Nilogen 50mg Capsules
Nilogen 150mg Capsules
Nilogen 200mg Capsules

1. NAME OF THE MEDICINAL PRODUCT

Nilogen 50mg Capsules
Nilogen 150mg Capsules
Nilogen 200mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nilogen 50mg Capsules: Each capsule contains 53.447mg of Nilotinib Hydrochloride equivalent to 50mg Nilotinib.

Nilogen 150mg Capsules: Each capsule contains 160.340mg of Nilotinib Hydrochloride equivalent to 150mg Nilotinib.

Nilogen 200mg Capsules: Each capsule contains 213.787mg of Nilotinib Hydrochloride equivalent to 200mg Nilotinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

50mg Hard Capsules
Off-white to pale yellow granules filled in capsule size 4 with red opaque cap and light yellow opaque body, imprinted with “NIL” on the cap and “50 mg” on the body with black ink.

150mg Hard Capsules
Off-white to pale yellow granules filled in red opaque capsule size 0, imprinted with “NIL” on the cap and “150 mg” on the body with black ink.

200mg Hard Capsules
Off-white to pale yellow granules filled in light yellow opaque capsule size 0, imprinted with “NIL” on the cap and “200 mg” on the body with red ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nilotinib is indicated for:

- the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).
  Clinical effectiveness of Nilotinib in adults with newly diagnosed Ph+ CML-CP is based on major molecular response rate at 12 months and complete cytogenetic response rate by 12 months.
- the treatment of pediatric patients 2 years of age and older with newly diagnosed Ph+

CML-CP.
Clinical effectiveness of Nilotinib in pediatric patients with newly diagnosed Ph+ CML-CP is based on major molecular response by 12 cycles and complete cytogenetic response at 12 cycles.

- the treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib.
  Clinical effectiveness of Nilotinib in adults with imatinib-resistant or -intolerant Ph+ CML-CP was based on the unconfirmed major cytogenetic and complete hematologic response rates.
  Clinical effectiveness of Nilotinib in imatinib-resistant or -intolerant Ph+ CML-AP for adult patients was based on the confirmed hematologic response rates and the unconfirmed major cytogenetic response rates.
- the treatment of pediatric patients 2 years of age and older with Ph+ CML-CP with resistance or intolerance to prior therapy including imatinib.
  Clinical effectiveness of Nilotinib in pediatric patients with imatinib-resistant or intolerant Ph+ CML-CP was based on the MMR rate at 6 cycles.
  No overall survival benefit has been demonstrated.

4.2 Posology and Method of Administration

Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML.

Posology
Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

If a dose is missed the patient should not take an additional dose, but take the usual prescribed next dose.

Posology for Philadelphia chromosome positive CML adult patients
The recommended dose is:

- 300 mg twice daily in newly diagnosed patients with CML in the chronic phase,
- 400 mg twice daily in patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy.

For a dose of 300 mg twice daily, 150 mg hard capsules are available.
For a dose of 400 mg once daily, 200 mg hard capsules are available.

Posology for Philadelphia chromosome positive CML paediatric patients
Dosing in paediatric patients is individualised and is based on body surface area (mg/m^2). The recommended dose of nilotinib is 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). Different strengths of Nilotinib hard capsules can be combined to attain the desired dose.

There is no experience with treatment of paediatric patients below 2 years of age. There are no data in newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

Table 1: Paediatric dosing scheme of nilotinib 230 mg/m^2 twice daily

Body Surface Area (BSA)	Dose in mg (twice daily)
Up to 0.32 m^2	50 mg
0.33 – 0.54 m^2	100 mg
0.55 – 0.76 m^2	150 mg
0.77 – 0.97 m^2	200 mg
0.98 – 1.19 m^2	250 mg
1.20 – 1.41 m^2	300 mg
1.42 – 1.63 m^2	350 mg
≥1.64 m^2	400 mg

Adult Philadelphia chromosome positive CML patients in chronic phase who have been treated with nilotinib as first-line therapy and who achieved a sustained deep molecular response (MR4.5)

Discontinuation of treatment may be considered in eligible adult Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of nilotinib therapy should be initiated by a physician experienced in the treatment of patients with CML.

Eligible patients who discontinue nilotinib therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS).

For patients who lose MR4 (MR4=BCR-ABL/ABL ≤0.01%IS) but not MMR (MMR=BCR-ABL/ABL ≤0.1%IS) during the treatment-free phase, BCR-ABL transcript levels should be monitored every 2 weeks until BCR-ABL levels return to a range between MR4 and MR4.5. Patients who maintain BCR-ABL levels between MMR and MR4 for a minimum of 4 consecutive measurements can return to the original monitoring schedule.

Patients who lose MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patients who re-initiate nilotinib therapy should have their BCR-ABL transcript levels monitored monthly until MMR is re-established and every 12 weeks thereafter.

