SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TILOMIA 150 capsules

TILOMIA 200 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TILOMIA 150: Each capsule contains nilotinib hydrochloride dihydrate equivalent to nilotinib 150 mg.

TILOMIA 200: Each capsule contains nilotinib hydrochloride dihydrate equivalent to nilotinib 200 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

TILOMIA 150: Opaque red cap and opaque red body size '1' hard gelatine capsules imprinted with 'H' on cap and '23' on body, filled with slightly yellow to yellowish granular powder.

TILOMIA 200: Opaque yellow cap and yellow body size '0' hard gelatine capsules imprinted with 'H' on cap and '24' on body, filled with slightly yellow to yellowish granular powder.

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.
- 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.

4.2 Posology and method of administration

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

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

TILOMIA may be given with hydroxyurea or anagrelide if clinically indicated.

Posology

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

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

Dose adjustments or modifications:

TILOMIA 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 below).

Table 1: Dose adjustments for neutropenia and thrombocytopenia

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

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. Few of these elevations were associated with clinical symptoms such as abdominal pain or a diagnosis of pancreatitis. Elevations in serum lipase did not lead to treatment discontinuation in any patient. 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

Children and adolescents:

Clinical studies have not been conducted in children and adolescents. TILOMIA should not be used in these categories of patients.

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 years 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 have excluded patients with serum creatinine concentration > 1,5 times the upper limit of the normalrange. Since nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment.

Patients with hepatic impairment:

TILOMIA 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.

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).

Method of administration

TILOMIA 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 sections 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 should be taken immediately. Not more than oneteaspoon of applesauce and no food other than applesauce must be used (see sections 4.4 and 5.2).

4.3 Contraindications

Known hypersensitivity to nilotinib or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

QT Prolongation: TILOMIA prolongs the QT interval. Correct hypokalaemia or hypomagnesaemia prior to administration and monitor periodically. Avoid 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. Ventricular repolarization abnormalities may have contributed to their occurrence.

Myelosuppression

Treatment with nilotinib is associated with thrombocytopenia, neutropenia and anaemia, (National Cancer Institute Common Toxicity Criteria grade 3 – 4). Occurrence is more frequent in patients with imatinib-resistant or intolerant CML, particularly 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 TILOMIA temporarily or dose reduction (see section 4.2).

QT prolongation

Nilotinib, as in TILOMIA, 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.

Significant prolongation of the QT interval may occur when

TILOMIA is inappropriately taken with strong CYP3A4 inhibitors and/or medicines with a known potential to prolong the QT interval, and/or food (see section 4.5). 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.

TILOMIA 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-dysrhythmic medicines 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 TILOMIA administration and should be monitored periodically during therapy.

Sudden death

Uncommon cases (0,1 to 1 %) 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 medicines. Ventricular repolarisation abnormalities may have been contributory factors. No cases of sudden death were reported in the Phase III 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 (0,1 to 1 %) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports.
Unexpected, rapid increase in body mass should be carefully investigated. If signs of severe fluid retention appear during treatment with TILOMIA, the aetiology should be evaluated, and patients treated accordingly (see section 4.2 for instructions on managing non-haematological toxicities).

Cardiovascular events

Cardiovascular events were reported in a randomised Phase III 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 (1,4 % and 1,1 % at 300 mg and 400 mg nilotinib twice daily, respectively),ischaemic heart disease(2,2 % and 6,1 % at 300 mg and 400 mg nilotinib twice daily, respectively) and ischaemic cerebrovascular events

(1,1 % and 2,2 % at 300 mg and 400 mg nilotinib twice daily, respectively). 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 (see section 4.2 for instructions on managing non-haematological toxicities).

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 (see section 4.8).

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 BCRABL, 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 (see sections 4.2 and 5.1).

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 (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.

Laboratory tests and monitoring

Blood lipids

In a Phase III study in newly diagnosed CML patients, 1,1 % of the 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 (see section 4.8). 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 (see section 4.2). If an 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 Phase III study in newly diagnosed CML patients, 6,9 % and 7,2 % of the 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 TILOMIA and monitored during treatment, as clinically indicated (see section 4.2). If test results warrant therapy, medical practitioners should follow their local standards of practice and treatment guidelines.

Interactions with other medicines

The administration of TILOMIA with medicines 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 medicines be required, it is recommended that TILOMIA 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 (see sections 4.2, 4.5 and 5.2).

