

Important Risk Minimization Information for Healthcare Professionals for Niloty (nilotinib)

Index

Introduction.....	3
QT prolongation.....	3
Cardiovascular events	4
Uncontrolled or significant cardiac disease/cardiac failure	4
Fluid retention.....	4
Hepatic transaminase and bilirubin elevations	4
Hepatic impairment.....	4
Pancreatitis.....	4
Blood glucose increased	5
Blood cholesterol increased	5
Interaction with food.....	5
Drug interaction with strong CYP3A4 inhibitors	5
Drug interaction with strong CYP3A4 inducers.....	5
Interaction with sensitive CYP3A4 substrates.....	6
Reproductive toxicity/pregnancy	6
Special monitoring of Ph ⁺ CML-CP patients who have achieved a sustained deep molecular response.....	7
NILOTYK.....	8
Adverse event reporting.....	10

Introduction

The purpose of this brochure is to provide health care professionals prescribing nilotinib with the potential serious adverse reactions that may occur with Nilotinib therapy and provide information on how to proactively prevent and/or reduce these events. It is advised to be read carefully before prescribing or dispensing or administering the product.

Nilotinib is indicated for

- The treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in the chronic phase (CP).
- The treatment of adult patients with CP and accelerated phase (AP) Ph+ CML with resistance or intolerance to at least one prior therapy, including imatinib.

The recommended dose of Nilotinib for Ph+ CML is:

- 300 mg twice daily for newly diagnosed adult patients in CP.
- 400 mg twice daily for imatinib-resistant or imatinib–intolerant adult patients in CP or AP.

QT prolongation

- Nilotinib may prolong the QT interval.
- Prolongation of the QT interval may occur when Nilotinib is inappropriately taken with food and/or strong CYP3A4 inhibitors and/or medicinal products known to prolong QT, such as antiarrhythmics, fluoroquinolones, antidepressants, and antipsychotics. The presence of hypokalemia and hypomagnesaemia may also further prolong the QT interval.
- Avoid its co-administration with food and concomitant use with strong CYP3A4 inhibitors and/or avoid medicinal products with a known potential to prolong QT.
- Monitor for hypokalaemia and hypomagnesaemia and correct deficiencies.
- Administer Nilotinib with caution in patients who are at significant risk of developing QTc prolongation or with long QT syndrome, uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia, or patients taking concomitant antiarrhythmic medicines (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol) or other drugs that may prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, and moxifloxacin).

Cardiovascular events

- Evaluate the cardiovascular status of patients and actively monitor and manage cardiovascular risk factors during Nilotinib therapy according to standard guidelines.
- Advise patients to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events.

Uncontrolled or significant cardiac disease/cardiac failure

- A baseline ECG is recommended prior to initiating therapy with Nilotinib and repeated as clinically indicated.
- Use Nilotinib with caution in patients with risk factors for cardiac/coronary heart disease and/or history of uncontrolled or significant cardiac disease. Monitor patient for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

Fluid retention

- Carefully investigate unexpected, rapid weight gain. If signs of severe fluid retention (such as cardiac failure or pulmonary oedema) appear during treatment with Nilotinib, evaluate the etiology and treat patients accordingly.
- Additionally, consider the possibility of other fluid-related complications, such as pleural effusion and pericardial effusion. Promptly assess the patient to determine the underlying cause and initiate treatment based on the identified etiology, while continuing to monitor for any further complications.

Hepatic transaminase and bilirubin elevations

- Bilirubin and hepatic transaminase levels should be tested monthly or as clinically indicated.

Hepatic impairment

- Hepatic impairment has a modest effect on the pharmacokinetics of Nilotinib. Therefore, use with caution in patients with hepatic impairment.
- Patients should be carefully screened by their doctor for signs of Hepatitis B infection before treatment is started.

Pancreatitis

- Elevations of lipase and amylase have been observed in patients taking Nilotinib. Use with caution in patients with a history of pancreatitis.

Blood glucose increased

- Increases in blood glucose levels have been reported with Nilotinib therapy. Therefore, blood glucose levels should be assessed prior to initiating nilotinib therapy and monitored during treatment.
- Lipid profiles should be assessed prior to initiating nilotinib therapy, at 3 and 6 months after initiation, and annually during chronic therapy.

Blood cholesterol increased

- Increases in blood cholesterol levels have been reported with Nilotinib therapy.

Interaction with food

- Prolongation of the QT interval may occur when nilotinib is inappropriately taken with food. Therefore, Nilotinib must NOT be taken with food. [see QT prolongation]
- Advise patients to avoid food for 2 hours before and at least 1 hour after taking Nilotinib.
- Avoid grapefruit juice or other CYP3A4-affecting foods (Seville oranges, starfruit) while on Nilotinib.

