PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DASAMIA 20, Film coated tablets

DASAMIA 50, Film coated tablets

DASAMIA 70, Film coated tablets

DASAMIA 100, Film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DASAMIA 20, film coated tablets contain 20 mg dasatinib.

DASAMIA 50, film coated tablets contain 50 mg dasatinib.

DASAMIA 70, film coated tablets contain 70 mg dasatinib.

DASAMIA 100, film coated tablets contain 100 mg dasatinib.

DASAMIA 20, film coated tablets contains 26,760 mg lactose monohydrate.

DASAMIA 50, film coated tablets contains 66,900 mg lactose monohydrate.

DASAMIA 70, film coated tablets contains 93,660 mg lactose monohydrate.

DASAMIA 100, film coated tablets contains 133,800 mg lactose monohydrate.

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

3. PHARMACEUTICAL FORM

DASAMIA 20 film coated tablets: White to off-white, biconvex, round, film-coated tablet, debossed with "851" on one side and plain on other side.

DASAMIA 50 film coated tablets: White to off-white, biconvex, oval, film-coated tablet, debossed with "852" on one side and plain on other side.

DASAMIA 70 film coated tablets: White to off-white, biconvex, round, film-coated tablet debossed with "853" on one side and plain on other side.

DASAMIA 100 film coated tablets: White to off-white, biconvex, oval, film-coated tablet, debossed with “855” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- DASAMIA 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.
- DASAMIA 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

The recommended starting dosage of DASAMIA for chronic phase CML is 100 mg once daily, administered orally. DASAMIA can be taken with or without a meal and should be taken consistently either in the morning or in the evening.

The recommended starting dosage of DASAMIA for accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL is 70 mg twice daily, administered orally. DASAMIA 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 in adults are summarised in table below.

Table 1: Dose adjustments for neutropenia and thrombocytopenia.

Chronic phase CML (starting dose 100 mg once daily)	ANC* < 0,5 x 10^9/L or platelets < 50 x 10^9/L	1) Stop DASAMIA until ANC ≥ 1,0 x 10^9/L and platelets ≥ 50 x 10^9/L. 2) Resume treatment with DASAMIA at the original starting dose. 3) If platelets < 25 x 10^9/L or recurrence of ANC < 0,5 x 10^9/L for > 7 days, repeat Step 1 and resume DASAMIA treatment 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 DASAMIA (for patients resistant or intolerant to prior including imatinib).
Accelerated phase CML, Blast phase CML and Ph+ ALL (starting dose 70 mg twice daily	ANC < 0,5 x 10^9/L or platelets < 10 x 10^9/L	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, stop DASAMIA until ANC ≥ 1,0 x 10^9/L and platelets ≥ 20 x 10^9/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume DASAMIA 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 twice daily.

* ANC: absolute neutrophil count

Non-haematological adverse reactions

If a severe non-haematological adverse reaction develops with DASAMIA 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**

Hepatic Impairment: See **section 5.2**

Geriatric: No clinically relevant age-related pharmacokinetic differences have been reported. No specific dose recommendation is necessary.

Paediatric Patients: The safety and efficacy of dasatinib in patients < 18 years of age have not been established.

Method of administration

DASAMIA is administered orally. Tablets should not be crushed or cut; they should be swallowed whole.

4.3 Contraindications

- DASAMIA is contra-indicated in patients with hypersensitivity to dasatinib or to any other component of DASAMIA.
- The concomitant use of H2 antagonists or proton pump inhibitors with DASAMIA 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 and medicines or substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving dasatinib, coadministration of a potent CYP3A4 inhibitor is not recommended (see **section 4.5**).

Concomitant use of dasatinib 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, coadministration of alternative medicines with less potential for CYP3A4 induction should be selected (see **section 4.5**).

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when dasatinib 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 and a histamine-2 (H2) antagonist (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminium hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H2 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 (see **section 4.5**).

Special populations

Based on the findings from a reported single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. Due to the limitations of this reported clinical study, caution is recommended when administering dasatinib to patients with hepatic impairment.

Important adverse reactions

Myelosuppression

Treatment with dasatinib is very commonly associated with thrombocytopenia, neutropenia, anaemia, which occur earlier and more frequently reported in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML. In patients with chronic phase CML, complete blood counts (CBCs) should be performed every two weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, CBCs should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or by dose reduction (see **sections 4.2 and 4.8)**.

