TLPH

Package leaflet: Information for the user
Ivonib 250 mg film-coated tablets
Ivosidenib

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, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1.What Ivonibis and what it is used for
2. What you need to know before you take Ivonib
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1.What Ivonibis and what it is used for

What Ivonib is
Ivonib is an isocitrate dehydrogenase-1 inhibitor that works by decreasing abnormal production of the oncometabolite 2-hydroxyglutarate (2-HG), leading to differentiation of malignant cells.

What Ivonibis used for
1.1Newly Diagnosed Acute Myeloid Leukemia Ivonib is indicated in combination with azacitidine or as monotherapy for the treatment of newly diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy
1.2Relapsed or Refractory Acute Myeloid Leukemia Ivonib is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test
1.3Relapsed or Refractory Myelodysplastic Syndromes Ivonib is indicated for the treatment of adult patients with relapsed or refractory myelodysplastic syndromes (MDS) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test
1.4Locally Advanced or Metastatic Cholangiocarcinoma Ivonib is indicated for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test
Ivonib is used to treat adults with acute myeloid leukemia (AML) that have a mutation in a gene called IDH1 and whose disease has come back or has not improved after previous treatment(s).
AML is a rapidly progressing cancer that forms in the bone marrow and can result in an increased number of white blood cells in the bloodstream.

How Ivonib works
In AML, patients develop large numbers of abnormal white blood cells. ivosidenib blocks the action of certain enzymes (kinases) needed for the abnormal cells to multiply and grow, thus preventing the growth of the cancer.

2.What you need to know before you take Ivonib

Do not take Ivonib
- if you are allergic to ivosidenib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to you doctor, pharmacist or nurse straight away:

-Differentiation Syndrome in AML and MDS
Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal.
Symptoms of differentiation syndrome in patients treated with Ivonib included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and creatinine increased.
QTc Interval Prolongation
Permanently discontinue Ivonib in patients who develop QTc interval prolongation with signs or symptoms of lifethreatening arrhythmia [
Guillain-Barré Syndrome
Monitor patients taking Ivonib for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue Ivonib in patients who are diagnosed with Guillain Barré syndrome

Other medicines and Ivonib
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Ivonibmay affect the way these medicines work, or these medicines may affect how Ivonibworks.
Effect of Other Drugs on Ivosidenib
- Co-administration of Ivonib with strong or moderate CYP3A4 inhibitors increased ivosidenib plasma concentrations
- Increased ivosidenib plasma concentrations may increase the risk of QTc interval prolongation
- Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with Ivonib.
- If co-administration of a strong CYP3A4 inhibitor is unavoidable, reduce Ivonib to 250 mg once daily

Strong CYP3A4 Inducers
- Co-administration of Ivonib with strong CYP3A4 inducers decreased ivosidenib plasma concentrations
- Avoid co-administration of strong CYP3A4 inducers with Ivonib.

QTc Prolonging Drugs
- Co-administration of Ivonib with QTc prolonging drugs may increase the risk of QTc interval prolongation
- Avoid co-administration of QTc prolonging drugs with Ivonib or replace with alternative therapies. ▪ If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation

Effect of Ivosidenib on Other Drugs
Ivosidenib induces CYP3A4 and may induce CYP2C9. Co-administration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease concentrations of drugs that are sensitive CYP2C9 substrates Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9 during Ivonib treatment. If co-administration of Ivonib with sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs.
Do not administer Ivonib with anti-fungal agents that are substrates of CYP3A4 due to expected loss of antifungal efficacy.
Co-administration of Ivonib may decrease the concentrations of hormonal contraceptives, consider alternative methods of contraception in patients receiving Ivonib.

Pregnancy and breast-feeding
Based on animal embryo-fetal toxicity studies, Ivonib may cause fetal harm when administered to a pregnant woman. There are no available data on Ivonib use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

There are no data on the presence of ivosidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during g treatment with Ivonib and for 1 month after the last dose.

Renal Impairment
No modification of the starting dose is recommended for patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m2 , MDRD). The pharmacokinetics and safety of ivosidenib in patients with severe renal impairment (eGFR < 30 mL/min/1.73m2 , MDRD) or renal impairment requiring dialysis are unknown .For patients with pre-existing severe renal impairment or who are requiring dialysis, consider the risks and potential benefits before initiating treatment with Ivonib.
Hepatic Impairment
No modification of the starting dose is recommended for patients with mild or moderate (Child Pugh A or B) hepatic impairment The pharmacokinetics and safety of ivosidenib in patients with severe hepatic impairment (Child-Pugh C) are unknown. For patients with pre-existing severe hepatic impairment, consider the risks and potential benefits before initiating treatment with Ivonib.

3.How to take Ivonib

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

Ivonibis taken by mouth as tablets.
Your doctor will tell you what dose of Ivonibto take.Your doctor may decide to increase or lower your dose or temporarily interrupt treatment. Continue treatment at the dose prescribed by your doctor.

