APPROVED PROFESSIONAL INFORMATION
DR. REDDY'S LABORATORIES (PTY) LTD
NILOTINIB 150 DRL & NILOTINIB 200 DRL
(nilotinib)
Capsules

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

NILOTINIB 150 DRL, capsule

NILOTINIB 200 DRL, capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NILOTINIB 150 DRL: Each capsule contains nilotinib hydrochloride monohydrate equivalent to 150 mg nilotinib base.

Contains sugar: 116,87 mg of lactose

NILOTINIB 200 DRL: Each capsule contains nilotinib hydrochloride monohydrate equivalent to 200 mg nilotinib base.

Contains sugar: 155,83 mg of lactose

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

NILOTINIB 150 DRL: White to pale yellow coloured granular powder filled in capsule shell with red opaque coloured cap and body imprinted with RDY on cap and 150 on body in black ink. Free from physical defects.

NILOTINIB 200 DRL: White to pale yellow coloured granular powder filled in capsule shell with light yellow opaque coloured cap and body imprinted with RDY on cap and 200 on body in black ink. Free from physical defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in chronic phase. Patients who have been treated with NILOTINIB DRL for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation (see sections 4.4 and 5.1).

Treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in adult patients resistant to or intolerant to 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 DRL for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation (see sections 4.4 and 5.1).

The term "sustained deep molecular response", is defined by the following criteria (see section 5.1 Pharmacodynamic properties: Clinical efficacy and safety).

For patients with newly diagnosed Ph+ CML - CP:

- the 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR – ABL / ABL ≤ 0,01 % IS), and maintained for one year
- the last assessment being MR4.5 (BCR – ABL / ABL ≤ 0,0032 % IS)
- no more than two assessments falling between MR4 and MR4.5 (0,0032 % IS < BCR – ABL / ABL ≤ 0,01 % IS).

For Ph+ CML - CP patients with at least one prior therapy including imatinib:

The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR – ABL / ABL ≤ 0,0032 % IS) during 1 year.

4.2 Posology and method of administration

Therapy should be initiated by a medical practitioner experienced in the treatment of patients with CML.

Posology

Dosing in patients with newly diagnosed Ph+ CML - chronic phase:

The recommended dose of NILOTINIB DRL is 300 mg twice daily. Treatment should be continued as long as the patient continues to benefit.

Dosing in patients with Ph+ CML - chronic phase and CML - accelerated phase resistant to or intolerant to at least one prior therapy including imatinib:

The recommended dose of NILOTINIB DRL is 400 mg twice daily. Treatment should be continued as long as the patient continues to benefit.

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

Discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with NILOTINIB DRL 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 DRL therapy should be initiated by a medical practitioner experienced in the treatment of patients with CML (see sections 4.4 and 5.1).

Eligible patients who discontinue NILOTINIB DRL 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 DRL 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 DRL therapy should have their BCR - ABL transcript levels monitored monthly until MMR is re-established and every 12 weeks thereafter (see section 4.4).

Monitoring recommendations and dose adjustments or modifications:

Increases in total serum cholesterol levels have been reported with nilotinib as in NILOTINIB DRL therapy (see section 4.4).

Lipid profiles should be determined prior to initiating NILOTINIB DRL 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 commonly with NILOTINIB DRL therapy (see section 4.4). Blood glucose levels should be assessed prior to initiating NILOTINIB DRL therapy and monitored during treatment (see section 4.4).

Due to possible occurrence of Tumor Lysis Syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with NILOTINIB DRL (see section 4.8), and medical practitioners should consider prescribing concomitant uric acid lowering medicines on an individual patient basis.

NILOTINIB DRL may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukaemia (see Table 1).

Table 1 Dose Adjustments for Neutropenia and Thrombocytopenia

• Newly diagnosed CML in chronic phase at 300 mg twice daily • Resistant or intolerant CML chronic phase at 400 mg twice daily	ANC* < 1 x 10^9/L and/or platelet counts < 50 x 10^9/L	1.Stop NILOTINIB DRL, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC 1 x 10^9/L and/or platelet counts < 50 x 10^9/L 3. If blood counts remain low a dose reduction to 400 mg once daily may be required.
• Resistant or intolerant CML in accelerated phase at 400 mg twice daily	(ANC) < 0,5 x 10^9/L or platelet counts < 10 x 10^9/L	1. Stop NILOTINIB DRL and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC > 1 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.

