Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	Fylibix 20; 50; 70; 80; 100
Dosage form and strength	:	Film-coated tablets. Each film-coated tablet contains dasatinib equal to 20 mg, 50 mg, 70 mg, 80 mg and 100 mg respectively.
Date of submission	:	10 June 2022

CLEAN PROFESSIONAL INFORMATION FOR FYLIBIX 20; 50; 70; 80; 100

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE:

FYLIBIX 20 (film-coated tablets)

FYLIBIX 50 (film-coated tablets)

FYLIBIX 70 (film-coated tablets)

FYLIBIX 80 (film-coated tablets)

FYLIBIX 100 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each FYLIBIX 20 film-coated tablet contains 20 mg dasatinib.

Each FYLIBIX 50 film-coated tablet contains 50 mg dasatinib.

Each FYLIBIX 70 film-coated tablet contains 70 mg dasatinib.

Each FYLIBIX 80 film-coated tablet contains 80 mg dasatinib.

Each FYLIBIX 100 film-coated tablet contains 100 mg dasatinib.

Excipient with known effect:

Each FYLIBIX 20 film-coated tablet contains sugar (27,60 mg of lactose monohydrate).

Each FYLIBIX 50 film-coated tablet contains sugar (69,00 mg lactose monohydrate).

Each FYLIBIX 70 film-coated tablet contains sugar (96,60 mg lactose monohydrate).

Each FYLIBIX 80 film-coated tablet contains sugar (110,40 mg lactose monohydrate).

Each FYLIBIX 100 film-coated tablet contains sugar (138,00 mg lactose monohydrate).

For full list of excipients, see Section 6.1.

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Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	Fylibix 20; 50; 70; 80; 100
Dosage form and strength	:	Film-coated tablets. Each film-coated tablet contains dasatinib equal to 20 mg, 50 mg, 70 mg, 80 mg and 100 mg respectively.
Date of submission	:	10 June 2022

3. PHARMACEUTICAL FORM:

FYLIBIX 20 (film-coated tablets):

White to off-white, biconvex, round film-coated tablet with “20” debossed on one side and plain on the other, with a diameter of 6,1 mm ± 5 %.

FYLIBIX 50 (film-coated tablets):

White to off-white, biconvex, oval film-coated tablet with “50” debossed on one side and plain on the other, with dimensions 10,9 mm × 5,8 mm ± 5 %.

FYLIBIX 70 (film-coated tablets):

White to off-white, biconvex, round film-coated tablet with “70” debossed on one side and plain on the other, with a diameter of 8,9 mm ± 5 %.

FYLIBIX 80 (film-coated tablets):

White to off-white, biconvex, triangular film-coated tablet with “80” debossed on one side and plain on the other, with dimensions 10,3 mm × 10,0 mm ± 5 %.

FYLIBIX 100 (film-coated tablets):

White to off-white, biconvex, oval film-coated tablet with “100” debossed on one side and plain on the other, with dimensions 14,8 mm × 7,2 mm ± 5 %.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

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

FYLIBIX 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.

FYLIBIX is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) with resistance or intolerance to prior therapy.

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	Fylibix 20; 50; 70; 80; 100
Dosage form and strength	:	Film-coated tablets. Each film-coated tablet contains dasatinib equal to 20 mg, 50 mg, 70 mg, 80 mg and 100 mg respectively.
Date of submission	:	10 June 2022

4.2 Posology and method of administration:

Posology:

The recommended starting dosage of FYLIBIX for chronic phase CML is 100 mg once daily.

The recommended starting dosage of FYLIBIX for accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL is 70 mg twice daily.

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 adjustment for neutropenia and thrombocytopenia:

Chronic Phase CML (starting dose 100 mg once daily)	ANC* < 0,5 × 10^9 /l or Platelets < 50 × 10^9 /l	1. Stop FYLIBIX until ANC ≥ 1,0 × 10^9 /l and platelets ≥ 50 × 10^9 /l. 2. Resume treatment with FYLIBIX at the original starting dose. 3. If platelets < 25 × 10^9 /l or recurrence of ANC < 0,5 × 10^9 /l for > 7 days, repeat step 1 and resume FYLIBIX 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 FYLIBIX (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 × 10^9 /l or Platelets < 10 × 10^9 /l	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, stop FYLIBIX until ANC ≥ 1,0 × 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 FYLIBIX 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 FYLIBIX 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 initial severity of the event.

Renal impairment:

(See section 5.2)

Hepatic impairment:

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	Fylibix 20; 50; 70; 80; 100
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Date of submission	:	10 June 2022

(See section 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 dasatinib in patients < 18 years of age have not been established.

Method of administration:

FYLIBIX film-coated tablets are to be administered orally. FYLIBIX film-coated tablets can be taken with or without a meal and should be taken consistently either in the morning or evening.

FYLIBIX film-coated tablets should not be crushed or cut; they should be swallowed whole.