Taking Ivonib
-The recommended dosage of Ivonib is 500 mg taken orally once daily until disease progression or unacceptable toxicity
For patients with AML or MDS without disease progression or unacceptable toxicity, continue
Ivonib for a minimum of 6 months to allow time for clinical response.
- Administer Ivonib with or without food.
- Do not administer Ivonib with a high-fat meal
- Do not split, crush, or chew Ivonib tablets.
- Administer Ivonib tablets orally about the same time each day.
- If a dose of Ivonib is vomited, do not administer a replacement dose; wait until the next scheduled dose is due.
- If a dose of Ivonib is missed or not taken at the usual time, administer the dose as soon as possible and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

Newly Diagnosed AML (Combination Regimen)
Start Ivonib administration on Cycle 1 Day 1 in combination with azacitidine 75 mg/m2 subcutaneously or intravenously once daily on Days 1-7 (or Days 1-5 and 8-9) of each 28-day cycle .Refer to the Prescribing Information for azacitidine for additional dosing information.

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

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

-Common side effects of Ivonib include fatigue, increase in white blood cells, joint pain, diarrhea, shortness of breath, swelling in the arms or legs, nausea, pain or sores in the mouth or throat, irregular heartbeat (QT prolongation), Guillain-Barré Syndrome rash, fever, cough and constipation. Women who are breastfeeding should not take Ivonib because it may cause harm to a newborn baby.

Acute Myeloid Leukemia
the most common adverse reactions including laboratory abnormalities were leukocytes decreased, diarrhea, hemoglobin decreased, platelets decreased, glucose increased, fatigue, alkaline phosphatase increased, edema, potassium decreased, nausea, vomiting, phosphatase decreased, decreased appetite, sodium decreased, leukocytosis, magnesium decreased, aspartate aminotransferase increased, arthralgia, dyspnea, uric acid increased, abdominal pain, creatinine increased, mucositis, rash, electrocardiogram QT prolonged, differentiation syndrome, calcium decreased, neutrophils decreased, and myalgia.
Newly Diagnosed AML
Common (≥ 5%) serious adverse reactions included differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES).
Common (≥ 10%) adverse reactions leading to dose interruption included electrocardiogram QT prolonged (14%) and differentiation syndrome (11%). Two (7%) patients required a dose reduction due to electrocardiogram QT prolonged. One patient each required permanent discontinuation due to diarrhea and PRES.
Relapsed or Refractory AML
The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%) and dyspnea (3%). Five out of 179 patients (3%) required a dose reduction due to an adverse reaction.
Adverse reactions leading to a dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), and increased transaminases (1%).
Adverse reactions leading to permanent discontinuation included Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and creatinine increased (1%).
Relapsed or Refractory Myelodysplastic Syndromes
Serious adverse reactions in ≥ 5% included differentiation syndrome (11%), fatigue (5%), and rash (5%).The most common (≥ 25%) adverse reactions, including laboratory abnormalities, were creatinine increased, hemoglobin decrease, arthralgia, albumin decreased, aspartate aminotransferase increased, fatigue, diarrhea, cough, sodium decreased, mucositis, decreased appetite, myalgia, phosphate decreased, pruritus, and rash.
Locally Advanced or Metastatic Cholangiocarcinoma
Serious adverse reactions pneumonia, ascites, hyperbilirubinemia, and jaundice cholestatic. acute kidney injury
adverse reactions leading to dose interruption were hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, ascites, and fatigue. electrocardiogram QT prolonged and neuropathy peripheral.
The most common adverse reactions were fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash.

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

5.How to store Ivonib
Keep this medicine out of the sight and reach of children.

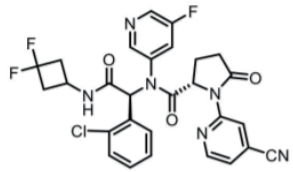
Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

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

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 Ivonib contains
- Ivonib (ivosidenib) is an inhibitor of isocitrate dehydrogenase 1 (IDH1) enzyme. The chemical name is (2S)-N-{(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)-amino]-2- oxoethyl}-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide. The chemical structure is:



The molecular formula is C28H22ClF3N6O3 and the molecular weight is 583.0 g/mol. Ivosidenib is practically insoluble in aqueous solutions between pH 1.2 and 7.4.
Each film-coated tablet contains 250 mg (ivosidenib).
- The other ingredients are:colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate

What Ivoniblooks like and contents of the pack
Ivonib250 mg Blue oval-shaped film-coated tablet
The tablets are provided in bottles and are available in packs containing 60 film-coated tablets .

Marketing Authorisation Holder
Tongmeng(Lao) Pharmaceutical and Food Co., Ltd
Rd13 South,31km,Ban Naphasuk,Saithany District
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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