Applicant: Teva Pharmaceuticals (Pty) Ltd	Product: DASATINIB TEVA 20, 50 , 70 & 100 - film-coated tablets
Reg No: DASATINIB 20 TEVA: 55/26/0448 DASATINIB 50 TEVA: 55/26/0449 DASATINIB 70 TEVA: 55/26/0450 DASATINIB 100 TEVA: 55/26/0451	Each film-coated tablet contains dasatinib monohydrate equivalent to 20 mg, 50 mg, 70 mg or 100 mg dasatinib.

PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

1. NAME OF MEDICINE:

DASATINIB 20 TEVA (film-coated tablets)

DASATINIB 50 TEVA (film-coated tablets)

DASATINIB 70 TEVA (film-coated tablets)

DASATINIB 100 TEVA (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

DASATINIB 20 TEVA: Each film-coated tablet contains dasatinib monohydrate, equivalent to dasatinib 20 mg.

Contains sugar (lactose monohydrate 26,26 mg).

DASATINIB 50 TEVA: Each film-coated tablet contains dasatinib monohydrate, equivalent to dasatinib 50 mg.

Contains sugar (lactose monohydrate 65,65 mg).

DASATINIB 70 TEVA Each film-coated tablet contains dasatinib monohydrate, equivalent to dasatinib 70 mg.

Contains sugar (lactose monohydrate 91,92 mg).

DASATINIB 100 TEVA: Each film-coated tablet contains dasatinib monohydrate, equivalent to dasatinib 100 mg.

Contains sugar (lactose monohydrate 131,31 mg).

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Film-coated tablets.

DASATINIB 20 TEVA film-coated tablets are round, white to off-white with bevelled edges and debossed '20' on one side of the tablet.

DASATINIB 50 TEVA film-coated tablets are oval, white to off-white with bevelled edges and debossed '50' on one side of the tablet.

DASATINIB 70 TEVA film-coated tablets are round, white to off-white with bevelled edges and debossed '70' on one side of the tablet.

DASATINIB 100 TEVA film-coated tablets are oval, white to off-white, with bevelled edges and debossed '100' on one side of the tablet.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

DASATINIB TEVA is indicated for the treatment of adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) in chronic phase.

DASATINIB TEVA is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.
DASATINIB TEVA is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) with resistance or intolerance to prior therapy.

4.2 Posology and method of administration:

Posology:

The recommended starting dosage of DASATINIB TEVA for chronic phase CML is 100 mg once daily, administered orally.

The recommended starting dosage of DASATINIB TEVA for accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL is 70 mg twice daily, administered orally. DASATINIB TEVA can be taken with or without a meal and should be taken consistently in the morning and in the evening.

Dose increase or reduction is recommended based on individual patient response and tolerability.

Dose escalation:

In clinical trials of CML and Ph+ ALL, dose escalation to a total maximum of 70 mg twice daily (chronic phase CML) or 90 mg twice daily (advanced phase CML or Ph+ ALL) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dosage.

Dose adjustment for undesirable effects:

Myelosuppression:

Myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Haematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications are summarised in **TABLE 1**.

TABLE 1: DOSE ADJUSTMENTS FOR NEUTROPENIA AND THROMBOCYTOPENIA:

Chronic Phase CML (starting dose 100 mg once daily)	ANC* < $0,5 \times 10^9$/l or Platelets < 50×10^9/l	1. Stop DASATINIB TEVA until ANC ≥ $1,0 \times 10^9$/l and platelets ≥ 50×10^9/l. 2. Resume treatment with DASATINIB TEVA at the original starting dose. 3. If platelets < 25×10^9/l or recurrence of ANC < $0,5 \times 10^9$/l for > 7 days, repeat Step 1 and resume DASATINIB TEVA at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue DASATINIB TEVA (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated Phase CML, Blast Phase	ANC < $0,5 \times 10^9$/l or	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy).