*ANC = absolute neutrophil count

If clinically significant moderate or severe non-haematologic toxicity develops, dosing should be interrupted, and may be

resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 300 mg (newly diagnosed Ph+ CML - CP) or 400 mg (resistant or intolerant Ph+ CML - chronic phase and CML - accelerated phase) twice daily should be attempted.

Asymptomatic serum lipase elevations were observed and also elevations associated with clinical symptoms such abdominal pain or a diagnosis of pancreatitis. Elevations in serum lipase did not lead to treatment discontinuation in any patient in clinical studies.

Overall, this finding was clinically manageable in the majority of patients without requirement for dose reduction or interruption. For Grade 3 to 4 lipase elevations, doses were reduced to 400 mg once daily (see section 4.8).

In clinical studies, the majority of bilirubin and hepatic transaminase laboratory abnormalities in patients were of low-grade toxicity which did not require dose interruption or reduction.

Treatment discontinuation due to elevated serum bilirubin occurred in only 1 patient (0,3 %).

For Grade 3 to 4 bilirubin or hepatic transaminase elevations, doses were reduced to 400 mg once daily (see section 4.8).

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

Special Populations

Elderly patients:

Approximately 12 % and 30 % of subjects in clinical studies (newly diagnosed Ph+ CML - CP and resistant or intolerant Ph+ CML - Chronic Phase and CML - Accelerated Phase) were 65 or over.

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

Patients with renal impairment:

Clinical studies have not been performed in patients with impaired renal function. Clinical studies excluded patients with serum creatinine concentration > 1,5 times the upper limit of the normal range. Since nilotinib and its metabolites are not

renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment. Total body clearance is not anticipated in patients with renal impairment.

Patients with hepatic impairment:

NILOTINIB DRL has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and/or 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.

Cases of hepatic failure including fatal outcome have occurred in patients treated with NILOTINIB DRL (see section 4.8).

Cardiac disorders:

In clinical studies, patients were excluded with clinically significant cardiac syndromes (e.g., complete left bundle branch block, unstable angina, uncontrolled congestive heart failure, or recent myocardial infarction).

Paediatric population

Safety and efficacy in children and adolescents below the age of 18 has not been established.

NILOTINIB DRL should not be used in these categories of patients.

Method of administration

NILOTINIB DRL should be taken twice daily approximately 12 hours apart and should not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken (see section 4.4, 4.5 and 5.2).

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and be taken immediately.

Not more than one teaspoon of applesauce and no food other than applesauce must be

used. (See sections 4.5 and 5.2)

4.3 Contraindications

- Hypersensitivity to the active substance (nilotinib) or to any of the excipients listed in section 6.1.
- Safety in pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

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. Correct hypokalaemia or hypomagnesaemia prior to administration and monitor periodically. Avoid concomitant therapy with medicines known to prolong the QT interval and strong CYP3A4 inhibitors. Use caution in patients with hepatic impairment. Obtain ECGs at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

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

- with congenital long QT syndrome
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia
- taking anti-dysrhythmic medicines or other medicines that may 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.

Sudden deaths:

There were sudden deaths reported in the safety population and the expanded access program, post-marketing and the

expanded access program and post-marketing. Co-morbidities in addition to the underlying malignancy were also frequently present as were concomitant medicines. Ventricular repolarisation abnormalities may have contributed to their occurrence.

Cardiovascular events:

Cardiovascular events were reported in a randomised, Phase III nilotinib trial in newly diagnosed CML patients and observed in the post-marketing reports. With a median time on therapy of 60,5 months in the clinical trial, cardiovascular events included occurred in 7,5 % of patients at 300 mg and 13,4 % at 400 mg twice a day in particular ischaemic heart disease events occurred in 3,9 % and 8,7 % respectively; peripheral arterial occlusive disease resulted occurred in 2,5 % of patients at both 300 mg and 400 mg twice a day and resulted in withdrawal in 0,4 % and 1,1 % of patients at 300 mg and 400 mg twice a day, respectively.