Bleeding related events

In patients with chronic phase CML, severe haemorrhage reported in few patients receiving dasatinib at the recommended dose. In patients with advanced phase CML or Ph+ ALL, severe central nervous system (CNS) haemorrhage, including fatalities, occurred in 1 % of patients receiving dasatinib at the recommended dose. Severe gastrointestinal haemorrhage, including fatalities, reported in 6 % of patients and generally required treatment interruptions and transfusions. Other cases of severe haemorrhage occurred in 2 % of patients. Most bleeding events in reported clinical studies were associated with severe thrombocytopenia. Additionally, reported in vitro and in vivo platelet assays suggest that dasatinib 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 is associated with fluid retention. After 5 years of follow-up in the reported Phase III newly diagnosed chronic phase CML study, severe fluid retention was reported in 5 % patients receiving dasatinib. In all patients with newly diagnosed or imatinib resistant or intolerant patients with chronic phase CML, severe fluid retention occurred in 6 % patients receiving dasatinib at the recommended dose. In patients with advanced phase CML or Ph+ ALL receiving dasatinib, 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. Severe pleural effusion may require thoracentesis. Dose modification should be considered (see **section 4.2**).
While the safety profile of dasatinib in the elderly population was reported to be similar to that in the younger population, patients aged 65 years and older are more likely to experience fluid retention events and dyspnoea and should be monitored closely.

Cardiac adverse reactions

Dasatinib was studied in a randomised trial in 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, dysrhythmias, palpitations, QT prolongation, and myocardial infarction (including fatal) were reported in patients taking dasatinib. Adverse cardiac events were more frequent in patients with risk factors or a previous medical 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, diaphoresis and should be evaluated and treated appropriately.
If these clinical signs or symptoms develop, medical practitioners are advised to interrupt DASAMIA administration and consider the need for alternative CML-specific treatment. After resolution, a functional assessment should be performed prior to resuming treatment with DASAMIA. DASAMIA 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). Patients continuing treatment should be monitored periodically.

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

Thrombotic microangiopathy (TMA)

BCR-ABL tyrosine kinase inhibitors have been associated with thrombotic microangiopathy (TMA), including individual case reports for dasatinib. If laboratory or clinical findings associated with TMA occur in a patient receiving DASAMIA, treatment with DASAMIA 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 DASAMIA should not be resumed.

Cerebrovascular events

Cerebrovascular events such as central nervous system haemorrhage, cerebral haematoma, cerebral haemorrhage, extradural haematoma, intracranial haemorrhage, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma and subdural haemorrhage have been associated with the use of tyrosine kinase inhibitors (TKI) (see **section 4.8**)

Pulmonary arterial hypertension

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

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib 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, DASAMIA should be permanently discontinued. Follow up should be performed according to

standard practice guidelines. Improvements in haemodynamic and clinical parameters have been reported in dasatinib-treated patients with PAH following cessation of dasatinib therapy.

QT prolongation

Reported in vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT interval). Of the patients with resistance or intolerance to prior imatinib therapy treated with dasatinib in reported clinical studies, 1 % had QT prolongation reported as an adverse reaction. One percent of these patients experienced a QTcF > 500 ms.

DASAMIA 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 DASAMIA administration.

Hepatitis B virus reactivation

BCR-ABL TKIs, including dasatinib have been associated with hepatitis B virus (HBV) reactivation including acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Screening for HBV should be considered in accordance with guidelines before starting therapy with DASAMIA. Consultation with a medical practitioner with expertise in the treatment of HBV is recommended for patients who test positive for HBV serology. Patients who are carriers of HBV and require treatment with DASAMIA should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop reactivation of HBV while receiving DASAMIA, prompt consultation with a medical practitioner with expertise in the treatment of HBV is recommended.

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. DASAMIA

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.

Excipients

Lactose

DASAMIA contains lactose. Patients with rare hereditary conditions of galactose intolerance e.g. total lactase deficiency, or glucose-galactose malabsorption should not take DASAMIA.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on DASAMIA.

Medicines that may increase dasatinib plasma concentrations

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and medicines that inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, telithromycin, grapefruit juice) may increase exposure to DASAMIA and should be avoided. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, the patient should be closely monitored for toxicity.

At clinically relevant concentrations, binding of dasatinib to plasma proteins is reported as 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.

Medicines that may decrease dasatinib plasma concentrations

CYP3A4 Inducers: Medicines that induce CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort (Hypericum perforatum) may reduce exposure to dasatinib. Concomitant use of potent CYP3A4 inducers with dasatinib is not recommended. In patients for whom CYP3A4 inducers are indicated, alternative medicines with no or minimal CYP3A4 induction potential should be selected. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is reported to decrease approximately 25 % with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Rifampicin: Data from a reported study of healthy subjects indicate that when a single morning dose of dasatinib was administered following 8 days of continuous evening administration of 600 mg of rifampicin, a potent CYP3A4 inducer, the mean Cmax, and AUC of dasatinib were decreased by 81 % and 82 %, respectively.