CML and Ph+ ALL (starting dose 70 mg twice daily)	Platelets < 10×10^9/l	2. If cytopenia is unrelated to leukaemia, stop DASATINIB TEVA until ANC ≥ $1,0 \times 10^9$/l and platelets ≥ 20×10^9/l and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume DASATINIB TEVA at a reduced dose of 50 mg twice daily (second episode) or 40 mg twice daily (third episode). 4. If cytopenia is related to leukaemia, consider dose escalation to 100 mg once daily.

Non-haematological adverse reactions:

If a severe non-haematological adverse reaction develops with DASATINIB TEVA use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event (see **section 4.4**).

Renal impairment:

(See section 5.2 - Special populations).

Hepatic impairment:

Cases of hepatic failure including fatal outcome have occurred in patients treated with DASATINIB TEVA (see **sections 4.8** and **5.2**).

Elderly:

No clinically relevant age-related pharmacokinetic differences have been observed. No specific dose recommendation is necessary in the elderly.

Paediatric patients:

The safety and efficacy of DASATINIB TEVA in patients < 18 years of age have not been established.

Method of administration:

DASATINIB TEVA can be taken with or without a meal and should be taken consistently either in the morning or in the evening.

Tablets should not be crushed or cut; they should be swallowed whole.

4.3 Contraindications:

DASATINIB TEVA is contraindicated in patients with hypersensitivity to dasatinib or to any other component of DASATINIB TEVA listed in **section 6.1**.

The concomitant use of H_2 antagonists or proton pump inhibitors with DASATINIB TEVA is not recommended.

4.4 Special warnings and precautions for use:

Clinically relevant interactions:

Dasatinib is a substrate and an inhibitor of cytochrome P450 (CYP) 3A4. Therefore, there is a potential for interaction with other concomitantly administered medicines that are metabolised primarily by or modulate the activity of CYP3A4 (see **section 4.5**).

Concomitant use of DASATINIB TEVA and medicinal products that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving DASATINIB TEVA, co-administration of a potent CYP3A4 inhibitor is not recommended (see **section 4.5**).

Concomitant use of DASATINIB TEVA and medicines that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John's Wort) may substantially reduce exposure to dasatinib, potentially increasing the risk of therapeutic failure. Therefore, in patients receiving DASATINIB TEVA, co-administration of alternative medicines with less

potential for CYP3A4 induction should be selected (see **section 4.5**).

Concomitant use of DASATINIB TEVA and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when DASATINIB TEVA is co-administered with CYP3A4 substrates of narrow therapeutic index, such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) (see **section 4.5**).

The concomitant use of DASATINIB TEVA and a histamine-2 (H_2) antagonist (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminium hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H_2 antagonists and proton pump inhibitors are not recommended, and aluminium hydroxide/magnesium hydroxide products should be administered up to 2 hours prior to, or 2 hours following the administration of DASATINIB TEVA (see **sections 4.3** and **4.5**).

Special populations:

Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose (see **section 5.2**). Due to the limitations of this clinical study, caution is recommended when administering DASATINIB TEVA to patients with hepatic impairment.

Important adverse reactions:

Myelosuppression:

Treatment with DASATINIB TEVA is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. In adult patients with advanced phase CML or Ph+ ALL treated with DASATINIB TEVA as monotherapy, complete blood counts (CBCs) should be performed weekly for the first 2 months, and then monthly thereafter, or as clinically indicated. In adult and paediatric patients with chronic phase CML, complete blood counts should be performed every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated. In paediatric patients with Ph+ ALL treated with DASATINIB TEVA in combination with chemotherapy, CBCs should be

performed prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, CBCs should be performed every 2 days until recovery (see **sections 4.2** and **4.8**). Myelosuppression is generally reversible and usually managed by withholding DASATINIB TEVA temporarily or by dose reduction.