Drug interaction with strong CYP3A4 inhibitors

- Nilotinib undergoes metabolism by CYP3A4, and concomitant use of strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, and ritonavir) can increase the Nilotinib serum concentration.
- Should treatment with any of these agents be required, Nilotinib therapy should be interrupted if possible. If transient interruption of treatment with Nilotinib is not possible, close monitoring of the patient for prolongation of the QT interval is indicated. [see QT prolongation]
- Avoid foods that are known to inhibit CYP3A4, such as grapefruit and grapefruit products, as these may also increase serum concentrations of Nilotinib.

Drug interaction with strong CYP3A4 inducers

- Nilotinib undergoes metabolism by CYP3A4, and concomitant use of medicinal products that are potent inducers of CYP3A4 may reduce Nilotinib serum concentration.
- In patients for whom CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) are indicated, consider alternative agents with less enzyme- induction potential.

- When co-administering nilotinib with strong CYP3A4 inhibitors, consider dose reduction and closely monitor QT interval prolongation. If dose reduction isn't feasible, frequent ECG monitoring is advised.

Interaction with sensitive CYP3A4 substrates

- Monitor patient and dose adjust as needed for drugs that are CYP3A4 substrates and have narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, quinidine, sirolimus and tacrolimus) when co-administered with Nilotinib.

Reproductive toxicity/pregnancy

- Nilotinib should not be used during pregnancy. If given during pregnancy, the patient must be informed of the potential risk to the fetus.
- Advise women of childbearing potential to use highly effective contraceptives during Nilotinib treatment and for up to 2 weeks after treatment.

Special monitoring of Ph+ CML-CP patients who have achieved a sustained deep molecular response

Eligibility for discontinuation of treatment

Discontinuation of Nilotinib should be initiated by a physician experienced in the treatment of patients with CML. Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Patients must have typical BCRABL transcripts to allow quantitation of BCR-ABL levels, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after Nilotinib treatment discontinuation.

Monitoring of patients who have discontinued therapy

Frequent monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5. BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation.

Time Points for BCR-ABL1 Transcript Level Assessments: After discontinuing nilotinib, BCR-ABL1 levels should be monitored monthly for the first year, every 6 weeks in the second year, and every 12 weeks thereafter. If MR4 is lost, BCR-ABL1 levels should be checked every 2 weeks until they stabilize between MR4 and MR4.5. Once stable for four consecutive measurements, the original monitoring schedule can be resumed.

Response Milestones and Corresponding Action Plans: Key milestones include Complete cytogenetic response, major molecular response (MMR) ($\text{BCR-ABL1} \leq 0.1\% \text{ IS}$), and MR4 ($\text{BCR-ABL1} \leq 0.01\% \text{ IS}$). If MMR or MR4 is lost, therapy should be re-initiated within 4 weeks. If MR4 or MR4.5 is lost during the treatment-free phase, treatment should be resumed, and monitoring should occur until the previous response is re-established. If milestones are not achieved, nilotinib therapy should be restarted and closely monitored.

Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained deep molecular response

After discontinuation of Nilotinib therapy within the framework of attempting treatment-free remission (TFR), patients may experience musculoskeletal symptoms more frequently than before treatment discontinuation, e.g., myalgia, pain in extremity, arthralgia, bone pain, spinal pain, or musculoskeletal pain.

For further information, refer to SPC and PIL

NILOTYK

Important note: Before prescribing, consult full prescribing information.

Presentation: Hard capsules containing 200 mg of nilotinib.

Indications: Treatment of adult patients with newly diagnosed philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP). Patients who have been treated with Nilotinib for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation; treatment of adult patients with chronic or accelerated phase (AP) Ph+ CML resistant to or intolerant of at least one prior therapy including imatinib. Ph+ CML patients in chronic phase, who have been previously treated with imatinib and whose treatment has been switched to Nilotinib for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation.

Dosage and Administration: For newly diagnosed Ph+ CML-CP, the recommended dosage is 300 mg twice daily. For patients with CP and AP Ph+ CML resistant to or intolerant to at least one prior therapy, including imatinib, the recommended dosage is 400 mg twice daily. Treatment discontinuation may be considered in patients who have sustained deep molecular response for at least 1 year after 3 years of treatment. Nilotinib must be taken twice daily, at 12-hour intervals, and should not be taken with food. A 2-hour fasting period before and 1 hour after the dose is required. If the patient cannot swallow capsules, the contents can be mixed with a teaspoon of applesauce.

Monitoring and Laboratory Tests: Patients on Nilotinib should have regular monitoring of their complete blood count (CBC) every two weeks for the first two months, and monthly thereafter. Blood glucose levels and lipid profiles should be assessed prior to starting treatment and monitored during therapy. A baseline ECG should be obtained, and repeated as clinically indicated to monitor QTc interval. Hepatitis B screening is essential before initiating therapy, and any hepatitis B reactivation must be closely monitored.

