SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TAZATRED 20 film-coated tablets (dasatinib)

TAZATRED 50 film-coated tablets (dasatinib)

TAZATRED 70 film-coated tablets (dasatinib)

TAZATRED 100 film-coated tablets (dasatinib)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAZATRED 20: Each film-coated tablet contains dasatinib 20 mg.

Excipient with known effect

4 mg lactose (as anhydrous) per tablet

TAZATRED 50: Each tablet contains dasatinib 50 mg.

Excipient with known effect

10 mg lactose (as anhydrous) per tablet

TAZATRED 70: Each tablet contains dasatinib 70 mg.

Excipient with known effect

14 mg lactose (as anhydrous) per tablet

TAZATRED 100: Each tablet contains dasatinib 100 mg.

Excipient with known effect

20 mg lactose (as anhydrous) per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TAZATRED 20 mg film-coated tablets are available as white to off-white, round shaped tablets debossed with "599" on one side and plain on other side.

TAZATRED 50 mg film-coated tablets are available as white to off-white, round shaped tablets debossed with "600" on one side and plain on other side.

TAZATRED 70 mg film-coated tablets are available as white to off-white, round shaped tablets debossed with "601" on one side and plain on other side.

TAZATRED 100 mg film-coated tablets are available as white to off-white, round shaped tablets debossed with "603" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

TAZATRED 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.

TAZATRED 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 TAZATRED for chronic phase CML is 100 mg once daily, administered orally. TAZATRED 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 TAZATRED for accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL is 70 mg twice daily, administered orally. TAZATRED 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 x 10^9/L or Platelets < 50 x 10^9/L	1. Stop TAZATRED until ANC ≥ 1,0 x 109/L and platelets ≥ 50 x 109/L. 2. Resume treatment with TAZATRED 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 or resume TAZATRED 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 TAZATRED (for patients resistant or intolerant to prior therapy 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 TAZATRED 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 TAZATRED at a reduced dose of 50 mg twice daily (second 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 TAZATRED 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).

Special populations

***Renal Impairment**:*

(See Section 5.1 and 5.2).

Hepatic Impairment:

(See Section 5.1 and 5.2).

Elderly population:

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 TAZATRED in patients < 18 years of age have not been established.

Method of administration

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

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

4.3 Contraindications

- Hypersensitivity to the active substance (dasatinib) or to any of the excipients (see Section 6.1).
- The concomitant use of H_2 antagonists or proton pump inhibitors with TAZATRED is not recommended.

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with TAZATRED is very commonly associated with thrombocytopenia, neutropenia and anaemia, which occur earlier and more frequently 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 TAZATRED temporarily or by dose reduction (see Sections 4.2 and 4.8).

Bleeding related events

In patients with chronic phase CML, severe haemorrhage occurred in 5 patients receiving dasatinib at the recommended dose (n=548).

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 (n=304). Severe gastrointestinal haemorrhage, including fatalities, occurred 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 clinical studies were associated with severe thrombocytopenia.

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

Fluid Retention

Dasatinib is associated with fluid retention. After 5 years of follow-up in the Phase III newly diagnosed chronic phase CML study (n=258), severe fluid retention was reported in 13 patients (5 %) receiving dasatinib.

In all patients with newly diagnosed or imatinib resistant or intolerant patients with chronic phase CML (n=548), severe fluid retention occurred in 32 (6 %) patients receiving TAZATRED 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 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 of 519 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. Adverse cardiac events were more frequent in patients with risk factors or a previous medical history of cardiac disease. 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.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), confirmed by right heart catheterisation, has been reported in association with dasatinib treatment, as in TAZATRED. 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 TAZATRED 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, TAZATRED 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 -treated patients with PAH following cessation of TAZATRED therapy.

QT Prolongation

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

After 5 years of follow-up in the Phase III clinical study of newly diagnosed chronic phase CML, 1 patient (< 1 %) in each of the dasatinib and imatinib treatment groups had QTc prolongation reported as an adverse reaction. The median changes in QTcF from baseline were 3,0 msec in dasatinib -treated patients. One patient (< 1 %) experienced QTcF > 500 msec.