Bleeding:

In patients with chronic phase CML, 1 % receiving DASATINIB TEVA had grade 3 or 4 haemorrhage. In clinical studies in patients with advanced phase CML receiving the recommended dose of DASATINIB TEVA, severe central nervous system (CNS) haemorrhage occurred in 1 % of patients. One case was fatal and was associated with Common Toxicity Criteria (CTC) grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 6 % of patients with advanced phase CML and generally required treatment interruptions and transfusions. Other grade 3 or 4 haemorrhage occurred in 2 % of patients with advanced phase CML. Most bleeding related adverse reactions in these patients were typically associated with grade 3 or 4 thrombocytopenia (see **section 4.8**). Additionally, *in vitro* and *in vivo* platelet assays suggest that DASATINIB TEVA treatment reversibly affects platelet activation.

Caution should be exercised if patients are required to take medicines that inhibit platelet function or anticoagulants.

Fluid retention:

DASATINIB TEVA is associated with fluid retention. After 5 years of follow-up in the Phase III newly diagnosed chronic phase CML study, severe fluid retention was reported in 13 patients (5 %) receiving DASATINIB TEVA.

In all patients with newly diagnosed or imatinib resistant or intolerant patients with chronic phase CML (n=548), severe fluid retention occurred in 6 % of patients receiving DASATINIB TEVA at the recommended dose.

In patients with advanced phase CML or Ph+ ALL receiving DASATINIB TEVA, severe fluid retention was reported in 8 % of patients, including severe pleural and pericardial effusion reported in 7 % and 1 % of patients, respectively. In these patients, severe pulmonary oedema and severe pulmonary hypertension were reported in 1

% of patients.

Patients who develop symptoms suggestive of pleural effusion or other fluid retention, such as new or worsened dyspnoea on exertion or at rest, pleuritic chest pain, or dry cough should be evaluated promptly with chest X-ray or additional diagnostic imaging as appropriate. Fluid retention events were typically managed by supportive care measures that may include diuretics or short courses of steroids (see **sections 4.2** and **4.8**). Patients aged 65 years and older are more likely than younger patients to experience pleural effusion, dyspnoea, cough, pericardial effusion and congestive heart failure, and should be monitored closely.

Pulmonary Arterial Hypertension (PAH):

Pulmonary arterial hypertension (PAH), confirmed by right heart catheterisation, has been reported in association with DASATINIB TEVA treatment. In these cases, PAH was reported after initiation of DASATINIB TEVA therapy, and after more than one year of treatment.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating DASATINIB TEVA therapy. Patients who develop dyspnoea and fatigue after initiation of therapy should be evaluated for more common aetiologies including pleural effusion, pulmonary oedema, anaemia, or lung infiltration. During this evaluation, guidelines for non-haematologic adverse reactions should be followed (see **section 4.2**). If the adverse reaction is severe, treatment must be withheld until the event has resolved or improved. If no alternative diagnosis is found, the diagnosis of PAH should be considered. If PAH is confirmed, DASATINIB TEVA should be permanently discontinued. Follow-up should be performed according to standard practice guidelines. Improvements in haemodynamic and clinical parameters have been observed in DASATINIB TEVA-treated patients with PAH following cessation of DASATINIB TEVA therapy.

QT Prolongation:

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT Interval).

Of the 2 182 patients with resistance or intolerance to prior imatinib therapy who received dasatinib in clinical

studies, 15 (1 %) had QTc prolongation reported as an adverse reaction. Twenty-one of these patients (1 %) experienced a QTcF >500 msec.

DASATINIB TEVA should be administered with caution to patients who have or may develop prolongation of QT interval. These include patients with hypokalaemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-dysrhythmic medicines or other medicines that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalaemia or hypomagnesemia should be corrected prior to DASATINIB TEVA administration.

Cardiac adverse reactions:

Dasatinib was studied in a randomised clinical study of patients with newly diagnosed CML in chronic phase which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking dasatinib. Cardiac adverse reactions were more frequent in patients with risk factors or a history of cardiac disease. Patients with risk factors (e.g. hypertension, hyperlipidaemia, diabetes) or a history of cardiac disease (e.g. prior percutaneous coronary intervention, documented coronary artery disease) should be monitored carefully for clinical signs or symptoms consistent with cardiac dysfunction such as chest pain, shortness of breath and diaphoresis.