Adult Philadelphia chromosome positive CML patients in chronic phase who have achieved a sustained deep molecular response (MR 4.5) on nilotinib following prior imatinib therapy

Discontinuation of treatment may be considered in eligible adult Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of nilotinib therapy should be initiated by a physician experienced in the treatment of patients with CML.

Eligible patients who discontinue nilotinib therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks

for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS).

Patients with confirmed loss of MR4 (MR4= BCR-ABL/ABL ≤0.01%IS) during the treatment-free phase (two consecutive measures separated by at least 4 weeks showing loss of MR4) or loss of major molecular response (MMR=BCR-ABL/ABL ≤0.1%IS) must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at either 300 mg or 400 mg twice daily. Patients who re-initiate nilotinib therapy should have their BCR-ABL transcript levels monitored monthly until previous major molecular response or MR4 level is re-established and every 12 weeks thereafter.

Dose adjustments or modifications

Nilotinib may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to the underlying leukaemia (see Table 2).

Table 2: Dose adjustments for neutropenia and thrombocytopenia

Adult patients with newly diagnosed chronic phase CML at 300 mg twice daily and imatinib-resistant or intolerant CML in chronic phase at 400 mg twice daily	ANC* <1.0 x 10^9/l and/or platelet counts <50 x 10^9/l	1. Treatment with nilotinib must be interrupted and blood count monitored. 2. Treatment must be resumed within 2 weeks at prior dose if ANC >1.0 x 10^9/l and/or platelets >50 x 10^9/l. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Adult patients with imatinib-resistant orintolerant CML in accelerated phase at 400 mg twice daily	ANC* <0.5 x 10^9/l and/or platelet counts <10 x 10^9/l	1. Treatment with nilotinib must be interrupted and blood count monitored. 2. Treatment must be resumed within 2 weeks at prior dose if ANC >1.0 x 10^9/l and/or platelets >20 x 10^9/l. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Paediatric patients with newly-diagnosed CML in chronic phase at 230 mg/m^2 twice daily and imatinib-resistant orintolerant CML in chronic phase at 230 mg/m^2 twice daily	ANC* <1.0 x 10^9/l and/or platelet counts <50 x 10^9/l	1. Treatment with nilotinib must be interrupted and blood count monitored. 2. Treatment must be resumed within 2 weeks at prior dose if ANC >1.5 x 10^9/l and/or platelets >75 x 10^9/l. 3. If blood counts remain low, a dose reduction to 230 mg/m^2 once daily may be required. 4. If event occurs after dose reduction, consider discontinuing treatment.

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and patients should be monitored and treated accordingly. If the prior dose was 300 mg twice daily in adult newly diagnosed patients with CML in the chronic phase, or 400 mg twice daily in adult patients with imatinib-resistant or intolerant CML in chronic or accelerated phase, or 230 mg/m^2 twice daily in paediatric patients, dosing may be resumed at 400 mg once daily in adult patients and at 230 mg/m^2 once daily in paediatric patients once the toxicity has resolved. If the prior dose was 400 mg once daily in adult patients or 230 mg/m^2 once daily in paediatric patients, treatment should be discontinued. If clinically appropriate, re-escalation of the dose to the starting dose of 300 mg twice daily in adult newly diagnosed patients with CML in the chronic phase or to 400 mg twice daily in adult patients with imatinib-resistant or intolerant CML in chronic or accelerated phase or to 230 mg/m^2 twice daily in paediatric patients should be considered.

Elevated serum lipase: For Grade 3-4 serum lipase elevations, doses in adult patients should be reduced to 400 mg once daily or interrupted. In paediatric patients, treatment must be interrupted until the event returns to Grade ≤1. Thereafter, if the prior dose was 230 mg/m^2 twice daily, treatment can be resumed at 230 mg/m^2 once daily. If the prior dose was 230 mg/m^2 once daily, treatment should be discontinued. Serum lipase levels should be tested monthly or as clinically indicated.

Elevated bilirubin and hepatic transaminases: For Grade 3-4 bilirubin and hepatic transaminase elevations in adult patients, doses should be reduced to 400 mg once daily or interrupted. For Grade ≥2 bilirubin elevations or Grade ≥3 hepatic transaminase elevations in paediatric patients, treatment must be interrupted until the levels return to Grade ≤1. Thereafter, if the prior dose was 230 mg/m^2 twice daily, treatment can be resumed at 230 mg/m^2 once daily. If the prior dose was 230 mg/m^2 once daily, and recovery to Grade ≤1 takes longer than 28 days, treatment should be discontinued. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated.

Special populations
Elderly
No major differences were observed for safety and efficacy in patients ≥65 years of age as compared to adults aged 18 to 65 years.

Renal impairment
Clinical studies have not been performed in patients with impaired renal function.
Since nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment.

Hepatic impairment
Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Dose adjustment is not considered necessary in patients with hepatic impairment. However, patients with hepatic impairment should be treated with caution.

Cardiac disorders
In studies, patients with uncontrolled or significant cardiac disease (e.g., recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia) were excluded. Caution should be exercised in patients with relevant cardiac disorders.