4.3. Contraindications:

- FYLIBIX is contra-indicated in patients with hypersensitivity to dasatinib or to any of the excipients listed in section 6.1.
- The concomitant use of H_2 antagonists or proton pump inhibitors with FYLIBIX 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 medicinal products that are metabolised primarily by or modulate the activity of CYP3A4 (see section 4.5).

Concomitant use of FYLIBIX and medicinal products 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 FYLIBIX and medicinal products 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 FYLIBIX, coadministration of alternative medicinal products with less potential for CYP3A4 induction should be selected (see section 4.5).

Concomitant use of FYLIBIX and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when FYLIBIX is coadministered with CYP3A4 substrates of narrow therapeutic index, such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) (see section 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 FYLIBIX to patients with hepatic impairment.

Important adverse reactions:

Myelosuppression:

Treatment with FYLIBIX is associated with anaemia, neutropenia and thrombocytopaenia. 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 FYLIBIX 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 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 temporarily or by dose reduction.

Bleeding:

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 patient with advanced phase CML. Most bleeding related adverse reactions in these patients were typically associated with grade 3 or 4 thrombocytopaenia (see section 4.8). Additionally, in vitro and in vivo platelet assays suggest that FYLIBIX treatment reversibly affects platelet activation.

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

Fluid retention:

FYLIBIX is associated with fluid retention.

Patients who develop symptoms suggestive of pleural effusion such as dyspnoea or dry cough should be evaluated by chest X-ray. Grade 3 or 4 pleural effusion may require thoracocentesis and oxygen therapy. Fluid retention adverse reactions were typically managed by supportive care measures that include

diuretics and short courses of steroids (see section 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):

PAH (pre-capillary pulmonary arterial hypertension confirmed by right heart catheterization) has been reported in association with dasatinib treatment (see section 4.8). In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib therapy. An echocardiography should be performed at treatment initiation in every patient presenting symptoms of cardiac disease and considered in patients with risk factors for cardiac or pulmonary disease. Patients who develop dyspnoea and fatigue after initiation of therapy should be evaluated for common etiologies including pleural effusion, pulmonary oedema, anaemia, or lung infiltration. In accordance with recommendations for management of non-haematologic adverse reactions (see section 4.2) the dose of dasatinib should be reduced or therapy interrupted during this evaluation. If no explanation is found, or if there is no improvement with dose reduction or interruption, the diagnosis of PAH should be considered. The diagnostic approach should follow standard practice guidelines. If PAH is confirmed, dasatinib 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 dasatinib therapy.

QT Prolongation:

FYLIBIX should be administered with caution to patients who have or may develop prolongation of QTc. These including patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicinal products or other medicinal products which lead to

QT prolongation, and cumulative high dose anthracycline therapy. Hypokalaemia or hypomagnesaemia should be corrected prior to FYLIBIX administration.

Cardiac adverse reactions:

The cardiac adverse reactions of congestive heart failure/cardiac dysfunction, pericardial effusion, dysrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) have been 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, physicians are advised to interrupt dasatinib 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 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.

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 dasatinib, treatment with dasatinib 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 FYLIBIX should not be resumed.

Hepatitis B reactivation:

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with FYLIBIX. 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 should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

FYLIBIX contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance total lactose deficiency or glucose-galactose malabsorption should not take FYLIBIX.

4.5. Interaction with other medicines and other forms of interaction:

Active substance that may increase dasatinib plasma concentrations:

Concomitant use of FYLIBIX and medicinal products 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. 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 approximately 96 % on the basis of *in vitro* experiments. No studies have been performed to evaluate dasatinib interaction with other protein-bound medicinal products. The potential for displacement and its clinical relevance are unknown.

Active substance 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 medicinal products 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 medicinal products 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. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving FYLIBIX therapy (see section 4.4).

Antacids:

Non-clinical data demonstrate that the solubility of dasatinib is pH-dependent. When antacids were administered 2 hours prior to a single dose of dasatinib, 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 FYLIBIX. Simultaneous administration of FYLIBIX with antacids should be avoided.

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

Concomitant use of FYLIBIX and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. 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 [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving FYLIBIX (see section 4.4)

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

Simvastatin:

Single dose data 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.

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:

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

Pregnancy:

Based on human experience, dasatinib is suspected to cause congenital malformations including neural tube defects, and harmful pharmacological effects on the foetus when administered during pregnancy. FYLIBIX should not be used during pregnancy unless the clinical condition of the women requires treatment with dasatinib. If FYLIBIX is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breast-feeding:

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.

Breast-feeding should be stopped during treatment with FYLIBIX.