If these clinical signs or symptoms develop, medical practitioners are advised to interrupt DASATINIB TEVA administration and consider the need for alternative CML-specific treatment. After resolution, a functional assessment should be performed prior to resuming treatment with dasatinib. DASATINIB TEVA may be resumed at the original dose for mild/moderate adverse reactions (≤ grade 2) and resumed at a dose level reduction for severe adverse reactions (≥ grade 3) (see **section 4.2**). Patients continuing treatment should be monitored periodically.

Patients with uncontrolled or significant cardiovascular disease were not included in the clinical studies.

Thrombotic microangiopathy (TMA):

BCR-ABL tyrosine kinase inhibitors have been associated with thrombotic microangiopathy (TMA), including individual case reports for DASATINIB TEVA (see **section 4.8**). If laboratory or clinical findings associated with TMA occur in a patient receiving DASATINIB TEVA, treatment with DASATINIB TEVA should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with DASATINIB TEVA should not be resumed.

Hepatitis B virus 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 DASATINIB TEVA. 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 DASATINIB TEVA should be closely monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) of active HBV infection throughout therapy and for several months following termination of therapy (see **section 4.8**).

Severe dermatologic reactions:

Cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, have been reported with the use of DASATINIB TEVA. DASATINIB TEVA should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified.

Elderly use:

Patients aged 65 years and older are more likely to experience the commonly reported adverse reactions of fatigue, pleural effusion, dyspnoea, cough, lower gastrointestinal haemorrhage, and appetite disturbance, and are more likely to experience the less frequently reported events of abdominal distention, dizziness, pericardial effusion, congestive heart failure, and weight decrease, and should be monitored closely.

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in DASATINIB TEVA:

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 DASATINIB TEVA should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

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

DASATINIB TEVA contains lactose:

DASATINIB TEVA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DASATINIB TEVA.

4.5 Interaction with other medicines and other forms of interaction:

Active substances that may increase dasatinib plasma concentrations:

In vitro studies indicate that dasatinib is a CYP3A4 substrate. Concomitant use of DASATINIB TEVA and

medicines or substances which potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, telithromycin, grapefruit juice) may increase exposure to dasatinib and should be avoided. Therefore, in patients receiving DASATINIB TEVA, systemic administration of a potent CYP3A4 inhibitor is not recommended (see **section 4.2**).

At clinically relevant concentrations, binding of dasatinib to plasma proteins is approximately 96 % on the basis of *in vitro* experiments. No studies have been performed to evaluate dasatinib interaction with other protein-bound medicines. The potential for displacement and its clinical relevance are unknown.

Active substances that may decrease dasatinib plasma concentrations:

When dasatinib was administered following 8 daily evening administrations of 600 mg rifampicin, a potent CYP3A4 inducer, the AUC of dasatinib was decreased by 82 %. Other medicines that induce CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John´s Wort) may also increase metabolism and decrease dasatinib plasma concentrations. Therefore, concomitant use of potent CYP3A4 inducers with dasatinib is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative medicines with less enzyme induction potential should be used. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25 % with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Histamine-2 antagonists and proton pump inhibitors:

Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure by > 60 %. In a single-dose study in healthy subjects, the administration of famotidine 10 hours prior to a single dose of DASATINIB TEVA reduced dasatinib exposure by 61 %. In a study of 14 healthy subjects, administration of a single 100-mg dose of DASATINIB TEVA 22 hours following a 4-day, 40-mg omeprazole dose at steady state reduced the AUC of dasatinib by 43 % and the C_{max} of dasatinib by 42 %. The use of antacids should be considered in place of H_2 antagonists or proton pump

inhibitors in patients receiving DASATINIB TEVA therapy (see **section 4.4**).