In 865 patients with leukaemia treated with dasatinib in Phase II clinical studies, the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4 - 6 msec; the upper 95 % confidence intervals for all mean changes from baseline were < 7 msec. Of the 2 182 patients with resistance or intolerance to prior imatinib therapy treated with dasatinib in clinical studies, 15 (1 %) had QT prolongation reported as an adverse reaction. Twenty-one of these patients (1 %) experienced a QTcF > 500 msec.

TAZATRED 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 medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalaemia or hypomagnesemia should be corrected prior to TAZATRED administration.

Thrombotic microangiopathy (TMA)

BCR-ABL tyrosine kinase inhibitors have been associated with thrombotic microangiopathy (TMA), including individual case reports for dasatinib (see section 4.8). If laboratory or clinical findings associated with TMA occur in a patient receiving TAZATRED, treatment with TAZATRED 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 TAZATRED should not be resumed.

Hepatitis B virus reactivation

BCR-ABL TKIs, including TAZATRED 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 TAZATRED. 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 TAZATRED 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 TAZATRED, 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.

TAZATRED should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified.

Geriatric 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, pericardia! effusion, congestive heart failure, and weight decrease, and should be monitored closely.

Excipients

Lactose

TAZATRED contains lactose. Patients with rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take TAZATRED.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on TAZATRED:

Medicines that may increase dasatinib plasma concentrations:

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. Concomitant use of TAZATRED and medicines that inhibit CYP3A4 (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, telithromycin, grapefruit juice) may increase exposure to TAZATRED 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.

Medicines that may decrease TAZATRED 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 TAZATRED. Concomitant use of potent CYP3A4 inducers with TAZATRED is not recommended. In patients for whom CYP3A4 inducers are indicated, alternative agents with no or minimal CYP3A4 induction potential should be selected.

Rifampicin: Data from a study of 20 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 C_{max} and AUC of dasatinib were decreased by 81 % and 82 %, respectively.

Antacids (aluminium hydroxide/magnesium hydroxide products): 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 TAZATRED. Simultaneous administration of TAZATRED with antacids should be avoided.

H_2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors reduces dasatinib exposure by > 60 %. The concomitant use of H_2 antagonists or proton pump inhibitors with TAZATRED is not recommended. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving TAZATRED therapy.

Effect of TAZATRED 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, cisapride, ciclosporin, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving TAZATRED.

Simvastatin: Single dose data from a study of 54 healthy subjects indicate that the mean C_{max} 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:

Both sexually active men and women of childbearing potential should use effective methods of contraception during treatment.

Pregnancy:

TAZATRED 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.

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

Breastfeeding:

Women who are taking TAZATRED should not breastfeed.

Fertility:

In animal studies, the fertility of male and female rats was not affected by treatment with dasatinib. Healthcare providers should counsel male patients of appropriate age about possible effects of TAZATRED on fertility, and this counselling may include consideration of semen deposition.

4.7 Effects on ability to drive and use machines

Dasatinib has minor influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised that they may

experience adverse reactions such as dizziness or blurred vision during treatment with TAZATRED. Therefore, caution should be recommended when driving a car or operating machines.

4.8 Undesirable effects

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, enterocolitis infection, sepsis (including uncommon reports of fatal outcomes).		Hepatitis B reactivation
Blood and lymphatic system disorders	Myelosuppression (including anaemia, neutropenia, thrombocytopenia), febrile neutropenia.	Lymphadenopathy, lymphopenia, pure red cell aplasia.	
Immune system disorders		Hypersensitivity (including erythema nodosum). Anaphylactic stock	

Endocrine system disorders		Hypothyroidism, hyperthyroidism, thyroiditis.	
Metabolism and nutrition disorders	Appetite disturbances, hyperuricaemia, Weight decreased; weight increased.	tumour lysis syndrome, dehydration, hypoalbuminaemia, hypercholesterolaemia, diabetes mellitus.	
Psychiatric disorders	Depression, insomnia.	Anxiety, confusional state, affect lability, decrease of libido.	
Nervous system disorders	Headache, dizziness, neuropathy (including peripheral neuropathy}, dysgeusia, somnolence.	CNS bleeding, amnesia, tremor, syncope, balance disorder, cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VII th nerve paralysis, dementia, ataxia.	
Eye disorders	visual disorder (including visual disturbance, blurred vision and reduced visual acuity), dry eye.	visual impairment, conjunctivitis, photophobia, increased lacrimation.	
Ear and	Tinnitus.	Hearing loss, vertigo.	