Contraindications: Hypersensitivity to nilotinib or to any of the excipients.

Warnings and precautions: Nilotinib can cause myelosuppression, including thrombocytopenia, neutropenia, and anemia, which are generally reversible with dose modifications. QT prolongation has been observed, so caution is advised in patients with a history of cardiac conditions or electrolyte disturbances such as hypokalemia or hypomagnesemia. Patients with significant cardiac risk factors or comorbidities should be closely monitored for signs of cardiovascular events. Fluid retention and unexpected weight gain should be evaluated, as they may indicate a more serious condition. Monitoring liver function (e.g., ALT, AST, bilirubin) and lipid levels is also recommended. In patients with hepatic impairment, dose adjustments or caution should be considered.

Pregnancy: •Women of child-bearing potential must use highly effective method of contraception while receiving Nilotinib and for up to 2 weeks after ending treatment. •Should not be used during pregnancy unless clearly necessary.

Breast-feeding: •Breast-feeding is not recommended.

Interactions: Nilotinib should not be used with CYP3A4 inhibitors, such as ketoconazole, ritonavir, or itraconazole, as they may increase nilotinib levels. Caution is needed when using it with CYP3A4 inducers (e.g., phenytoin, rifampicin), as these may reduce its effectiveness. Co-administration with QT-prolonging drugs or anti-arrhythmic medicines should be avoided, as this may increase the risk of cardiac arrhythmias. H2 blockers should be administered 10 hours before or 2 hours after NILOTYK, and antacids should be administered 2 hours before or after NILOTYK.

Adverse drug reactions:

Very common: Nilotinib therapy may lead to several common adverse effects including headache, nausea, constipation, vomiting, abdominal pain (upper), rash, pruritus, alopecia, myalgia, arthralgia, fatigue, and myelosuppression (such as thrombocytopenia, neutropenia, and anaemia). Metabolic and laboratory abnormalities like hypophosphataemia, hyperbilirubinaemia, increased alanine aminotransferase, aspartate aminotransferase, lipase, and lipoprotein cholesterol (including low-density and high-density lipoproteins), total cholesterol, and triglycerides are also commonly observed. Musculoskeletal issues such as musculoskeletal pain, bone pain, and spinal pain may also occur upon discontinuation of Nilotinib.

Common: Other common side effects include folliculitis, upper respiratory tract infection (e.g., pharyngitis, nasopharyngitis), skin papilloma, leukopenia, eosinophilia, and conditions like febrile neutropenia, pancytopenia, and lymphopenia. Metabolic disturbances such as diabetes mellitus, hyperglycaemia, and hyperlipidaemia (including increased cholesterol and triglycerides) have been noted. Electrolyte imbalances (including hypomagnesaemia, hypokalaemia, hyponatraemia, and hyperphosphataemia) are common. Neurological symptoms like depression, insomnia, dizziness, peripheral neuropathy, and vertigo have also been reported. Cardiovascular adverse effects include arrhythmias, palpitations, hypertension, and prolonged QT interval. Gastrointestinal issues such as diarrhoea, abdominal pain, pancreatitis, and dyspepsia may also occur.

Uncommon: Uncommon effects include pneumonia, urinary tract infections, gastroenteritis, bronchitis, herpes virus infections, candidiasis, and thyroid issues (hyperthyroidism, hypothyroidism). Cardiac issues, such as myocardial infarction, coronary artery disease, and cardiac failure, have been observed, as well as cerebrovascular events (including stroke and transient ischaemic attack). Gastrointestinal haemorrhage, melena, and issues related to liver function like hepatotoxicity, toxic hepatitis, and jaundice can occur. Dermatological side effects such as exfoliative rash, skin ulcer, palmar-plantar erythrodysesthesia syndrome, and photosensitivity are reported in a smaller subset of patients.

Frequency not known: Severe reactions may include sepsis, abscesses, hypersensitivity, thrombocytopenia, and leukocytosis. Neurological issues like disorientation, amnesia, cerebrovascular accidents, and vision impairment can occur. Cardiovascular events such as

shock, thrombosis, hypotension, and pulmonary hypertension have been reported. Rare gastrointestinal complications include gastric ulcers and oesophagitis. Hepatic effects like hepatomegaly, psoriasis, erythema multiforme, and photosensitivity may occur. Renal issues such as renal failure, haematuria, urinary incontinence and hepatitis B reactivation have also been observed.

Adverse event reporting

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

Please report suspected adverse drug reactions (ADRs) to The National Pharmacovigilance Centre (NPC);

SFDA Call Centre: 19999

E-mail: npc.drug@sfd.gov.sa

Website: <https://ade.sfd.gov.sa/>



For further copies of this guide please contact Al-Hobail Pharmaceutical for Medical information, please contact:

920006647 Ext (110)

Or email

mousa@al-hobail.com