Antacids:

Non-clinical data demonstrate that the solubility of dasatinib is pH-dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with DASATINIB TEVA reduced the AUC of a single dose of DASATINIB TEVA by 55 % and the C_{max} by 58 %. However, when antacids were administered 2 hours prior to a single dose of DASATINIB TEVA, no relevant changes in dasatinib concentration or exposure were observed. Thus, antacids may be administered up to 2 hours prior to or 2 hours following DASATINIB TEVA (see **section 4.4**).

Active substances that may have their plasma concentrations altered by dasatinib:

Concomitant use of DASATINIB TEVA and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. In a study in healthy subjects, a single 100 mg dose of dasatinib increased AUC and C_{max} exposure to simvastatin, a known CYP3A4 substrate, by 20 and 37 % respectively. It cannot be excluded that the effect is larger after multiple doses of dasatinib. Therefore, CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids e.g. ergotamine, dihydroergotamine) should be administered with caution in patients receiving DASATINIB TEVA (see **section 4.4**).

In vitro data indicate a potential risk for interaction with CYP2C8 substrates, such as glitazones.

Paediatric population:

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation:

Women of childbearing potential/Contraception in males and females:

Sexually active male or female patients taking DASATINIB TEVA should use adequate contraception during

treatment.

Pregnancy:

DASATINIB TEVA may cause foetal harm when administered to a pregnant woman.

There have been post-marketing reports of spontaneous abortion and foetal and infant anomalies from women who have taken DASATINIB TEVA during pregnancy.

DASATINIB TEVA is not recommended for use in women who are pregnant or contemplating pregnancy. If DASATINIB TEVA is used during pregnancy, or if the patient becomes pregnant while taking DASATINIB TEVA, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding:

Women who are taking DASATINIB TEVA should not breastfeed.

Fertility:

Medical practitioners and other healthcare providers should counsel male patients of appropriate age about possible effects of DASATINIB TEVA on fertility, and this counselling may include consideration of semen deposition.

4.7 Effects on ability to drive and use machines:

DASATINIB TEVA has minor influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as dizziness or blurred vision during treatment with DASATINIB TEVA. Therefore, caution should be recommended when driving a car or operating machines.

4.8 Undesirable effects:

TABLE 2: TABULATED SUMMARY OF ADVERSE REACTIONS:

Infections and infestations:	
Frequent	infection (including bacterial, viral, fungal, non-specified), pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection (including cytomegalovirus - CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
Frequency unknown	hepatitis B reactivation
Blood and lymphatic system disorders:	
Frequent	myelosuppression (including anaemia, neutropenia, thrombocytopenia), febrile neutropenia
Less frequent	lymphadenopathy, lymphopenia, aplasia pure red cell
Immune system disorders:	
Less frequent	hypersensitivity (including erythema nodosum), anaphylactic shock
Endocrine disorders:	
Less frequent	hypothyroidism, hyperthyroidism, thyroiditis
Metabolism and nutrition disorders:	
Frequent	appetite disturbances[a], hyperuricaemia
Less frequent	tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia, diabetes mellitus
Psychiatric disorders:	
Frequent	depression, insomnia
Less frequent	anxiety, confusional state, affect lability, libido decreased
Nervous system disorders:	
Frequent	headache, dizziness, neuropathy (including peripheral neuropathy), dysgeusia, somnolence
Less frequent	CNS bleeding*[b], amnesia, tremor, syncope, balance disorder, cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis,

	dementia, ataxia
Eye disorders:	
Frequent	visual disorder (including visual disturbance, blurred vision and reduced visual acuity), dry eye
Less frequent	visual impairment, conjunctivitis, photophobia, increased lacrimation
Ear and labyrinth disorders:	
Frequent	tinnitus
Less frequent	hearing loss, vertigo
Cardiac disorders:	
Frequent	congestive heart failure/cardiac dysfunction*[c], pericardial effusion*, dysrhythmia (including tachycardia), palpitations
Less frequent	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular dysrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T-wave abnormal, troponin increased, cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
Frequency unknown	atrial fibrillation/atrial flutter
Vascular disorders:	
Frequent	haemorrhage [d], hypertension, flushing
Less frequent	hypotension, thrombophlebitis, thrombosis, deep vein thrombosis, livedo reticularis
Frequency unknown	thrombotic microangiopathy, pulmonary embolism
Respiratory, thoracic and mediastinal disorders:	
Frequent	pleural effusion*, dyspnoea, pulmonary oedema*, pulmonary hypertension*, lung infiltration, pneumonitis, cough
Less frequent	pulmonary arterial hypertension, bronchospasm, asthma, pulmonary embolism,