Increases in total serum cholesterol levels have been reported with nilotinib therapy. Lipid

profiles should be determined prior to initiating nilotinib therapy, assessed at month 3 and 6 after initiating therapy and at least yearly during chronic therapy.

Increases in blood glucose levels have been reported with nilotinib therapy. Blood glucose levels should be assessed prior to initiating nilotinib therapy and monitored during treatment.

Paediatric population
The safety and efficacy of nilotinib in paediatric patients with Philadelphia chromosome positive CML in chronic phase from 2 to less than 18 years of age have been established. There is no experience in paediatric patients below 2 years of age or in paediatric patients with Philadelphia chromosome positive CML in accelerated phase or blast crisis. There are no data in newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

Method of administration

Nilotinib should be taken twice daily approximately 12 hours apart and must not be taken with food. The hard capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken.

For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce (puréed apple) and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special Warnings and Precautions for Use

Myelosuppression
Treatment with nilotinib is associated with (National Cancer Institute Common Toxicity Criteria grade 3-4) thrombocytopenia, neutropenia and anaemia. Occurrence is more frequent in patients with imatinib-resistant or intolerant CML, in particular in patients with accelerated-phase CML. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding nilotinib temporarily or dose reduction.

QT prolongation
Nilotinib has been shown to prolong cardiac ventricular repolarisation as measured by the QT interval on the surface ECG in a concentration-dependent manner in adult and paediatric patients.

In the study in patients with newly diagnosed CML in chronic phase receiving 300 mg nilotinib twice daily, the change from baseline in mean time-averaged QTcF interval at steady state was 6 msec. No patient had a QTcF >480 msec. No episodes of torsade de pointes were observed.

In the study in imatinib-resistant and intolerant CML patients in chronic and accelerated phase receiving 400 mg nilotinib twice daily, the change from baseline in mean time-averaged QTcF interval at steady state was 5 and 8 msec, respectively. QTcF of >500 msec was observed in <1% of these patients. No episodes of torsade de pointes were observed in clinical studies.

In a healthy volunteer study with exposures that were comparable to the exposures observed in patients, the time-averaged mean placebo-subtracted QTcF change from baseline was 7 msec (CI ± 4 msec). No subject had a QTcF >450 msec. Additionally, no clinically relevant arrhythmias were observed during the conduct of the trial. In particular, no episodes of torsade de pointes (transient or sustained) were observed.

Significant prolongation of the QT interval may occur when nilotinib is inappropriately taken with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong the QT interval, and/or food. The presence of hypokalaemia and hypomagnesaemia may further enhance this effect. Prolongation of the QT interval may expose patients to the risk of fatal outcome.

Nilotinib should be used with caution in patients who have or who are at significant risk of developing prolongation of QTc, such as those:

- with congenital long QT prolongation
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation.

Close monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating nilotinib therapy and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to nilotinib administration and should be monitored periodically during therapy.

Sudden death

Uncommon cases of sudden deaths have been reported in patients with imatinib-resistant or intolerant CML in chronic phase or accelerated phase with a past medical history of cardiac disease or significant cardiac risk factors. Co-morbidities in addition to the underlying malignancy were also frequently present as were concomitant medicinal products. Ventricular repolarisation abnormalities may have been contributory factors. No cases of sudden death were reported in the study in newly diagnosed patients with CML in chronic phase.

Fluid retention and oedema

Severe forms of drug-related fluid retention such as pleural effusion, pulmonary oedema, and pericardial effusion were uncommonly observed in a study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the aetiology should be evaluated and patients treated accordingly.

Cardiovascular events

Cardiovascular events were reported in a study in newly diagnosed CML patients and observed in post-marketing reports. In this clinical study with a median on-therapy time of 60.5 months, Grade 3-4 cardiovascular events included peripheral arterial occlusive disease,

ischaemic heart disease and ischaemic cerebrovascular events. Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during nilotinib therapy according to standard guidelines. Appropriate therapy should be prescribed to manage cardiovascular risk factors.

Hepatitis B reactivation
Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with nilotinib. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with nilotinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Special monitoring of adult Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response

Eligibility for discontinuation of treatment
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 BCR-ABL transcripts to allow quantitation of BCR-ABL, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after discontinuation of treatment with nilotinib.

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/ABL ≤0.0032% IS). BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation.

Loss of major molecular response (MMR=BCR-ABL/ABL ≤0.1%IS) in CML patients who received nilotinib as first- or second-line therapy, or confirmed loss of MR4 (two consecutive measures separated by at least 4 weeks showing loss of MR4 (MR4=BCR-ABL/ABL≤0.01%IS)) in CML patients who received nilotinib as second-line therapy will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Molecular relapse can occur during the treatment-free phase, and long-term outcome data are not yet available. It is therefore crucial to perform frequent monitoring of BCR-ABL transcript levels and complete blood count with differential in order to detect possible loss of remission. For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

Laboratory tests and monitoring

Blood lipids

In a study in newly diagnosed CML patients, patients treated with 400 mg nilotinib twice daily showed a Grade 3-4 elevation in total cholesterol; no Grade 3-4 elevations were however observed in the 300 mg twice daily dose group. It is recommended that the lipid profiles be determined before initiating treatment with nilotinib, assessed at month 3 and 6 after initiating therapy and at least yearly during chronic therapy. If a HMG-CoA reductase inhibitor (a lipid-lowering agent) is required, please refer to section 4.5 before initiating treatment since certain HMG-CoA reductase inhibitors are also metabolised by the CYP3A4 pathway.