Fertility:

Medical practitioner and other healthcare providers should counsel male patients of appropriate age about possible effects of dasatinib 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. Patients should be advised that they may experience adverse reactions such as dizziness or blurred vision during treatment with dasatinib. 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, thrombocytopaenia) febrile neutropenia, pancytopenia
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	anorexia, 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, neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
Less Frequent	CNS bleeding*[b], syncope, tremor, amnesia, balance disorder cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia
Eye disorders:	
Frequent	visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
Less Frequent	visual impairment, conjunctivitis, photophobia, lacrimation increased
Ear and labyrinth disorders:	
Frequent	tinnitus
Less Frequent	hearing loss, vertigo
Cardiac disorders:	
Frequent	congestive heart failure/cardiac dysfunction*[c], pericardial effusion*, arrhythmia (including tachycardia), palpitations

Less Frequent	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular arrhythmia (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, embolism, livedo reticularis
Frequency unknown	thrombotic microangiopathy
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

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Frequency unknown	interstitial lung disease
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*
Hepatobiliary disorders:	
Less Frequent	hepatitis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders:	
Frequent	skin rash[e], alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
Less Frequent	Acute febrile, neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysaesthesia 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	gynecomastia, menstrual disorder, irregular menstruation
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, temperature intolerance
Investigations:	
Frequent	weight decreased, weight increased
Less Frequent	blood creatine phosphokinase increased, gamma-glutamyltransferase increased

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, haemorrhage intracranial, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.

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

[d] Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions 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 psoriaisis, 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] 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 or to concomitant medicinal product.

[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 on selected adverse reactions 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 Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via patientsafety.sacg@novartis.com

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Date of submission	:	10 June 2022

4.9. Overdose:

The highest 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 dose should be closely monitored for myelosuppression and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

***Category and class*:** A 26 Cytostatic agents

***Pharmacotherapeutic group*:** antineoplastic agents, protein kinase inhibitors.

***ATC code*:** L01XE06

Pharmacodynamics:

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 is a potent, subnanomolar inhibitor of the BCR-ABL kinase with potency at 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 leukaemic cell lines representing variants of imatinib-sensitive and resistant disease. These 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 modules 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 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 a high-fat meal indicated a 14 % increase in the mean AUC of dasatinib. A low-fat meal 30 minutes prior to dasatinib resulted in a 21 % increase in the mean AUC of dasatinib. The observed food effects do not represent clinically relevant changes in exposure. 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 interoccasion 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- ccasion variability in exposure is not expected to affect the cumulative exposure and efficacy or safety.

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	Fylibix 20; 50; 70; 80; 100
Dosage form and strength	:	Film-coated tablets. Each film-coated tablet contains dasatinib equal to 20 mg, 50 mg, 70 mg, 80 mg and 100 mg respectively.
Date of submission	:	10 June 2022

Distribution:

In patients, dasatinib has a large apparent volume of distribution (2,505 L), coefficient of variation (CV % 93 %), suggesting that the medicinal product 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.

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.

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	Fylibix 20; 50; 70; 80; 100
Dosage form and strength	:	Film-coated tablets. Each film-coated tablet contains dasatinib equal to 20 mg, 50 mg, 70 mg, 80 mg and 100 mg respectively.
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Hepatic impairment:

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

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Cellulose, Microcrystalline (E460)

Lactose Monohydrate

Croscarmellose Sodium

Hydroxypropylcellulose (E463)

Magnesium Stearate (E470b)

Poly (Vinyl Alcohol) (E1203)

Titanium Dioxide (E171)

Talc (E553b)

Glyceryl Monostearate (E471)

Sodium Laurilsulfate

6.2. Incompatibilities:

Not applicable.

6.3. Shelf life:

36 months

6.4. Special precautions for storage:

Store at or below 30 °C.

This medicine does not require any special storage conditions.

6.5. Nature and contents of container:

FYLIBIX 20, 50, 70, 80-and 100 mg film-coated tablets are packed in Aluminium-OPA/Alu/PVC blisters or in High Density Polyethylene (HDPE) bottles with plastic (HDPE) canister containing silica gel.

Aluminium-OPA/Alu/PVC blisters, consist of:

- an OPA/Alu/PVC forming foil consisting of aluminium layer coated with oriented polyamide (OPA) film on one side and polyvinyl chloride (PVC) film on the other side.
- an aluminium sealing foil.

HDPE bottles are white, plastic containers with screwed mouth that are stoppered with a white, plastic, child resistant cap.

Pack sizes:

The available pack sizes are 30's and 60's.

Not all pack sizes are marketed.

The blister packs are packed into an outer cardboard carton.

6.6. Special precautions for disposal and other handling:

The film-coated tablets consist of a core tablet, surrounded by a film coating to prevent exposure of healthcare professionals to the active substance. 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	Fylibix 20; 50; 70; 80; 100
Dosage form and strength	:	Film-coated tablets. Each film-coated tablet contains dasatinib equal to 20 mg, 50 mg, 70 mg, 80 mg and 100 mg respectively.
Date of submission	:	10 June 2022

Jukskei View

2090

8. REGISTRATION NUMBERS:

FYLIBIX 20: To be allocated by SAHPRA upon registration

FYLIBIX 50: To be allocated by SAHPRA upon registration

FYLIBIX 70: To be allocated by SAHPRA upon registration

FYLIBIX 80: To be allocated by SAHPRA upon registration

FYLIBIX 100: To be allocated by SAHPRA upon registration

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

Date of first authorisation: To be allocated by SAHPRA upon registration

10. DATE OF REVISION OF THE TEXT:

Not applicable.

[1]Company Reg. No.: 1990/001979/07