder or reduced kidney function. Your doctor may want to take additional precautions.
- a history of alcohol abuse
- had a prior heart attack or stroke
- a history of blood clots in your blood vessels
- a history of renal artery stenosis (narrowing of the blood vessels to one or both kidneys)
- heart problems, including heart failure, irregular heartbeats, and QT prolongation
- high blood pressure
- a history of bleeding issues
- ever had or might now have a hepatitis B infection. This is because Iclusig could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

Your doctor will perform:

- evaluations of your heart function and the condition of your arteries and veins
- a complete blood count
This will be repeated every 2 weeks for the first 3 months after starting the therapy. Afterwards it is performed monthly or as indicated by the doctor.
- checks of the serum protein known as lipase
A serum protein called lipase will be checked every 2 weeks for the first 2 months, then periodically. A break in treatment or a decrease in dose may be required when lipase is increased.
- liver tests
Liver function tests will be performed periodically, as indicated by your doctor.

Children and adolescents

Do not give this medicine to children under 18 years because no data are available in children.

Other medicines and Iclusig

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. The following medicines can affect or be affected by Iclusig:

- **ketoconazole, itraconazole, voriconazole:** medicines to treat fungal infections.
- **indinavir, nelfinavir, ritonavir, saquinavir:** medicines to treat HIV infection.
- **clarithromycin, telithromycin, troleandomycin:** medicines to treat bacterial infections.
- **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:** medicines to treat epilepsy.
- **rifabutin, rifampicin:** medicines to treat tuberculosis or certain other infections.
- **digoxin:** a medicine to treat heart weakness.
- **dabigatran:** a medicine to prevent the formation of blood clots.
- **colchicine:** a medicine to treat gout attacks.
- **pravastatin, rosuvastatin:** medicines to lower elevated cholesterol levels.
- **methotrexate:** a medicine to treat severe joint inflammation (rheumatoid arthritis), cancer and the skin disease psoriasis.
- **sulfasalazine:** a medicine to treat severe bowel and rheumatic joint inflammation.

Iclusig with food and drink

Avoid grapefruit products such as grapefruit juice.

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.

- **Contraceptive advice for men and women**
Women of childbearing age being treated with Iclusig should avoid becoming pregnant. **Men** receiving treatment with Iclusig are advised not to father a child during treatment. Effective contraception must be used during treatment.
Only use Iclusig during pregnancy **if your doctor tells you it is absolutely necessary**, as potential risks exist for the unborn child.
- **Breast-feeding**
Stop breast-feeding during treatment with Iclusig. It is not known if Iclusig passes into breast milk.

Driving and using machines

You should take special care when driving and using machines as patients taking Iclusig may experience visual disturbance, dizziness, sleepiness, and tiredness.

Iclusig contains lactose

If you have been told by your doctor that you have an intolerance to milk sugar (lactose) contact your doctor before taking this medicine.

3. How to take Iclusig

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

Iclusig therapy should be prescribed by a doctor experienced in leukaemia treatment.

Iclusig is available as:

- a 45 mg film-coated tablet for the recommended dose.
- a 15 mg film-coated tablet to allow for dose adjustments.

The recommended starting dose is one 45 mg film-coated tablet once daily.

Your doctor may reduce your dose or tell you to temporarily stop taking Iclusig if:

- an appropriate response to the treatment is reached
- the number of white blood cells called neutrophils is reduced.
- the number of blood platelets is reduced.
- a severe side effect occurs, not affecting the blood
 - pancreas inflammation.
 - increased levels of the serum proteins lipase or amylase.
- you develop heart or blood vessel problems.
- you have a liver disorder.

Iclusig use may be resumed at the same, or a reduced dose, after the event is resolved or controlled. Your doctor may evaluate your response to the treatment at regular intervals.

Method of use

Swallow the tablets whole, with a glass of water. The tablets can be taken with or without food. Do not crush or dissolve the tablets.

Do not swallow the desiccant canister contained in the bottle.

Duration of use

Make sure you take Iclusig daily for as long as it is prescribed. This is a long-term treatment.

If you take more Iclusig than you should

Talk to your doctor immediately if this occurs.

If you forget to take Iclusig

Do not take a double dose to make up for a forgotten dose. Take your next dose at your regular time.

If you stop taking Iclusig

Do not stop taking Iclusig without your doctor's permission.

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.

Patients aged 65 and over are more likely to be affected by side effects.

Seek medical attention immediately if you experience any of the **following serious** side effects.

If abnormal results from blood tests are received, a doctor should be contacted immediately.