Antacids (aluminium hydroxide/magnesium hydroxide products): Reported non-clinical data demonstrate that the solubility of dasatinib is pH dependent. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of DASAMIA. Simultaneous administration of DASAMIA with antacids should be avoided.

H2 antagonists/proton pump inhibitors: Long-term suppression of gastric acid secretion by H2 antagonists or proton pump inhibitors reduces dasatinib exposure by >60 %. The concomitant use of H2 antagonists or proton pump inhibitors with DASAMIA is not recommended. The use of antacids should be considered in place of H2 antagonists or proton pump inhibitors in patients receiving DASAMIA therapy.

Effect of dasatinib on other medicines

CYP3A4 substrates: Dasatinib is an inhibitor of CYP3A4. Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, ciclosporin, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)

should be administered with caution in patients receiving DASAMIA. Reported in vitro data indicate a potential risk for interaction with CYP2C8 substrates, such as glitazones.

Simvastatin: Single dose data from a reported study of healthy subjects indicate that the mean Cmax and AUC of simvastatin, a CYP3A4 substrate, were increased by 37 % and 20 %, respectively, when simvastatin was administered in combination with a single 100 mg dose of dasatinib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

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

Pregnancy

Based on reported human experience, dasatinib is suspected to cause congenital malformations including neural tube defects, and harmful pharmacological effects on the foetus when administered during pregnancy. Reported studies in animals have shown reproductive toxicity.

Dasatinib 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 during pregnancy.

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

Breastfeeding

There is insufficient/limited information on the excretion of dasatinib in human or animal breast milk. Physico-chemical and available pharmacodynamic/toxicological data on dasatinib point to excretion in breast milk and a risk to the suckling child cannot be excluded. Women who are taking DASAMIA should not breastfeed.

Fertility

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

4.7 Effects on ability to drive and use machines

DASAMIA 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 DASAMIA. Therefore, cautions should be recommended when driving a car or operating machines. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Table 2: Tabulated summary of adverse reactions

System Organ Class	Frequent	Less frequent	Frequency not known
Infections and infestations	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).	-	Hepatitis B reactivation
Blood and lymphatic system disorders	Myelosuppression (including anaemia, neutropenia,	Lymphadenopathy lymphopenia, pure red cell aplasia	-

	thrombocytopenia), febrile neutropenia		
Immune system disorders	-	Hypersensitivity (including erythema nodosum), anaphylactic shock	-
Endocrine disorders	-	Hypothyroidism, hyperthyroidism, thyroiditis	-
Metabolism and nutrition disorders	Appetite disturbances[a], hyperuricaemia	Tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia, diabetes mellitus	-
Psychiatric disorders	Depression, insomnia	Anxiety, confusional state, affect lability, decrease of libido	-
Nervous System disorders	Headache, neuropathy (including, peripheral neuropathy), dizziness, dysgeusia, somnolence,	CNS bleeding[b], syncope, tremor, amnesia, balance disorder, cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis,	-

		dementia, ataxia.	
Eye disorders	Visual disorder (including visual disturbance, vision, blurred, and visual acuity reduced), dry eye	Visual impairment, conjunctivitis, photophobia, lacrimation increased	-
Ear and labyrinth disorders	Tinnitus	Hearing loss, vertigo	-
Cardiac disorders	Congestive heart failure/cardiac dysfunction [c], pericardial effusion, arrhythmia (including tachycardia), palpitations	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, pleuro-pericarditis	Atrial fibrillation/ atrial flutter

Vascular disorders	Haemorrhage[d], hypertension, flushing	Hypotension, thrombophlebitis, thrombosis, deep vein thrombosis, embolism, livedo reticularis.	Thrombotic micro-angiopathy
Respiratory, Thoracic and mediastinal disorders	Pleural effusion, dyspnoea, pulmonary oedema, pulmonary hypertension, lung infiltration, pneumonitis, cough	Pulmonary arterial hypertension, bronchospasm, asthma, dysphonia, acute respiratory distress syndrome, chylothorax	Interstitial lung disease
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain, gastrointestinal bleeding,colitis (including neutropaenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis) dyspepsia, abdominal distension, constipation, oral soft tissue disorder	Pancreatitis (including Acute pancreatitis) upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia, gastroesophageal reflux disease, Protein-losing gastroenteropathy, ileus, anal fistula	Fatal gastro-intestinal haemorrhage