Blood glucose
In a study in newly diagnosed CML patients, patients treated with 400 mg nilotinib and 300 mg nilotinib twice daily, respectively, showed a Grade 3-4 elevation in blood glucose. It is recommended that the glucose levels be assessed before initiating treatment with nilotinib and monitored during treatment, as clinically indicated. If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Interactions with other medicinal products
The administration of nilotinib with agents that are strong CYP3A4 inhibitors (including, but not limited to, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) should be avoided. Should treatment with any of these agents be required, it is recommended that nilotinib therapy be interrupted if possible. If transient interruption of treatment is not possible, close monitoring of the individual for prolongation of the QT interval is indicated.

Concomitant use of nilotinib with medicinal products that are potent inducers of CYP3A4 (e.g., phenytoin, rifampicin, carbamazepine, phenobarbital and St. John's Wort) is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving nilotinib, co-administration of alternative therapeutic agents with less potential for CYP3A4 induction should be selected.

Food effect
The bioavailability of nilotinib is increased by food. Nilotinib must not be taken in conjunction with food and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided. For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used.

Hepatic impairment
Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of 200 mg of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state C_{max} of nilotinib showed an increase of 29%, 18% and 22%, respectively. Clinical studies have excluded patients with alanine transaminase (ALT) and/or aspartate transaminase (AST) >2.5 (or >5, if related to disease) times the upper limit of the normal range and/or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Patients with hepatic impairment might therefore have increased exposure to nilotinib and should be treated with caution.

Serum lipase
Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, nilotinib therapy should be interrupted and appropriate diagnostic measures considered to exclude pancreatitis.

Total gastrectomy
The bioavailability of nilotinib might be reduced in patients with total gastrectomy. More frequent follow-up of these patients should be considered.

Tumour lysis syndrome
Due to possible occurrence of tumour lysis syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating nilotinib therapy.

Lactose
Nilogen hard capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric population
Laboratory abnormalities of mild to moderate transient elevations of aminotransferases and total bilirubin have been observed in children at a higher frequency than in adults, indicating a higher risk of hepatotoxicity in the paediatric population. Liver function (bilirubin and hepatic transaminases levels) should be monitored monthly or as clinically indicated. Elevations of bilirubin and hepatic transaminases should be managed by withholding nilotinib temporarily, dose reduction and/or discontinuation of nilotinib. The long-term effects of prolonged treatment with nilotinib in paediatric patients are unknown. In a study in the CML paediatric population, growth retardation has been documented in patients treated with nilotinib. Close monitoring of growth in paediatric patients under nilotinib treatment is recommended.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Nilotinib may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) if clinically indicated. It may be given with hydroxyurea or anagrelide if clinically indicated.

Nilotinib is mainly metabolised in the liver with CYP3A4 expected to be the main contributor to the oxidative metabolism. Nilotinib is also a substrate for the multi-drug efflux pump, P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by substances that affect CYP3A4 and/or P-gp.

Substances that may increase nilotinib serum concentrations
Concomitant administration of nilotinib with imatinib (a substrate and moderator of P-gp and CYP3A4), had a slight inhibitory effect on CYP3A4 and/or P-gp. The AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%. These changes are unlikely to be clinically important.

The exposure to nilotinib in healthy subjects was increased 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concomitant treatment with strong CYP3A4 inhibitors, including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin, should therefore be avoided. Increased exposure to nilotinib might also be expected with moderate CYP3A4 inhibitors. Alternative concomitant medicinal products with no or minimal CYP3A4 inhibition should be considered.

Substances that may decrease nilotinib serum concentrations
Rifampicin, a potent CYP3A4 inducer, decreases nilotinib C_{max} by 64% and reduces nilotinib AUC by 80%. Rifampicin and nilotinib should not be used concomitantly.

The concomitant administration of other medicinal products that induce CYP3A4 (e.g. phenytoin, carbamazepine, phenobarbital and St. John's Wort) is likewise likely to reduce exposure to nilotinib to a clinically relevant extent. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected.

Nilotinib has pH dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in C_{max} and 34% decrease in $AUC_{0-\infty}$). Nilotinib may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

In a healthy subjects study, no significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of nilotinib was administered 10 hours after and 2 hours before famotidine. Therefore, when the concurrent use of a H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of nilotinib.