Concomitant use of TILOMIA with medicines 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 TILOMIA, co-administration of alternative therapeutic medicines with less potential for CYP3A4 induction should be selected (see section 4.5).

Food effect

The bioavailability of nilotinib, as in TILOMIA, is increased by food. TILOMIA must not be taken in conjunction with food (see sections 4.2 and 4.5) 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 (see section 5.2).

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 (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,

TILOMIA 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 (see section 5.2). 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 TILOMIA therapy (see section 4.8).

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 (see section 4.8). 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 (see section 4.2). The long-term effects of prolonged treatment with nilotinib in children and adolescents are unknown.

4.5 Interaction with other medicines and other forms of interaction

TILOMIA 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 (see section 4.4). Increased exposure to nilotinib might also be expected with moderate CYP3A4 inhibitors. Alternative concomitant

medicines 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 medicines 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 medicines 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.

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).

Anti-dysrhythmic medicines 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 antidysrhythmic medicines such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicines that may

lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, methadone and moxifloxacin (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

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. Animal studies have shown reproductive toxicity. TILOMIA 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 fetus.

If a woman who is being treated with TILOMIA 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 nilotinib treatment during pregnancy (see sections 4.2 and 4.4).

Breastfeeding

It is unknown whether nilotinib is excreted in human milk. Available toxicological data in animals have shown excretion of nilotinib in milk (see section 5.3). Since a risk to the newborns/infants cannot be excluded, women should not breastfeed during TILOMIA treatment and for 2 weeks after the last dose.

Fertility

Animal studies did not show an effect on fertility in male and female rats (see section 5.3).

Sexually active male or female patients taking TILOMIA should use adequate contraception.

4.7 Effects on ability to drive and use machines

TILOMIA has no or negligible influence on the ability to drive a vehicle 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 a vehicle or use machines safely should refrain from these activities as long as the undesirable effects persist (see section 4.8).

4.8 Undesirable effects

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 (≥ 10 %) 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 frequently (< 10 % and ≥ 5 %) were of mild to moderate severity, manageable and generally did not require dose reduction.

Treatment-emergent haematological toxicities include myelosuppression: thrombocytopenia (18 %), neutropenia (15 %) and anaemia (8 %). Biochemical adverse drug reactions include increased alanine aminotransferase (24 %), hyperbilirubinaemia (16 %), increased aspartate aminotransferase (12 %), increased lipase (11 %), increased blood bilirubin (10 %), hyperglycaemia (4 %), hypercholesterolaemia (3 %) and hypertriglyceridaemia (< 1 %). Pleural and pericardial effusions, regardless of causality, occurred in 2 % and < 1% of patients, respectively, receiving nilotinib 300 mg twice daily.

Gastrointestinal haemorrhage, regardless of causality, was reported in 3 % of these 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 medicine. QTcF increase from baseline exceeding 60 msec was observed in < 1 % of patients while on the study medicine.

No sudden deaths or episodes of torsades 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 (≥ 10 %) 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 frequently (< 10 % and ≥ 5 %) and have been of mild to moderate severity (Grade 1 or 2).

Discontinuation due to adverse drug reactions was observed in 16 % of chronic phase and 10 % of accelerated phase patients.

Treatment-emergent haematological toxicities include myelosuppression: thrombocytopenia (31 %), neutropenia (17 %) and anaemia (14 %). Pleural and pericardial effusions as well as complications of fluid retention occurred in < 1 % of patients receiving TILOMIA.

Cardiac failure was observed in < 1 % of patients. Gastrointestinal and CNS haemorrhage were reported in 1 % and < 1 % of patients, respectively.QTcF exceeding 500 msec was observed in < 1 % of patients. No episodes of torsades de pointes (transient or sustained) were observed.

Table 2: Non-haematological adverse reactions (≥ 5 % of all patients)*

	Newly diagnosed CML-CP 300 mg twice daily n = 279		**Imatinib-resistant or intolerant CML-CP and CML-AP 400 mg twice daily n = 458**			
	60-month analysis		**24-month analysis**			
System organ class/ Adverse reaction	**All grades**	**Grade 3 – 4**	**All grades**	**Grade 3 – 4**	**CML-CP n = 321 Grade 3 – 4**	**CML-AP n = 137 Grade 3 – 4**
	%	**%**	**%**	**%**	**%**	**%**
Metabolism and nutrition disorders						
Frequent:						
Decreased appetite **	4	0	8	< 1	< 1	0
Nervous system disorders						
Frequent:						