	acute respiratory distress syndrome, dysphonia
Frequency unknown	interstitial lung disease, acute respiratory distress syndrome
Gastrointestinal disorders:	
Frequent	diarrhoea, vomiting, nausea, abdominal pain, gastrointestinal bleeding*, colitis (including neutropenic colitis), gastritis, mucosal inflammation, (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
Less frequent	pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease, protein-losing gastroenteropathy, ileus, anal fistula
Frequency unknown	fatal gastrointestinal haemorrhage*, acute pancreatitis
Hepatobiliary disorders:	
Less frequent	hepatitis, cholestasis, cholecystitis
Frequency unknown	hepatic failure including fatal events*
Skin and subcutaneous tissue disorders:	
Frequent	skin rash[e], alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
Less frequent	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder, leukocytoclastic vasculitis, skin fibrosis
Frequency unknown	Stevens-Johnson syndrome[f]
Musculoskeletal and connective tissue disorders:	
Frequent	musculoskeletal pain[g], arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
Less frequent	rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis, epiphyses delayed fusion[h], growth retardation[h]

Renal and urinary disorders:	
Less frequent	renal impairment (including renal failure), urinary frequency, proteinuria
Frequency unknown	nephrotic syndrome
Pregnancy, puerperium and perinatal conditions:	
Less frequent	abortion
Reproductive system and breast disorders:	
Less frequent	gynaecomastia, menstrual disorder
General disorders and administration site conditions:	
Frequent	peripheral oedema[i], fatigue, pyrexia, face oedema[j], asthenia, pain, chest pain, generalised oedema*[k], chills
Less frequent	malaise, other superficial oedema[l], gait disturbance
Investigations:	
Frequent	decreased weight, increased weight
Less frequent	increased blood creatine phosphokinase, increased gamma-glutamyltransferase
Frequency unknown	hypophosphataemia, hypokalaemia, hypocalcaemia, elevated SGPT (ALT), elevated SGOT (AST), elevated bilirubin, elevated creatinine
Injury, poisoning, and procedural complications:	
Frequent	contusion

[a] Includes decreased appetite, early satiety, increased appetite.

[b] Includes central nervous system haemorrhage, cerebral haematoma, cerebral haemorrhage, extradural haematoma, intracranial haemorrhage, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma and subdural haemorrhage.

[c] Includes increased brain natriuretic peptide, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure, acute cardiac failure, chronic cardiac failure, congestive cardiac failure, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, decreased ejection fraction, ventricular

failure, left ventricular failure, right ventricular failure, and ventricular hypokinesia.

[d] Excludes gastrointestinal bleeding and CNS bleeding; these ADRs are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.

[e] Includes drug eruption erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriasis, rash, erythematous rash, follicular rash, generalised rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, skin exfoliation, skin irritation, urticaria vesiculosa, vesicular rash, toxic skin eruption and vasculitic rash.

[f] In the post-marketing setting, individual cases of Stevens-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to DASATINIB TEVA or to concomitant medicine.

[g] Musculoskeletal pain reported during or after discontinuing treatment.

[h] Frequency reported as common in paediatric studies.

[i] Gravitational oedema, localised oedema, oedema peripheral.

[j] Conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face.

[k] Fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, peripheral swelling, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.

[l] Genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling.

[*] For additional details, see section ***Description of selected adverse reactions***.

Description of selected adverse reactions:

Myelosuppression:

Treatment with DASATINIB TEVA is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is earlier and more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML (see **section 4.4**).