In the same study as above, administration of an antacid (aluminium hydroxide/magnesium hydroxide/simethicone) 2 hours before or after a single 400 mg dose of nilotinib also did not alter nilotinib pharmacokinetics. Therefore, if necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of nilotinib.

Substances that may have their systemic concentration altered by nilotinib
In vitro, nilotinib is a relatively strong inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1, with Ki value being lowest for CYP2C9 (Ki=0.13 microM).

A single-dose drug-drug interaction study in healthy volunteers with 25 mg warfarin, a sensitive CYP2C9 substrate, and 800 mg nilotinib did not result in any changes in warfarin pharmacokinetic parameters or warfarin pharmacodynamics measured as prothrombin time (PT) and international normalised ratio (INR). There are no steady-state data. This study suggests that a clinically meaningful drug-drug interaction between nilotinib and warfarin is less likely up to a dose of 25 mg of warfarin. Due to lack of steady-state data, control of warfarin pharmacodynamic markers (INR or PT) following initiation of nilotinib therapy (at least during the first 2 weeks) is recommended.

In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure (AUC and C_{max}) of oral midazolam (a substrate of CYP3A4) 2.6-fold and 2.0-fold, respectively. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other medicinal products primarily metabolised by CYP3A4 (e.g. certain HMG-

CoA reductase inhibitors) may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for medicinal products that are CYP3A4 substrates and have a narrow therapeutic index (including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with nilotinib.

Anti-arrhythmic medicinal products and other substances that may prolong the QT interval
Nilotinib should be used with caution in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicinal products that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, methadone and moxifloxacin.

Food interactions
The absorption and bioavailability of nilotinib are increased if it is taken with food, resulting in a higher serum concentration. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception
Women of childbearing potential have to use highly effective contraception during treatment with nilotinib and for up to two weeks after ending treatment.

Pregnancy
There are no or limited amount of data from the use of nilotinib in pregnant women. Studies in animals have shown reproductive toxicity. Nilotinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with nilotinib. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

If a woman who is being treated with nilotinib is considering pregnancy, treatment discontinuation may be considered based on the eligibility criteria for discontinuing treatment. There is a limited amount of data on pregnancies in patients while attempting treatment-free remission (TFR). If pregnancy is planned during the TFR phase, the patient must be informed of a potential need to re-initiate nilotinib treatment during pregnancy.

Breast-feeding
It is unknown whether nilotinib is excreted in human milk. Available toxicological data in animals have shown excretion of nilotinib in milk. Since a risk to the newborns/infants cannot be excluded, women should not breast-feed during nilotinib treatment and for 2 weeks after the last dose.

Fertility
Animal studies did not show an effect on fertility in male and female rats.

4.7 Effects on Ability to Drive and Use Machines

Nilotinib has no or negligible influence on the ability to drive and use machines. However, it is recommended that patients experiencing dizziness, fatigue, visual impairment or other undesirable effects with a potential impact on the ability to drive or use machines safely should refrain from these activities as long as the undesirable effects persist.

4.8 Undesirable Effects

Summary of the safety profile

The data described below reflect exposure to nilotinib in a study in patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily and from a study in adult patients with imatinib-resistant or intolerant CML in chronic phase and accelerated phase treated at the recommended dose of 400 mg twice daily. Safety information from two nilotinib treatment discontinuation studies is also provided.

In adult patients with newly diagnosed CML in chronic phase

The median duration of exposure was 60.5 months (range 0.1-70.8 months).

The most frequent non-haematological adverse reactions were rash, pruritus, headache, nausea, fatigue, alopecia, myalgia and upper abdominal pain. Most of these adverse reactions were mild to moderate in severity. Constipation, dry skin, asthenia, muscle spasms, diarrhoea, arthralgia, abdominal pain, vomiting and peripheral oedema were observed less commonly were of mild to moderate severity, manageable and generally did not require dose reduction.

Treatment-emergent haematological toxicities include myelosuppression: thrombocytopenia, neutropenia and anaemia. Biochemical adverse drug reactions include alanine aminotransferase increased, hyperbilirubinaemia, aspartate aminotransferase increased, lipase increased, blood bilirubin increased, hyperglycaemia, hypercholesterolaemia and hypertriglyceridaemia. Pleural and pericardial effusions, regardless of causality, occurred in patients receiving nilotinib 300 mg twice daily. Gastrointestinal haemorrhage, regardless of causality, was reported in patients.

The change from baseline in mean time-averaged QTcF interval at steady state was 6 msec. No patient had an absolute QTcF >500 msec while on the study medicinal product. QTcF increase from baseline exceeding 60 msec was observed in <1% of patients while on the study medicinal product. No sudden deaths or episodes of torsade de pointes (transient or sustained) were observed. No decrease from baseline in mean left ventricular ejection fraction (LVEF) was observed at any time during treatment. No patient had a LVEF of <45% during treatment nor an absolute reduction in LVEF of more than 15%.

Discontinuation due to adverse drug reactions was observed in 10% of patients.