Headache	16	2	15	1	2	< 1
Gastrointestinal disorders						
Frequent:						
Nausea	14	< 1	20	< 1	< 1	< 1
Constipation	10	0	12	< 1	< 1	0
Diarrhoea	9	< 1	11	2	2	< 1
Vomiting	6	0	10	< 1	< 1	0
Upper abdominal pain	10	1	5	< 1	< 1	0
Abdominal pain	6	0	6	< 1	< 1	< 1
Dyspepsia	5	0	3	0	0	0
Skin and subcutaneous tissue disorders						
Frequent:						
Rash	33	< 1	28	1	2	0
Pruritus	18	< 1	24	< 1	< 1	0
Alopecia	10	0	9	0	0	0
Dry skin	10	0	5	0	0	0
Erythema	3	0	5	< 1	< 1	0
Musculoskeletal and connective tissue disorders						
Frequent:						
Myalgia	10	< 1	10	< 1	< 1	< 1
Muscle spasms	9	0	8	< 1	< 1	0
Arthralgia	8	< 1	7	< 1	1	0
Bone pain	4	0	6	< 1	< 1	0
Pain in extremity	5	< 1	5	< 1	< 1	< 1
General disorders and administration site conditions						
Frequent:						
Fatigue	12	0	17	1	1	< 1
Asthenia	9	< 1	6	0	0	0
Oedema peripheral	5	< 1	6	0	0	0

* Percentages are rounded to integer for presentation in this table. However, percentages with one decimal precision are used to identify terms with a frequency of at least 5 % and to classify terms according to frequency categories.

**Also includes preferred term anorexia.

Table 3: Adverse reactions in adult patients

Infections and infestations	
Frequent:	folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis)
Less frequent:	pneumonia, urinary tract infection, gastroenteritis, bronchitis, herpes virus infection, candidiasis (including oral candidiasis)
Frequency unknown:	sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Frequent:	skin papilloma
Frequency unknown:	oral papilloma, paraproteinaemia
Blood and lymphatic system disorders	
Frequent:	leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia
Less frequent:	thrombocythaemia, leukocytosis
Immune system disorders	
Frequency unknown:	hypersensitivity
Endocrine disorders	
Less frequent:	hyperthyroidism, hypothyroidism
Frequency unknown:	hyperparathyroidism secondary, thyroiditis
Metabolism and nutrition disorders	
Frequent:	hypophosphataemia (including blood phosphorus decreased), electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia
Less frequent:	dehydration, increased appetite, gout, dyslipidaemia
Frequency unknown:	hyperuricaemia, hypoglycaemia

Psychiatric disorders	
Frequent:	depression, insomnia, anxiety
Frequency unknown:	disorientation, confusional state, amnesia, dysphoria
Nervous system disorders	
Frequent:	dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia
Less frequent:	intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia
Frequency unknown:	cerebrovascular incident, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome
Eye disorders	
Frequent:	eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia)
Less frequent:	visual impairment, blurred vision, conjunctival haemorrhage, reduced visual acuity, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation
Frequency unknown:	papilloedema, chorioretinopathy, diplopia, photophobia, eye swelling, blepharitis, eye pain, allergic conjunctivitis, ocular surface disease
Ear and labyrinth disorders	
Frequent:	vertigo
Frequency unknown:	impaired hearing, ear pain, tinnitus
Cardiac disorders	
Frequent:	angina pectoris, dysrhythmia (including atroventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation,

	bradycardia), palpitations, prolonged electrocardiogram QT
Less frequent:	cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, pericardial effusion, cyanosis
Frequency unknown:	ventricular dysfunction, pericarditis, decreased ejection fraction
Vascular disorders	
Frequent:	hypertension, flushing, peripheral artery stenosis
Less frequent:	hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis
Frequency unknown:	haemorrhagic shock, hypotension, thrombosis
Respiratory, thoracic and mediastinal disorders	
Frequent:	dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia
Less frequent:	pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation
Frequency unknown:	pulmonary hypertension, wheezing, oropharyngeal pain
Gastrointestinal disorders	
Frequent:	pancreatitis, abdominal discomfort, abdominal distension, dysgeusia, flatulence
Less frequent:	gastrointestinal haemorrhage, melaena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth
Frequency unknown:	gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis
Hepatobiliary disorders	