Bleeding:

Bleeding medicine-related adverse reactions, ranging from petechiae and epistaxis to grade 3 or 4 gastrointestinal haemorrhage and CNS bleeding, were reported in patients taking DASATINIB TEVA (see **section 4.4**).

Fluid retention:

Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as 'fluid retention'.

Pulmonary Arterial Hypertension (PAH):

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib exposure. In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment. Patients with PAH reported during dasatinib treatment were often taking concomitant medicines or had co-morbidities in addition to the underlying malignancy. Improvements in haemodynamic and clinical parameters have been observed in patients with PAH following discontinuation of dasatinib.

QT prolongation:

In the study in patients with newly diagnosed chronic phase CML, one patient (< 1 %) of the DASATINIB TEVA-treated patients had a QTcF > 500 msec after a minimum of 12 months follow-up (see **section 4.4**). No additional patients were reported to have QTcF > 500 msec after a minimum of 60 months follow-up.

Cardiac adverse reactions:

Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (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**).

Biochemistry:

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcaemia, hypokalaemia and hypophosphataemia were reported in all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption.

In general, decreased calcium levels were not associated with clinical symptoms. Patients developing Grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose:

Experience with overdose of DASATINIB TEVA in clinical studies is limited to isolated cases. Overdose of 280 mg per day for one week was reported in two patients and both developed a significant decrease in platelet counts. Since DASATINIB TEVA is associated with severe myelosuppression (see **section 4.4**), patients who ingest more than the recommended dosage should be closely monitored for myelosuppression and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 26 Cytostatic agents

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01XE06

Dasatinib inhibits the activity of the BCR-ABL kinase and SRC family kinases (SRC, LCK, YES, FYN), along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. Dasatinib inhibits the BCR-ABL kinase at a concentration of 0,6 to 0,8 nM. It binds to both the inactive and active conformations of the BCR-ABL enzyme.

Mechanism of action:

In vitro, dasatinib is active in leukaemic cell lines representing variants of imatinib sensitive and resistant disease.

In vivo, in separate experiments using murine models of CML, dasatinib prevented the progression of chronic CML to blast phase and prolonged the survival of mice bearing patient-derived CML cell lines grown at various sites, including the central nervous system (CNS).

5.2 Pharmacokinetic properties:

Absorption:

Dasatinib is rapidly absorbed in patients following oral administration, with peak concentrations between 0,5-3 hours. Following oral administration, the increase in the mean exposure (AUC_t) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg twice daily. The overall mean terminal half-life of dasatinib is approximately 5-6 hours in patients.

Data from healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following consumption of a high-fat meal indicated a 14 % increase in the mean AUC of dasatinib. Consumption of a low-fat meal 30 minutes prior to dasatinib resulted in a 21 % increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant. Dasatinib exposure variability is higher under fasted conditions (47 % CV) compared to light-fat meal (39 % CV) and high-fat meal (32 % CV) conditions.

Based on the patient population PK analysis, variability in dasatinib exposure was estimated to be mainly due to inter-occasion variability in bioavailability (44 % CV) and, to a lesser extent, due to inter-individual variability in bioavailability and inter-individual variability in clearance (30 % and 32 % CV, respectively). The random inter-occasion variability in exposure is not expected to affect the cumulative exposure and efficacy or safety.

Distribution:

In patients, dasatinib has a large apparent volume of distribution (2,505 L), coefficient of variation (CV % 93 %), suggesting that the medicine is extensively distributed in the extravascular space. At clinically relevant concentrations of dasatinib, binding to plasma proteins was approximately 96 % on the basis of *in vitro* experiments.

Biotransformation:

Dasatinib is extensively metabolised in humans with multiple enzymes involved in the generation of the metabolites. In healthy subjects administered 100 mg of ^{14}C-labelled dasatinib, unchanged dasatinib represented 29 % of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the product. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib.