In adult patients with imatinib-resistant or intolerant CML in chronic phase and accelerated phase

The most frequent non-haematological drug-related adverse events were rash, pruritus, nausea, fatigue, headache, vomiting, myalgia, constipation and diarrhoea. Most of these adverse events were mild to moderate in severity. Alopecia, muscle spasms, decreased appetite, arthralgia, abdominal pain, bone pain, peripheral oedema, asthenia, upper abdominal pain, dry skin, erythema and pain in extremity were observed less commonly and have been of mild to moderate severity (Grade 1 or 2). Discontinuation due to adverse drug reactions was observed in chronic phase and accelerated phase patients.

Treatment-emergent haematological toxicities include myelosuppression: thrombocytopenia, neutropenia and anaemia. Pleural and pericardial effusions as well as complications of fluid retention occurred in patients receiving nilotinib. Cardiac failure was observed in patients. Gastrointestinal and CNS haemorrhage were reported in patients.

QTcF exceeding 500 msec was observed in patients. No episodes of torsade de pointes (transient or sustained) were observed.

Tabulated list of adverse reactions
The adverse reactions are ranked under heading of frequency using the following convention: very common, common, uncommon, rare, very rare and not known. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Most frequently reported adverse reactions in nilotinib studies
Non-haematological adverse reactions (excluding laboratory abnormalities) that are reported in at least 5% of the adult patients in Nilotinib studies that serve as the basis for the approved indications are shown in Table 3.

Table 3: Non-haematological adverse reactions (≥5% of all patients)

System organ class/ Adverse reaction	**Newly diagnosed CML-CP 300 mg twice daily**	**Imatinib-resistant or intolerant CML-CP and CML-AP 400 mg twice daily**
	Frequency	**Frequency**
Metabolism and nutrition disorders		
Decreased appetite **	Common	Common
Nervous system disorders		
Headache	Very Common	Very Common
Gastrointestinal disorders		
Nausea	Very Common	Very Common
Constipation	Common	Very Common
Diarrhoea	Common	Very Common
Vomiting	Common	Very Common
Upper abdominal pain	Very Common	Common
Abdominal pain	Common	Common
Dyspepsia	Common	Common
Skin and subcutaneous tissue disorders		
Rash	Very Common	Very Common
Pruritus	Very Common	Very Common
Alopecia	Very Common	Common
Dry skin	Common	Common
Erythema	Common	Common
Musculoskeletal and connective tissue disorders		
Myalgia	Very Common	Very Common
Muscle spasms	Common	Common
Arthralgia	Common	Common
Bone pain	Common	Common
Pain in extremity	Common	Common
General disorders and administration site conditions		

Fatigue	Very Common	Very Common
Asthenia	Common	Common
Oedema peripheral	Common	Common

** Also includes preferred term anorexia

Adverse reactions that were reported in adult patients in the nilotinib studies which serve as a basis for the approved indications at a frequency of less than 5% are shown in Table 4. For laboratory abnormalities, very common adverse reactions not included in Table 3 are also reported. These adverse reactions are included based on clinical relevance.

Table 4: Adverse reactions in adult patients in nilotinib studies (<5% of all patients)

Infections and infestations	
Common:	Folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis)
Uncommon:	Pneumonia, urinary tract infection, gastroenteritis, bronchitis, herpes virus infection, candidiasis (including oral candidiasis)
Not known:	Sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Skin papilloma
Not known:	Oral papilloma, paraproteinaemia
Blood and lymphatic system disorders	
Common:	Leukopenia, eosinophilia, febrile neutropenia, pancytopenia,lymphopenia
Uncommon:	Thrombocythaemia, leukocytosis
Immune system disorders	
Not known:	Hypersensitivity
Endocrine disorders	
Uncommon:	Hyperthyroidism, hypothyroidism
Not known:	Hyperparathyroidism secondary, thyroiditis
Metabolism and nutrition disorders	
Very common:	Hypophosphataemia (including blood phosphorus decreased)
Common:	Electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia
Uncommon:	Dehydration, increased appetite, gout, dyslipidaemia
Not known:	Hyperuricaemia, hypoglycaemia
Psychiatric disorders	
Common:	Depression, insomnia, anxiety
Not known:	Disorientation, confusional state, amnesia, dysphoria
Nervous system disorders	
Common:	Dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia
Uncommon:	Intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia
Not known:	Cerebrovascular accident, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome
Eye disorders	
Common:	Eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye

	(including xerophthalmia)
Uncommon:	Visual impairment, vision blurred, conjunctival haemorrhage, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation
Not known:	Papilloedema, chorioretinopathy, diplopia, photophobia, eye swelling, blepharitis, eye pain, conjunctivitis allergic, ocular surface disease
Ear and labyrinth disorders	
Common:	Vertigo
Not known:	Hearing impaired, ear pain, tinnitus
Cardiac disorders	
Common:	Angina pectoris, arrhythmia (including atroventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, bradycardia), palpitations, electrocardiogram QT prolonged
Uncommon:	Cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, pericardial effusion, cyanosis
Not known:	Ventricular dysfunction, pericarditis, ejection fraction decreased
Vascular disorders	
Common:	Hypertension, flushing, peripheral artery stenosis
Uncommon:	Hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis
Not known:	Shock haemorrhagic, hypotension, thrombosis
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia
Uncommon:	Pulmonary oedema, pleural effusion, interstitial lung disease, pleuriticpain, pleurisy, pharyngolaryngeal pain, throat irritation
Not known:	Pulmonary hypertension, wheezing, oropharyngeal pain
Gastrointestinal disorders	
Common:	Pancreatitis, abdominal discomfort, abdominal distension, dysgeusia, flatulence
Uncommon:	Gastrointestinal haemorrhage, melaena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth,gastritis, sensitivity of teeth
Not known:	Gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis
Hepatobiliary disorders	
Very common:	Hyperbilirubinaemia (including blood bilirubin increased)
Common:	Hepatic function abnormal
Uncommon:	Hepatotoxicity, toxic hepatitis, jaundice
Not known:	Cholestasis, hepatomegaly
Skin and subcutaneous tissue disorders	
Common:	Night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis (including allergic, exfoliative and acneiform)
Uncommon:	Exfoliative rash, drug eruption, skin pain, ecchymosis, swelling face
Not known:	Erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cysts, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis, psoriasis
Musculoskeletal and connective tissue disorders	
Common:	Musculoskeletal chest pain, musculoskeletal pain, back pain, flank pain,

	neck pain, muscular weakness
Uncommon:	Musculoskeletal stiffness, joint swelling
Not known:	Arthritis
Renal and urinary disorders	
Common:	Pollakiuria
Uncommon:	Dysuria, micturition urgency, nocturia
Not known:	Renal failure, haematuria, urinary incontinence, chromaturia
Reproductive system and breast disorders	
Uncommon:	Breast pain, gynaecomastia, erectile dysfunction
Not known:	Breast induration, menorrhagia, nipple swelling
General disorders and administration site conditions	
Common:	Chest pain (including non-cardiac chest pain), pain, pyrexia, chest discomfort, malaise
Uncommon:	Face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold)
Not known:	Localised oedema
Investigations	
Very common:	Alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased
Common:	Haemoglobin decreased, blood amylase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, weight decreased, weight increased, blood insulin increased, globulins decreased
Uncommon:	Blood lactate dehydrogenase increased, blood glucose decreased, bloodurea increased
Not known:	Troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased

Clinically relevant or severe abnormalities of routine haematological or biochemistry laboratory values in adult patients are presented in Table 5.

Table 5: Grade 3-4 laboratory abnormalities*

	Newly diagnosed CML-CP 300 mg twice daily (%)	**Imatinib-resistant or intolerant CML-CP and CML-AP 400 mg twice daily**	
		CML-CP (%)	**CML-AP (%)**
Haematological parameters			
Myelosuppression			
- Neutropenia	12	31	42
- Thrombocytopenia	10	30	42
- Anaemia	4	11	27
Biochemistry parameters			
- Elevated creatinine	0	1	<1
- Elevated lipase	9	18	18
- Elevated SGOT (AST)	1	3	2
- Elevated SGPT (ALT)	4	4	4
- Hypophosphataemia	8	17	15
- Elevated bilirubin (total)	4	7	9

- Elevated glucose	7	12	6
- Elevated cholesterol (total)	0	**	**
- Elevated triglycerides	0	**	**

* Percentages with one decimal precision are used and rounded to integer for presentation in this table
** Parameters not collected

Treatment discontinuation in adult Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response
After discontinuation of nilotinib therapy within the framework of attempting 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.

In a study with newly diagnosed adult patients with Ph+ CML in chronic phase, musculoskeletal symptoms were reported within a year of nilotinib discontinuation in 24.7% versus 16.3% within the previous year on nilotinib treatment.

In a study with adult patients with Ph+ CML in chronic phase on nilotinib treatment and previously treated with imatinib, musculoskeletal symptoms were reported within a year of discontinuation in 42.1% versus 14.3% within the previous year on nilotinib treatment.

Description of selected adverse reactions

Sudden death
Uncommon cases of sudden deaths have been reported in nilotinib clinical trials and/or compassionate use programs in patients with imatinib-resistant or intolerant CML in chronic phase or accelerated phase with a past medical history of cardiac disease or significant cardiac risk factors.

Hepatitis B reactivation
Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Post-marketing experience
The following adverse reactions have been derived from post-marketing experience with nilotinib via spontaneous case reports, literature cases, expanded access programmes, and clinical studies other than the global registration trials. Since these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to nilotinib exposure.

Frequency very common: Growth retardation has been documented in paediatric patients treated with nilotinib.

Frequency rare: Cases of tumour lysis syndrome have been reported in patients treated with nilotinib.

Frequency unknown: Cases of facial paralysis have been reported in patients treated with nilotinib.