labyrinth disorders			
Cardiac disorders	Congestive heart failure/cardiac dysfunction, pericardia! effusion, dysrhythmia (including tachycardia), palpitations.	Cardiomegaly, angina pectoris, myocardial infarction (including fatal outcomes), electrocardiogram QT prolonged, pericarditis, ventricular dysrhythmia (Including ventricular tachycardia), electrocardiogram T wave abnormal, increased troponin, acute coronary syndrome, myocarditis, cor pulmonale, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis.	Atrial fibrillation/atrial flutter.
Vascular disorders	Haemorrhage, hypertension, flushing.	Hypotension, thrombophlebitis, deep vein thrombosis, pulmonary embolism, livedo reticularis.	Thrombotic microangiopathy.

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.	Interstitial lung disease.
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, gastrointestinal bleeding, abdominal distension, mucosa! inflammation (Including mucositis/stomatitis), colitis (including neutropenic colitis), gastritis, oral soft tissue disorder, dyspepsia, constipation.	Pancreatitis, upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia, gastro-oesophageal reflux disease, protein-losing gastroenteropathy, ileus, acute pancreatitis, anal fistula	Fatal gastrointestinal haemorrhage.
Hepatobiliary disorders		Hepatitis, cholestasis, cholecystitis.	
Skin and subcutaneous tissue disorders	Skin rash, pruritus, alopecia, acne, dry skin, urticaria, hyperhydrosis, dermatitis (Including eczema).	Neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail	Stevens-Johnson syndrome.

		disorder, palmar-plantar erythrodysaesthesia syndrome, hair disorder, leukocytoclastic vasculitis, skin fibrosis.	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm.	Rhabdomyolysis, osteonecrosis, tendonitis, muscle inflammation, Arthritis. Epiphyseal delayed fusion growth retardation.	
Renal and urinary disorders		Renal failure, urinary frequency, proteinuria, renal impairment.	Nephrotic syndrome.
Pregnancy, puerperium and perinatal conditions		Abortion.	
Reproductive system and breast disorders		Gynaecomastia, menstrual disorder.	

General disorders and administration site conditions	Peripheral oedema, fatigue, pyrexia, face oedema, asthenia, pain, chest pain, generalised oedema, chills	Malaise, other superficial oedema, gait disturbance.	
Investigations		Blood creatine phosphokinase increased, gamma-glutamyltransferase increased.	
Injury, poisoning, and procedural complications	Contusion.		

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 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 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 TAZATRED is associated with severe myelosuppression (see section 4.4), patients who ingest more than the recommended dose should be closely monitored for myelosuppression and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 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 approximately 5 to 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.

Distribution:

In patients, dasatinib has 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 approximately 96 %.

Metabolism:

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 [^{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.

Elimination:

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.

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. TAZATRED should be used with caution in patients with hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous lactose.

Colloidal Silicon Dioxide

Croscarmellose sodium.

Magnesium stearate.

Microcrystalline cellulose.

Hydrogenated castor oil (powder).

Opadry® white.

Opadry® white contains: hypromellose, titanium dioxide and triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters:

20 mg: 24 months

50 mg: 18 months

70 mg: 24 months

100 mg: 24 months.

Bottles:

20 mg: 24 months

50 mg: 24 months

70 mg: 24 months

100 mg: 24 months.

6.4 Special precautions for storage

Store at or below 30 °C. Keep well closed after first opening.

6.5 Nature and contents of container

TAZATRED 20, 50, 70, 100 film-coated tablets are packaged in Alu-Alu blisters of 10, in pack sizes of 30's or 60's.

TAZATRED 20, 50, 70, 100 film-coated tablets are packaged in 75cc HDPE bottles closed with child resistant closures in pack sizes of 30's or 60's, The bottles contain one silica gel desiccant.

6.6 Special precautions for disposal and other 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 CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

TAZATRED 20: 55/26/0797

TAZATRED 50: 55/26/0798

TAZATRED 70: 55/26/0799

TAZATRED 100: 55/26/0800

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 March 2023

10. DATE OF REVISION OFTEXT