Hepatobiliary disorders	-	Hepatitis, cholecystitis, cholestasis	-
Skin and Subcutaneous tissue disorders	Skin rash[e], alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis	Neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesiasyndrome, hair disorder, leukocytoclastic vasculitis, skin fibrosis	Stevens-Johnson syndrome[f] toxic necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, arthralgia, myalgia, Muscular weakness, musculoskeletal stiffness, muscle spasm	Rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis, epiphyses delayed fusion, growth retardation.	-
Renal and urinary disorders	-	Renal failure, urinary frequency, proteinuria, renal impairment.	Nephrotic syndrome
Reproductive system and breast disorders	-	Gynecomastia, menstrual disorder.	-
General disorders and administration site conditions	Peripheral oedema, fatigue, pyrexia, face oedema[g],	Malaise, other superficial oedema[i] gait disturbance	-

	asthenia, pain, chest pain, generalised oedema[h], chills		
Investigations	Decreased weight, increased weight	Increased blood creatinine phosphokinase, increased Gamma- glutamyl-transferase	-
Injury, poisoning, and procedural complications	Confusion	-	-

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

[f] Includes gravitational oedema, localised oedema, peripheral oedema

[g] Included conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, mouth oedema, orbital oedema, periorbital oedema, face swelling.

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

[i] Included genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling.

Reported post-marketing experience

The following additional adverse reactions have been identified during post approval use of dasatinib. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Special populations

While the safety profile of dasatinib in elderly was reported to be similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adverse reactions such as fatigue, pleural effusion, dyspnoea, cough, lower gastrointestinal haemorrhage, and appetite disturbance and more likely to experience less frequently reported adverse reactions such as abdominal distention, dizziness, pericardial effusion, congestive heart failure, and weight decrease and should be monitored closely (see **section 4.4**).

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 asked to report any suspected adverse reactions to SAHPRA 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

Experience with overdose of dasatinib in reported 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 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

A26 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 - 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 leukemic cell lines representing variants of imatinib sensitive and resistant disease. These reported non-clinical studies show that dasatinib can overcome imatinib resistance resulting from BCR-ABL overexpression, BCR-ABL kinase domain mutations, activation of alternate signalling pathways involving the SRC family kinases (LYN, HCK) and multidrug resistance gene overexpression. Additionally, dasatinib inhibits SRC family kinases at subnanomolar concentrations.

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.

5.2 Pharmacokinetic properties

Absorption

Dasatinib is rapidly absorbed in patients following oral administration with peak concentrations reported between 0,5 and 6 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 reported as approximately 5 to 6 hours in patients.

Reported 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 reported to be higher under fasted conditions (47 % CV) compared to light-fat meal (39 % CV) and high-fat meal (32 % CV) conditions.

Based on the reported 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 inexposure is not expected to affect the cumulative exposure and efficacy or safety.

Distribution

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

Biotransformation

Dasatinib is extensively metabolised in humans with multiple enzymes involved in the generation of the metabolites. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib. In healthy subjects administered 100 mg of [14C]-labelled dasatinib, unchanged dasatinib reported 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.

Elimination

The mean terminal half-life of dasatinib is reported as 3 hours to 5 hours. The mean apparent oral clearance is reported as 363,8 L/hr (CV % 81,3 %).

Elimination is predominantly in the faeces, mostly as metabolites. It has been reported that following a single oral dose of [14C]-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.

Special populations

Renal impairment: Since the renal clearance of dasatinib and its metabolites is < 4 %, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic impairment: Since dasatinib is mainly metabolised through the liver, exposure to dasatinib is expected to increase if liver function is impaired. Dasatinib should be used with caution in patients with hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose amonohydrate, Calcium hydrogen phosphate anhydrous, Croscarmellose sodium, Hydroxypropyl cellulose, Colloidal anhydrous silica, Magnesium stearate, Opadry White 03K580013 (Hypromellose, Titanium dioxide, Triacetin, Purified water)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 ºC in original package.

6.5 Nature and contents of container

DASAMIA 20, DASAMIA 50 and **DASAMIA 70**

Carton containing 5 blisters of 12 tablets packaged in the Aluminium/Aluminium blister consisting of 242 mm Cold Form Laminate Form Pack with Desiccant 25 OPA/45 AL/HDPE/PE+ Desiccant/HDPE and 240 mm Push Through Lidding Foil 20 micron AL/15 GSM PE for Form Pack Desiccant.

DASAMIA 100

Carton containing 3 blisters of 10 tablets packaged in the Aluminium/Aluminium consisting of 242 mm Cold Form Laminate Form Pack with Desiccant 25 OPA/45 AL/HDPE/PE+Desiccant/HDPE (Expo) and 240 mm Push Through Lidding Foil 20 micron AL/15 GSM PE for Form Pack Desiccant

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

14 Lautre Road, Stormill, Ext.1 Roodepoort,

Johannesburg, 1724

8. REGISTRATION NUMBERS

DASAMIA 20: 56/26/0207

DASAMIA 50: 56/26/0208

DASAMIA 70: 56/26/0209

DASAMIA 100: 56/26/0210

9. DATE OF FIRST AUTHORISATION

15 August 2023

10. DATE OF REVISION OF THE TEXT