NILOTINIB DRL should not be used as first line therapy in patients with prior severe peripheral arterial occlusive disease (PAOD), including angina pectoris. In patients with mild to moderate pre-existing PAOD, nilotinib may be prescribed with caution. If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. The cardiovascular status of patients should be evaluated, and cardiovascular risk factors should be monitored and actively managed prior to initiating and during NILOTINIB DRL therapy according to standard guidelines (please refer to section 4.2).

Fluid retention and oedema:

Severe fluid retention manifestations occurred in 8 % of patients treated with nilotinib. These cases included patients developing pleural effusion, pericardial effusion, including cardiac tamponade (0,1 to 1 %). Unexpected, rapid weight gain should be carefully investigated.

If signs of severe fluid retention appear during treatment with NILOTINIB DRL, the aetiology should be evaluated and patients treated accordingly (please refer to dosage and directions for use and side effects).

Hepatitis B reactivation:

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR - ABL tyrosine kinase inhibitor (TKI), such as NILOTINIB DRL. Some cases involving medicines of the BCR - ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or death.

Patients should be tested for hepatitis B infection before initiating treatment with NILOTINIB DRL. Patients currently on NILOTINIB DRL should have baseline testing for hepatitis B infection in order to identify chronic carriers of the virus. 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 hepatitis B infection during treatment. Carriers of hepatitis B virus who require treatment with NILOTINIB DRL should be frequently monitored for signs and symptoms of active hepatitis B 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 DRL.

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 (see sections 4.2 and 5.1).

Loss of major molecular response (MMR = BCR – ABL / ABL ≤ 0,1 % IS) 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)) 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 (see section 4.2). For patients who fail to achieve MMR after three months of treatment re initiation, BCR - ABL kinase domain mutation testing should be performed.

Myelosuppression:

Treatment with nilotinib is associated with (National Cancer Institute Common Toxicity Criteria (NCI CTC) Grade 3 – 4) thrombocytopenia, neutropenia and anaemia. The occurrence is more frequent in patients with imatinib-resistant or intolerant CML and, in particular in patients with Chronic Myelogenous Leukaemia-Accelerated Phase (CML-AP). 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 DRL temporarily or reducing the dose (see section 4.2).

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, doses should be interrupted, and appropriate diagnostics should be considered in order to exclude pancreatitis.

Liver function abnormality:

Nilotinib may result in elevations in bilirubin, AST / ALT, and alkaline phosphatase. Check hepatic function tests

periodically.

Electrolyte abnormalities:

Nilotinib can cause hypophosphataemia, hypokalaemia, hyperkalaemia, hypocalcaemia, and hyponatraemia. Correct electrolyte abnormalities prior to initiating NILOTINIB DRL and monitor periodically during therapy.

Hepatic impairment:

Nilotinib has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and or AST > 2,5 (or > 5, if related to disease) times the upper limit of normal range and/or total bilirubin > 1,5 times the upper limit of the normal range.

Metabolism of nilotinib is mainly hepatic. Caution is recommended in patients with hepatic impairment (see section 4.2). Caution is recommended in these patients and QT interval should be monitored closely.

Interactions:

Avoid concomitant use of strong inhibitors or inducers of CYP3A4. If patients must be co-administered a strong CYP3A4 inhibitor, dose reduction should be considered and the QT interval should be monitored closely.

Total gastrectomy:

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

Tumour lysis syndrome:

Cases of tumour lysis syndrome have been reported in patients treated with nilotinib. For monitoring recommendations please refer to section 4.2.

Food effect:

The bioavailability of nilotinib is increased by food. NILOTINIB DRL should not be taken in conjunction with food (see section 4.2 and 4.6) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken.

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and should be taken immediately.

Not more than one teaspoon of applesauce and no food other than applesauce must be used.

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

Class effects:

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in NILOTINIB DRL.

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events (e.g., cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction).

These cerebrovascular adverse events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

Patients on treatment with NILOTINIB DRL should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with NILOTINIB DRL should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

Laboratory tests and monitoring:

Blood lipids

In a Phase III study in newly diagnosed CML patients 27,6 % on 300 mg nilotinib twice daily and 26,7 % on 400 mg nilotinib twice daily developed total cholesterol abnormalities or had worsening of total cholesterol abnormalities and 1,1

% had grade 3 / 4 elevations in serum cholesterol. It is recommended that the lipid profiles be determined before initiating treatment with NILOTINIB DRL, assessed at month 3 and 6 after initiating therapy, and at least once yearly during chronic therapy (see section 4.2). If a HMG CoA reductase inhibitor, (a lipid lowering agents) is needed, please refer to Interactions (Interaction with other medicinal products and other forms of interaction) before starting treatment since certain HMG CoA reductase inhibitors are also metabolised by the CYP3A4 pathway.

Blood glucose

In a Phase III study in newly diagnosed CML patients, 6,9 % of the patients treated with 400 mg nilotinib twice a day had a Grade ¾ elevation in blood glucose; and 7,2 % of the patients treated with 300 mg nilotinib twice a day had a Grade 3 / 4 elevation in blood glucose.

It is recommended that the glucose levels should be assessed before initiating treatment with NILOTINIB DRL and monitored during treatment as clinically indicated (please refer to section 4.2). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Excipients:

Lactose

Since the capsules contain lactose, NILOTINIB DRL is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or of, glucose-galactose malabsorption or galactosaemia.

4.5 Interaction with other medicines and other forms of interaction

NILOTINIB DRL 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-medicine efflux pump, P-glycoprotein (Pgp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by medicines that affect CYP3A4 and/or

Pgp.

Medicines 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 bioavailability of nilotinib in healthy subjects was increased by 3-fold when co administered with the strong CYP3A4 inhibitor ketoconazole. Concurrent treatment with strong CYP3A4 inhibitors, including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin and telithromycin) should therefore be avoided (see section 4.4).

Increased exposure to nilotinib might also be expected with moderate CYP3A4 inhibitors.

Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

Medicines that may decrease nilotinib serum concentrations:

Rifampicin, a potent CYP3A4 inducer, decreases nilotinib Cmax by 64 % and reduces nilotinib AUC by 80%.

The concomitant administration of medications that induce CYP3A4 (e.g., phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered.

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 Cmax and 34 % decrease in AUC0 - ∞). NILOTINIB DRL 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 DRL.

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 DRL 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 DRL.

Medicines that may have their systemic concentration altered by nilotinib:

Nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6 in vitro, with Ki value being lowest for CYP2C9 (Ki = 0,13 microM). Enzyme induction studies indicate that nilotinib can be considered to be an in vitro inducer of CYP2B6, CYP2C8 and CYP2C9 activities.

In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure of oral midazolam (a substrate of CYP3A4) 2.6 - fold. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other medicines primarily metabolised by CYP3A4 (e.g., certain HMG - CoA reductase inhibitors) may be increased when co-administered with NILATRED. Appropriate monitoring and dose adjustment may be necessary for medicines that are CYP3A4 substrates and have a narrow therapeutic index (including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with NILOTINIB DRL.

In healthy subjects, nilotinib at clinically relevant concentrations was not found to alter the pharmacokinetics or pharmacodynamics of warfarin, a sensitive CYP2C9 substrate.

NILOTINIB DRL can be used concurrently with warfarin without increasing the anticoagulant effect.

Concomitant treatment with cholesterol lowering agents (e.g., statins), which are metabolised via the CYP3A4 pathway, should be administered with caution since systemic exposure may increase (see section 4.4) and may increase the potential for statin-induced myopathy, including rhabdomyolysis.

Antidysrhythmic medicines and other medicines that may prolong QT:

NILOTINIB DRL should be used with caution in patients who have or may develop prolongation of QT including those patients taking anti-dysrhythmic medicines such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicines that may lead to QT disopyramide, procainamide, quinidine and sotalol or other medicines that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, moxifloxacin and methadone. (See

section 4.4)

Food interactions:

The absorption and bioavailability of nilotinib are increased if it is taken with food, resulting in a higher serum concentration (see sections 4.2, 4.4 and 5.2). 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

NILOTINIB DRL should not be used during pregnancy as safety and efficacy in pregnancy and lactation has not been established.