Frequent:	hyperbilirubinaemia (including blood bilirubin increased), hepatic function abnormal
Less frequent:	hepatotoxicity, toxic hepatitis, jaundice
Frequency unknown:	cholestasis, hepatomegaly
Skin and subcutaneous tissue disorders	
Frequent:	night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis (including allergic, exfoliative and acneiform)
Less frequent:	exfoliative rash, drug eruption, skin pain, ecchymosis, swelling of the face
Frequency unknown:	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	
Frequent:	musculoskeletal chest pain, musculoskeletal pain, back pain, flank pain, neck pain, muscular weakness
Less frequent:	musculoskeletal stiffness, joint swelling
Frequency unknown:	arthritis
Renal and urinary disorders	
Frequent:	pollakiuria
Less frequent:	dysuria, micturition urgency, nocturia
Frequency unknown:	renal failure, haematuria, urinary incontinence, chromaturia
Reproductive system and breast disorders	
Less frequent:	breast pain, gynaecomastia, erectile dysfunction
Frequency unknown:	breast induration, menorrhagia, nipple swelling
General disorders and administration site conditions	

Frequent:	chest pain (including non-cardiac chest pain), pain, pyrexia, chest discomfort, malaise
Less frequent:	face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold)
Frequency unknown:	localised oedema
Investigations	
Frequent:	increased alanine aminotransferase, increased aspartate aminotransferase, increased lipase, increased lipoprotein cholesterol (including low density and high density), increased total cholesterol, increased blood triglycerides, decreased haemoglobin, increased blood amylase, increased blood alkaline phosphatase, increased gamma-glutamyltransferase, increased blood creatinine phosphokinase, decreased or increased body mass, increased blood insulin, decreased globulins
Less frequent:	increased blood lactate dehydrogenase, decreased blood glucose, increased blood urea
Frequency unknown:	increased troponin, increased blood bilirubin unconjugated, decreased blood insulin, decreased insulin C-peptide, increased blood parathyroid hormone

Clinically relevant or severe abnormalities of routine haematological or biochemistry laboratory values in adult patients are presented in Table 4.

Table 4 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**	
	n = 279 (%)	**CML-CP n = 321 (%)**	**CML-AP n = 137 (%)**
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.

Description of selected adverse reactions

Sudden death

Less frequently occurring cases (0,1 to 1 %) of sudden deaths have been reported in 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 (see section 4.4).

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 (see section 4.4).

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.

Less frequent: Cases of tumour lysis syndrome 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 (n = 69) has been investigated in two studies (see section 5.1). 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 (Grade 3/4: 13,0 %) and transaminase elevation (AST Grade 3/4: 1,4 %, ALT Grade 3/4: 8,7 %) which were reported at a higher frequency than in adult patients. Bilirubin and hepatic transaminase levels should be monitored during treatment (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TILOMIA is important. It allows continued monitoring of the benefit/risk balance of TILOMIA. Health care providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

Category and class: A.26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE08

5.1 Pharmacodynamic properties

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. 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 Pharmacokinetic properties

Absorption

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

Nilotinib absorption (relative bioavailability) might 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.

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 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.

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.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Dibasic calcium phosphate dihydrate

Povidone

Colloidal silicon dioxide

Magnesium stearate

Capsule shell

Iron oxide red (E172) (only for TILOMIA 150)

Iron oxide yellow (E172)

Sodium laurilsulfate

Titanium dioxide (E171)

Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

- Store at or below 25 °C. Protect from light and moisture.
- Keep capsules in original container until required for use.

6.5 Nature and contents of container

Round, white opaque HDPE 60 mL container, closed with a child resistant plastic cap with a pulp liner, containing a 2 gram silica gel desiccant.

Pack size: 28 capsules.

Aluminium/aluminium blister strips of cold PVC/aluminium/OPA forming foil and plain aluminium lidding foil, containing 6 or 10 capsules per blister strip.

Pack sizes: 36 (6 blister strips containg 6 capsules) or 60 (6 blister strips containg 10 capsules).

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Jean Park Chambers, 252 Jean Avenue

Building 6, Unit 17 & 18.

Centurion

8. REGISTRATION NUMBER(S)

TILOMIA 150 : 54/26/0274

TILOMIA 200 : 54/26/0275

9. DATE OF FIRST AUTHORISATION

28 APRIL 2021

10. DATE OF REVISION OF THE TEXT

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