Paediatric population
The safety of nilotinib in paediatric patients (from 2 to <18 years of age) with Philadelphia chromosome positive CML in chronic phase has been investigated in two studies. In paediatric patients, the frequency, type and severity of adverse reactions observed have been generally consistent with those observed in adults, with the exception of the laboratory abnormalities hyperbilirubinaemia and transaminase elevation (AST & ALT) which were reported at a higher frequency than in adult patients. Bilirubin and hepatic transaminase levels should be monitored during treatment.

Growth retardation in paediatric population
In an interim analysis in a study in the CML paediatric population, with a median exposure of 33 months in each cohort (newly diagnosed and resistant or intolerant Ph+ CML-CP), growth retardation (crossing two main percentile lines from baseline) has been documented in 12.1%. Close monitoring of growth in paediatric patients under nilotinib treatment is recommended.

4.9 Overdose

Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of nilotinib hard capsules were ingested in combination with alcohol and other medicinal products. Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomes were reported as recovered.

In the event of overdose, the patient should be observed and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EA03

Mechanism of action
Nilotinib is a potent inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells. The substance binds with high affinity to the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukaemia cells from CML patients. In murine models of CML, as a single agent nilotinib reduces tumour burden and prolongs survival following oral administration.

Pharmacodynamic effects
Nilotinib has little or no effect against the majority of other protein kinases examined, including Src, except for the PDGF, KIT and Ephrin receptor kinases, which it inhibits at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML.

Table 6: Kinase profile of nilotinib (phosphorylation IC_{50} nM)

BCR-ABL	PDGFR	KIT
20	69	210

5.2 Pharmacokinetic Properties

Absorption
Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30%. The absolute bioavailability of nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%. In healthy volunteers, C_{max} and area under the serum concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively, compared to fasting conditions when nilotinib is given with food. Administration of nilotinib 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively.

Nilotinib absorption (relative bioavailability) might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

Distribution
The blood-to-plasma ratio of nilotinib is 0.71. Plasma protein binding is approximately 98% on the basis of in vitro experiments.

Biotransformation
Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of nilotinib. Nilotinib is primarily metabolised by CYP3A4, with possible minor contribution from CYP2C8.

Elimination
After a single dose of radiolabelled nilotinib in healthy subjects, more than 90% of the dose was eliminated within 7 days, mainly in faeces (94% of the dose). Unchanged nilotinib accounted for 69% of the dose.

The apparent elimination half-life estimated from the multiple-dose pharmacokinetics with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib pharmacokinetics was moderate to high.

Linearity/non-linearity
Steady-state nilotinib exposure was dose-dependent, with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once-daily dosing. Daily systemic exposure to nilotinib with 400 mg twice-daily dosing at steady state was 35% higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg twice daily was approximately 13.4% higher than at a dose level of 300 mg twice daily. The average nilotinib trough and peak concentrations over 12 months were approximately 15.7% and 14.8% higher following 400 mg twice-daily dosing compared to 300 mg twice daily. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice daily to 600 mg twice daily.

Steady-state conditions were essentially achieved by day 8. An increase in serum exposure to

nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice-daily dosing.

Bioavailability/bioequivalence studies
Single-dose administration of 400 mg nilotinib, using 2 hard capsules of 200 mg whereby the content of each hard capsule was dispersed in one teaspoon of apple sauce, was shown to be bioequivalent with a single-dose administration of 2 intact hard capsules of 200 mg.

Paediatric population
Following administration of nilotinib in paediatric patients at 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg), steady-state exposure and clearance of nilotinib were found to be similar (within 2-fold) to adult patients treated with 400 mg twice daily. The pharmacokinetic exposure of nilotinib following a single or multiple doses appeared to be comparable between paediatric patients from 2 years to <10 years and from ≥10 years to <18 years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule

Content:

Anhydrous Lactose, Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Poloxamer

Shell:

Hydroxypropylmethylcellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Please refer to the expiry date on the product labels.

6.4 Special Precautions for Storage

Store below 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and Content of Container

Nilogen 50mg Capsules: Transparent PVC/Alu blisters sealed in triple laminated aluminium pouch containing two molecular sieve sachets (2gm each) and packed in the outer carton [1 pouch (2x20's), 3 pouches (6x20's)]. Not all pack sizes will be marketed.

Nilogen 150mg Capsules: Transparent PVC/Alu blisters sealed in triple laminated aluminium pouch containing two molecular sieve sachets (2gm each) and packed in the outer carton [1 pouch (2x14's), 4 pouches (8x14's)]. Not all pack sizes will be marketed.

Nilogen 200mg Capsules: Transparent PVC/Alu blisters sealed in triple laminated aluminium pouch containing two molecular sieve sachets (2gm each) and packed in the outer carton [1 pouch (2x14's), 4 pouches (8x14's)]. Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MANUFACTURER

Manufactured by:
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8 DATE OF REVISION

10/09/2024

Package insert is drafted in Times New Roman with font size of 11, subject to change based on any other legible font and font size.