Serious side effects (common: affects 1 to 10 users in 100):

- lung infection
- pancreas inflammation. Inform your doctor immediately if pancreas inflammation occurs. Symptoms are severe pain in the stomach and back.
- fever, often with other signs of infection due to decreased number of white blood cells
- heart attack
- changes in blood levels:
 - decreased number of red blood cells (symptoms include: weakness, dizziness, fatigue)
 - decreased number of blood platelets (symptoms include: increased tendency to bleed or bruise)
 - decreased number of white blood cells called neutrophils (symptoms include: increase tendency of infection)
 - increased level of the serum protein known as lipase
- a heart rhythm disorder, abnormal pulse
- heart failure (symptoms include: weakness, fatigue, swollen legs)
- uncomfortable pressure, fullness, squeezing or pain in the centre of the chest (Angina pectoris) and chest pain not in connection with the heart
- high blood pressure
- narrowing of the arteries in the brain

- problems of the blood vessels in the heart muscle
- blood infection
- injury in the kidney
- swollen, or red area of skin that feels hot and tender (cellulitis)
- dehydration
- urinary infection
- stroke
- breathing difficulties
- fluid in the thorax (may cause breathing difficulty)
- diarrhoea
- blood clot in a deep vein, sudden vein obstruction, blood clot in a blood vessel of the lung (symptoms include: hot flush, flushing, redness of the face, breathing difficulty)
- 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 limbs)
- low blood pressure
- bacteria in the blood (bacteremia)
- blood clot in the carotid artery
- colitis due to C. difficile bacteria
- constipation
- sodium decrease in the blood
- skin cancer (squamous cell cancer of the skin)
- syncope
- increased tendency to bleed or bruise

Other possible side effects that may occur with the following frequencies are:

Very common side effects (affects more than 1 per 10 users):

- upper airway infection
- decreased appetite
- insomnia
- headache, dizziness
- cough
- diarrhoea, vomiting, nausea
- increased blood levels of several liver enzymes called:
 - alanine aminotransferase
 - aspartate aminotransferase
- rash, dry skin
- pain in bones, joints, back, arms or legs, muscle spasms
- fatigue, accumulation of fluid in arms and/or legs, fever, pain

Common side effects (affects 1 to 10 users in 100):

- inflammation of hair follicles, swollen, red area of skin or underneath skin that feels hot and tender
- decreased activity of 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 fat values of triglycerides
- 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 or sensation, abnormal sensation such as prickling, tingling and itchiness

- blurred vision, dry eye, infection in the eye
- tissue swelling in eyelid or around the eyes, caused by excess fluid
- palpitation
- pain in one or both legs when walking or exercising, which disappears after some minutes of rest
- hot flush, flushing
- nosebleed, difficulty producing voice sounds, hypertension in the lungs
- increased blood levels of liver and pancreatic enzymes:
 - amylase
 - alkaline phosphatase
 - gamma-glutamyltransferase
- heartburn caused by reflux of stomach juices, inflammation in the mouth, abdominal swelling or discomfort or indigestion, dry mouth
- increased blood level of bilirubin - the yellow breakdown substance of the blood pigment
- pain in muscles, skeletal system or neck
- skin rash, itching, 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
- stomach bleeding (symptoms include: stomach pain, vomiting blood)

Uncommon side effects (affects 1 to 10 users in 1,000):

- metabolic disorders caused by the break-down products of dying cancer cells
- bleeding in the brain
- obstruction of the blood vessels in the eye, visual disturbance
- 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 (narrowing of the blood vessels to one or both kidneys)
- circulatory problems in the spleen
- liver damage, jaundice (symptoms include: yellowing of the skin and eyes)

Not known (frequency cannot be estimated from the available data):

- recurrence (reactivation) of Hepatitis B infection when you have had hepatitis B in the past (a liver infection).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system:

UK

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard.

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace, IRL - Dublin 2

Tel: +353 1 6764971; Fax: +353 1 6762517

Website: www.hpra.ie; e-mail: medsafety@hpra.ie

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Iclusig

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 bottle label and carton after EXP. The expiry date refers to the last day of that month.

Store in the original container in order to protect from light.

The bottle contains one sealed plastic canister containing a molecular sieve desiccant. Keep the canister in the bottle. Do not swallow the desiccant canister.

6. Contents of the pack and other information

What Iclusig contains

- The active substance is ponatinib.
Each 15 mg film-coated tablet contains 15 mg ponatinib (as ponatinib hydrochloride).
Each 45 mg film-coated tablet contains 45 mg ponatinib (as ponatinib hydrochloride).
- The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, silica (colloidal anhydrous), magnesium stearate, talc, macrogol 4000, polyvinyl alcohol, titanium dioxide (E171).

What Iclusig looks like and contents of the pack

Iclusig film-coated tablets are white, round and rounded on the upper and lower side.

Iclusig 15 mg film-coated tablets are approximately 6 mm in diameter with "A5" on one side.

Iclusig 45 mg film-coated tablets are approximately 9 mm in diameter with "AP4" on one side.

Iclusig is available in plastic bottles, each containing one canister of molecular sieve desiccant.

Bottles are packed within a cardboard box.

Bottles of Iclusig 15 mg contain either 30, 60 or 180 film-coated tablets.

Bottles of Iclusig 45 mg contain either 30 or 90 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Incyte Biosciences UK Ltd.
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This leaflet was last revised in 11/2016.

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.