Women of childbearing potential/Contraception

Women of childbearing potential must be advised to use highly effective contraception (methods that result in less than 1 % pregnancy rates) while receiving NILOTINIB DRL and up to 2 weeks after ending treatment.

Sexually active males taking NILOTINIB DRL should also use highly effective contraception NILOTINIB DRL remains in semen for up to 2 weeks after ending treatment.

Pregnancy

NILOTINIB DRL can cause foetal harm when administered to a pregnant woman.

Reproductive studies in rats and rabbits have demonstrated that nilotinib induced embryo-toxicity and/or feto-toxicity (following prenatal exposure to nilotinib) at exposures equal to the one achieved in humans at the maximum recommended human dose of 400 mg twice daily.

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 as described in sections 4.2 and 4.4. 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 treatment with NILOTINIB DRL during

pregnancy (see sections 4.2 and 4.4).

Breastfeeding

Studies in animals demonstrate that nilotinib is excreted into breast milk.

The effects of low-dose exposure of the infant to nilotinib are unknown, Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is contraindicated during treatment and for at least 15 days after stopping treatment with NILOTINIB DRL.

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 DRL 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 safely drive or use machines should refrain from these activities as long as these undesirable effects persist. (See section 4.8).

4.8 Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Frequent	Less frequent	Unknown frequency
Infections and infestations	folliculitis, pneumonia, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis).	bronchitis, urinary tract infection, herpes virus infection, candidiasis (including oral candidiasis), gastroenteritis.	sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation.
Neoplasms Benign, Malignant and Unspecified	skin papilloma		oral papilloma, paraproteinaemia

Blood and lymphatic system disorders	leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia.		thrombocythaemia, leucocytosis
Immune system disorders			hypersensitivity.
Endocrine disorders		hyperthyroidism, hypothyroidism.	thyroiditis, secondary hyperparathyroidism
Metabolism and nutrition disorders	electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypophosphataemia, hypercalcaemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridemia, decreased appetite.	gout, dehydration, increased appetite, dyslipidaemia.	hyperuricaemia, hypoglycaemia.
Psychiatric disorders	depression, insomnia, anxiety.		confusional state, disorientation, amnesia, dysphoria.
Nervous system disorders	dizziness, peripheral neuropathy, paraesthesia, hypoaesthesia.	intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction loss of consciousness (including syncope),	cerebrovascular accident, basilar artery stenosis, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome.

		migraine, tremor, disturbance in attention, hyperaesthesia.	
Eye disorders	eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia).	vision impairment, blurred vision, visual acuity reduced, eye irritation, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), conjunctival haemorrhage.	papilloedema, diplopia, eye swelling, photophobia, blepharitis, eye pain, chorioretinopathy, allergic conjunctivitis.
Ear and labyrinth disorders	vertigo.		hearing impaired, ear pain, tinnitus.
Cardiac disorders	angina pectoris, dysrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, bradycardia), palpitations, electrocardiogram QT prolonged, cardiac failure.	myocardial infarction, coronary artery disease, cardiac murmur, pericardial effusion, tamponade, cyanosis.	pericarditis, ventricular dysfunction, ejection fraction decrease.
Vascular disorders	flushing, hypertension, peripheral artery stenosis.	hypertensive crisis, peripheral arterial occlusive disease, haematoma, atherosclerosis, intermittent claudication, arterial stenosis limb.	shock haemorrhagic, hypotension, thrombosis, peripheral artery stenosis.
Respiratory,	dyspnoea, exertional	interstitial lung disease,	pulmonary

thoracic, and mediastinal disorders	dyspnoea, epistaxis, cough, dysphonia.	pleuritic pain, pharyngolaryngeal pain, pleural effusion, pleurisy, pulmonary oedema, throat irritation.	hypertension, wheezing, oropharyngeal pain.
Gastro-intestinal disorders	pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, dysgeusia, flatulence.	gastrointestinal haemorrhage, gastroesophageal reflux, stomatitis, melaena, mouth ulceration, stomatitis, dry mouth, gastritis, oesophageal pain, sensitivity of teeth.	gastric ulcer, gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, ulcerative oesophagitis, sub-ileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, sensitivity of teeth, gingivitis.
Hepatobiliary disorders	hyperbilirubinemia (including blood bilirubin increased), abnormal hepatic function.	hepatotoxicity, toxic hepatitis, jaundice.	cholestasis, hepatomegaly.
Skin and subcutaneous tissue disorders	night sweats, erythema, hyperhidrosis, contusion, acne, dermatitis, (including allergic and acneiform), urticaria.	exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling face.	erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous

			hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis, psoriasis.
Musculoskeletal and connective tissue disorders	musculoskeletal chest pain, musculoskeletal pain, flank pain, muscular weakness.	musculoskeletal stiffness, joint swelling.	arthritis.
Renal and urinary disorders	pollakiuria.	dysuria, micturition urgency, nocturia.	haematuria, urinary incontinence, renal failure, chromaturia.
Reproductive system and breast disorders		breast pain, erectile dysfunction, gynaecomastia.	breast induration, menorrhagia, nipple swelling.
General disorders and administration site conditions	chest pain (including non-cardiac chest pain), pain (including neck pain and back pain), pyrexia, chest discomfort, malaise.	face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold).	localised oedema.
Investigations	increased alanine aminotransferase, increased aspartate aminotransferase, increased lipase, increased cholesterol (including low density and high-density lipoproteins), increased total	increased blood lactate dehydrogenase, increased blood urea.	increased troponin, increased blood bilirubin unconjugated, decreased blood insulin, decreased insulin C-peptide, increased blood parathyroid

	cholesterol, increased blood triglycerides, decreased haemoglobin, increased blood amylase, decreased weight, increased gamma-glutamyltransferase, increased weight, increased blood creatinine phosphokinase, decreased globulins. increased blood alkaline phosphatase, increased blood insulin.		hormone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

For any information about this medicine, please contact the local representative of the Holder of Certificate of Registration: Dr. Reddy's Laboratories (Pty) Ltd. Tel: +27 11 324 2100.

4.9 Overdose

Isolated reports on intentional overdose with nilotinib were reported, where unspecified number of nilotinib capsules were ingested in combination with alcohol and other drugs. 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

Pharmacological classification: A26 Cytostatic agents

Pharmacotherapeutic group: BCR - ABL tyrosine kinase inhibitors, ATC code: L01EA03.

5.1 Pharmacodynamic properties

Mechanism of action

Nilotinib is a potent and selective inhibitor of the ABL tyrosine kinase activity of the BCR - ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells.

Nilotinib 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 forms of BCR - ABL[PM1]. 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.

5.2 Pharmacokinetics properties

Absorption:

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30 %. In healthy volunteers, Cmax 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 (see section 4.2, 4.4 and 4.5).

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

Single dose administration of 400 mg nilotinib, using two capsules of 200 mg whereby the content of each capsule was dispersed in one teaspoon of applesauce, was shown to be bioequivalent with a single dose administration of 2 intact capsules of 200 mg.

Distribution:

Blood-to-plasma ratio of nilotinib is 0,68. 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, greater than 90 % of the dose was eliminated within 7 days mainly in faeces. Parent compound accounted for 69 % of the dose.

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 serum exposure to nilotinib of 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 with 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.

Characteristics in patients:

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Colloidal silicon dioxide;

Crospovidone;

Lactose monohydrate;

Magnesium stearate;

Poloxamer;

Purified water.

Capsule shell:

Ferric oxide, red;

Ferric oxide, yellow;

Gelatin;

Purified water;

S.L.S;

Titanium dioxide.

Printing ink:

Iron oxide, black.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C in the original package.

Protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

NILOTINIB 150 DRL: 28, 30, 112 or 120 capsules in clear PVC/PVdC (polyvinylchloride/polyvinylidene chloride) blisters with an aluminium foil backing.

NILOTINIB 200 DRL: 28, 30, 112 or 120 capsules clear PVC/PVdC (polyvinylchloride/polyvinylidene chloride) blisters with an aluminium foil backing.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements**.**

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBERS

NILOTINIB 150 DRL: 59/26/0508

NILOTINIB 200 DRL: 59/26/0509

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 June 2026

10 DATE OF REVISION OF THE TEXT