Elimination:

The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363,8 L/hr (CV % 81,3 %). Elimination is predominantly in the faeces, mostly as metabolites. Following a single oral dose of [^{14}C]-labelled dasatinib, approximately 89 % of the dose was eliminated within 10 days, with 4 % and 85 % of the radioactivity recovered in the urine and faeces, respectively. Unchanged dasatinib accounted for 0,1 % and 19 % of the dose in urine and faeces, respectively, with the remainder of the dose as metabolites.

Characteristics in specific groups of subjects or patients:

Hepatic and renal impairment:

Since dasatinib is mainly metabolized through the liver, exposure to dasatinib is expected to increase if liver function is impaired. DASATINIB TEVA should be used with caution in patients with hepatic impairment.

Dasatinib and its metabolites are minimally excreted via the kidney.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core:

Croscarmellose sodium, type A

Cellulose, microcrystalline, type 101 & 102

Hydroxypropyl cellulose, type E

Lactose monohydrate

Magnesium stearate

Film-coating:

Opadry YS-1 7027 white contains:

Hypromellose 2910 (6 cP)

Titanium dioxide

Triacetin

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 months

HDPE bottles with 30 film-coated tablets can be used for 1 month after first opening.

HDPE bottles with 60 film-coated tablets can be used for 2 months after first opening.

HDPE bottles with 100 film-coated tablets can be used for 3 months after first opening.

6.4 Special precautions for storage:

Store at or below 25 °C.

Store in the original package to protect from moisture. Keep well closed after first opening.

HDPE bottles with 30 film-coated tablets can be used for 1 month after first opening. HDPE bottles with 60 film-coated tablets can be used for 2 months after first opening. HDPE bottles with 100 film-coated tablets can be used for 3 months after first opening (see **section 6.3**).

6.5 Nature and contents of container:

DASATINIB TEVA film-coated tablets are packed in two types of packaging items:

Blisters:

Tablets are packed into OPA/Al/PVC//Al blisters. The blister(s) and leaflet are inserted into a carton unit box.

Pack sizes for DASATINIB 20 TEVA, DASATINIB 50 TEVA and DASATINIB 70 TEVA: 30 and 60 film-coated tablets in blisters or 56 x 1 and 60 x 1 film-coated tablets in perforated unit-dose blisters.

Pack sizes for DASATINIB 100 TEVA: 30 film-coated tablets in blisters or 30 x 1 film-coated tablets in perforated unit-dose blisters.

Bottles:

DASATINIB 20 TEVA, DASATINIB 50 TEVA and DASATINIB 70 TEVA film-coated tablets are packaged in a white, high density polyethylene (HDPE) bottle containing 60 tablets with a polypropylene (PP) child resistant closure with inner seal for induction sealing.

DASATINIB 100 TEVA film-coated tablets are packaged in a white, high density polyethylene (HDPE) bottle containing 30 tablets with a polypropylene (PP) child resistant closure with inner seal for induction sealing.

Each bottle and leaflet are inserted into a carton unit box.

One canister of desiccant (1 g) is inserted into each HDPE bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling:

The use of gloves when handling the tablets is recommended, especially if the tablets are crushed or broken. Healthcare professionals should wear disposable chemotherapy gloves for appropriate disposal in order to minimise the risk of dermal exposure. Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. REGISTRATION NUMBERS:

DASATINIB 20 TEVA: 55/26/0448

DASATINIB 50 TEVA: 55/26/0449

DASATINIB 70 TEVA: 55/26/0450

DASATINIB 100 TEVA: 55/26/0451

Applicant: Teva Pharmaceuticals (Pty) Ltd	Product: DASATINIB TEVA 20, 50 , 70 & 100 - film-coated tablets
Reg No: DASATINIB 20 TEVA: 55/26/0448 DASATINIB 50 TEVA: 55/26/0449 DASATINIB 70 TEVA: 55/26/0450 DASATINIB 100 TEVA: 55/26/0451	Each film-coated tablet contains dasatinib monohydrate equivalent to 20 mg, 50 mg, 70 mg or 100 mg dasatinib.

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION:

15 November 2022

10. DATE OF REVISION OF THE TEXT: