Applicant : Eurolab (Pty) Ltd
Proprietary name : Mivesta 100 mg & 400 mg
Dosage form and strength : Film-coated tablets
Date of submission : 26 January 2023
Approval date : 13 January 2023

APPROVED PROFESSIONAL INFORMATION FOR

MIVESTA

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MIVESTA 100 (film-coated tablets)

MIVESTA 400 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MIVESTA 100: Each film-coated tablet contains imatinib mesilate equivalent to 100 mg imatinib

MIVESTA 400: Each film-coated tablet contains imatinib mesilate equivalent to 400 mg imatinib

MIVESTA tablets are sugar free.

3 PHARMACEUTICAL FORM

MIVESTA 100: Brownish orange, round, biconvex, film-coated tablets, debossed with 'IM' and 'T1' on either side of the score and plain on the other side.

MIVESTA 400: Brownish orange, oval shaped, biconvex, film-coated tablets, debossed with 'IM' and 'T2' on either side of the score and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML).
- Adult and paediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- Adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with systemic mastocytosis (SM) without the D816V c-Kit mutation and eosinophilia.
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.
- Adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

4.2 Posology and method of administration

Therapy should be initiated by a medical practitioner experienced in the treatment of patients with chronic myeloid leukaemia or GIST respectively.

The prescribed dose should be administered orally, once daily with a meal and a large glass of water, to minimize the risk of gastrointestinal disturbances. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the

appropriate volume of beverage (approximately 50 ml for a 100 mg tablet, and 200 ml for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Adult Dosage in CML

The recommended dosage of **MIVESTA** is 400 mg daily for patients in chronic phase CML and 600 mg daily for patients in accelerated phase or blast crisis. Treatment should be continued as long as the patient continues to benefit.

Dose increase from 400 mg to 600 mg or to 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg (given as 400 mg twice daily) in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reactions and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenic response after 12 months or treatment; or loss of a previously achieved haematological response and/or cytogenic response.

Dosage for CML in children

Dosing in children should be on the basis of body surface area (mg/m^2). The dose 340 mg/m^2 daily is recommended for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose or alternatively the daily dose may be split into two administrations – one in the morning and one in the evening. There is no experience with the use of **MIVESTA** in children under the age of 2 years.

Dosage in Ph+ ALL

The recommended dose of **MIVESTA** is 600 mg daily for patients with Ph+ ALL.

Dosage in MDS/MPD

The recommended dose of **MIVESTA** is 400 mg daily for patients with MDS/MPD.

Dosage in SM

For patients with SM associated with eosinophilia, a clonal haematological disease related to the fusion kinase FIP1L1-PDGFRa, a starting dose of 100 mg daily is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Dosage in HES/CEL

For HES/CEL patients with demonstrated FIP1L1-PDGFRa fusion kinase, a starting dose of 100 mg daily is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of side effects if assessments demonstrate an insufficient response to therapy.

Dosage in GIST

The recommended dose of **MIVESTA** is 400 mg daily for patients with unresectable and/or metastatic, malignant GIST. A dose increase from 400 mg to 600 mg or 800 mg for patients may be considered in the absence of side effects if assessments demonstrate an insufficient response to therapy.

Treatment with **MIVESTA** in GIST patients should be continued until disease progression.

Dosage in DFSP

The recommended dose of **MIVESTA** is 800 mg daily for patients with DFSP.

Dose adjustments for side effects

Non-haematological side effects:

If a severe non-haematological side effect develops with **MIVESTA** use, treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin > 3 x institutional upper limit of normal (IULN) or in liver transaminases > 5 x IULN occur, **MIVESTA** should be withheld until bilirubin levels have returned to a < 1,5 x IULN and transaminase levels to < 2,5 x IULN. Treatment with **MIVESTA** may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg or from 600 to 400 mg, or from 800 mg to 600 mg and in children from 340 to 260 mg/m^2 daily.

Haematological side effects:

Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below

Dose adjustments for neutropenia and thrombocytopenia:

SM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1,0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop **MIVESTA** until ANC ≥ 1,5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with **MIVESTA** at previous dose (i.e. before severe side effect).
Chronic phase CML, MDS/MPD, SM, HES/CEL and GIST (starting dose 400 mg)	ANC < 1,0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop **MIVESTA** until ANC ≥ 1,5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with **MIVESTA** at previous dose (i.e. before severe side effect). 3. In the event of recurrence of ANC < 1,0 x 10^9/l and/or < 50 x 10^9/l, repeat step 1 and resume **MIVESTA** at reduced dose of 300 mg.

Paediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1,0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop **MIVESTA** until ANC ≥ 1,5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with **MIVESTA** at previous dose (i.e. before severe side effect). 3. In the event of recurrence of ANC < 1,0 x 10^9/l and/or < 50 x 10^9/l, repeat step 1 and resume **MIVESTA** at reduced dose of 260 mg.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg [c])	[a]ANC < 0,5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of **MIVESTA** to 400 mg [b]. 3. If cytopenia persists for *2* weeks, reduce further to 300 mg [d]. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop **MIVESTA** until ANC 1,0 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 300 mg [d].
DFSP (starting dose 800 mg)	ANC < 1,0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop **MIVESTA** until ANC ≥ 1,5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with **MIVESTA** at 600 mg 3. In the event of recurrence of ANC < 1,0 x 10^9/l and/or < 50 x 10^9/l, repeat step 1 and resume **MIVESTA** at reduced dose of 400 mg.

ANC = absolute neutrophil count

[a] Occurring after at least 1 month of treatment

[b] 260 mg/m^2 in children

[c] 340 mg/m^2 in children

[d] 200 mg/m^2 in children.

Special Populations:

Children

There is very limited experience with the use of **MIVESTA** in children for other indications.

Hepatic insufficiency

MIVESTA is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if the patient develops unacceptable toxicity (see section 4.4 and section 5.2).

Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidney. However, in severe renal insufficiency caution is recommended. Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as a starting dose. The dose can be reduced if not tolerated. If tolerated it can be increased for lack of efficacy.

Elderly patients

No specific dose recommendation is necessary in the elderly.

4.3 Contraindications

Hypersensitivity to imatinib, the metabolite N-demethylated piperazine derivative, or to any of the inactive ingredients of **MIVESTA** (see section 6.1).

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

MIVESTA should be taken with food and a large glass of water to minimise the risk of gastrointestinal disturbances.

When **MIVESTA** is co-administered with other medications, there is a potential for ~~drug~~ medicine interactions (see section 4.5).

Patients with cardiac disease

Patients with cardiac disease, risk factors for cardiac failure or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.

In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding **MIVESTA**.

Myelodysplastic/myeloproliferative diseases with PDGFR gene re-arrangements and systemic mastocytosis, might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or SM associated with high eosinophil levels before imatinib is administered. If either is abnormal, follow-up with a cardiology specialist and the prophylactic use of systemic steroids (1 – 2 mg/kg) for one to two weeks concomitantly with **MIVESTA** should be considered at the initiation of therapy.

Ischaemic Central Nervous System Reactions

Cerebrovascular adverse events identified as class related adverse events, have occurred in patients treated with tyrosine kinase inhibitors, such as **MIVESTA**. These cerebrovascular adverse events are cerebrovascular accident (CA), transient ischaemic attack (TIA), ischaemic stroke (IS), and cerebral infarction (CI).

These cerebrovascular events may occur in patients on treatment with **MIVESTA** with or without risk factors for these events and may occur at any time during treatment with **MIVESTA**.

Patients on treatment with **MIVESTA** should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events. Treatment with **MIVESTA** should be discontinued, and alternative treatment options be considered in patients who develop these class related cerebrovascular adverse events.

Hepatotoxicity

Metabolism of **MIVESTA** is mainly hepatic, and only 13 % of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections 4.2 and 5.2). It should be noted that GIST patients may have hepatic metastases which could lead to hepatic impairment.

Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When **MIVESTA** is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia can be observed. Monitoring of liver function is recommended in circumstances where **MIVESTA** is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.8).

Fluid retention

Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ~~and~~ ascites, superficial oedema) have been reported in approximately 2,5 % of newly diagnosed CML patients taking **MIVESTA**. Therefore, it is highly recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if

necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly and cardiac patients. Therefore, caution should be exercised in patients with cardiac dysfunction.

Gastrointestinal haemorrhage

In GIST patients, gastrointestinal (GI) haemorrhage and haemorrhages at the site of tumours were reported (see section 4.8). Patients should therefore be monitored for gastrointestinal symptoms at the start of therapy.

Patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoural haemorrhages were reported (see section 4.8). Based on the available data, no predisposing factors (e.g. tumour size, tumour location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of haemorrhage. Since increased vascularity and propensity for bleeding is a part of the nature and clinical course of GIST, standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied.

In addition, gastric antral vascular ectasia (GAVE), a rare cause of gastrointestinal haemorrhage, has been reported in patients with CML, ALL and other diseases (see section 4.8). When needed, discontinuation of **MIVESTA** treatment may be considered.

Tumour lysis syndrome

Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of **MIVESTA** (see section 4.8).

Hypothyroidism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with **MIVESTA** (see section 4.5). Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.

Laboratory tests

Complete blood counts must be performed regularly during therapy with **MIVESTA**.

Treatment of CML patients with **MIVESTA** has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is dependent on the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with **MIVESTA** may be interrupted or the dose may be reduced, as recommended in section 4.2.

Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving **MIVESTA**.

In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated (see section 4.2).

Long-term treatment with imatinib may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of imatinib therapy and closely monitored during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction. If renal dysfunction is observed, appropriate

management and treatment should be prescribed in accordance with standard treatment guidelines.

As recommended under section 4.2, Non-haematological adverse reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with **MIVESTA.**

MIVESTA and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance is known to decrease with age, and age did not significantly affect **MIVESTA** kinetics.

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 **MIVESTA**. 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 **MIVESTA** 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).

Phototoxicity

Exposure to direct sunlight should be avoided or minimised due to the risk of phototoxicity associated with imatinib treatment. Patients should be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

Thrombotic microangiopathy

BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA) (see section 4.8). If laboratory or clinical findings associated with TMA occur in a patient receiving **MIVESTA**, treatment 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 **MIVESTA** should not be resumed.

Paediatric population

There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under imatinib treatment is recommended (see section 4.8).

4.5 Interactions with other medicines and other forms of interaction

Medicines that may increase MIVESTA plasma concentrations

- Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. protease inhibitors such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin) could decrease metabolism and increase **MIVESTA** concentrations. There was a significant increase in exposure to **MIVESTA** (the mean C_{max} and AUC of **MIVESTA** rose by 26 % and 40 %, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be taken when administering **MIVESTA** with inhibitors of the CYP3A4 family.

Medicines that may decrease MIVESTA plasma concentrations

- Substances that are inducers of CYP3A4 activity could increase metabolism and decrease **MIVESTA** plasma concentrations. Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or *Hypericum perforatum* (also known as St John's Wort) may significantly reduce exposure to **MIVESTA**. Caution should be taken when administering **MIVESTA** with inhibitors of CYP3A4. Concomitant use of rifampicin or other strong CYP3A4 inducers and imatinib should be avoided.

Medicines that may have their plasma concentration altered by MIVESTA

- **MIVESTA** increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3,5-fold, respectively, indicating an inhibition of the CYP3A4 by **MIVESTA**. Therefore, caution is recommended when administering **MIVESTA** with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). **MIVESTA** may increase plasma concentrations of other CYP3A4 metabolised medicines (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).
- **MIVESTA** also inhibits CYP2C9 and CYP2C19 activity *in vitro*. PT prolongation was observed following co-administration with warfarin. When giving coumarins, short-term PT monitoring is therefore necessary at the start and end of **MIVESTA** therapy and when altering the dosage. Alternatively, the use of low molecular weight heparin should be considered.
- *In vitro*, **MIVESTA** inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is therefore potentially increased when co-administered with **MIVESTA**. No specific studies have been performed however and caution is

recommended. Dose adjustments do not seem to be necessary when imatinib is co-administrated with CYP2D6 substrates, however caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol clinical monitoring should be considered.

- *In vitro*, imatinib inhibits paracetamol O-glucuronidation with Ki value of 58,5 micromol/l. This inhibition has not been observed *in vivo* after the administration of imatinib 400 mg and paracetamol 1000 mg. Higher doses of imatinib and paracetamol have not been studied. Caution should therefore be exercised when using high doses of **MIVESTA** and paracetamol concomitantly.
- In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be decreased when imatinib is co-administered (see section 4.4). Caution is therefore recommended. However, the mechanism of the observed interaction is presently unknown.
- In Ph+ ALL patients, there is clinical experience of co-administering imatinib with chemotherapy (see section 5.1), but medicine-medicine interactions between imatinib and chemotherapy regimens are not well characterised. Imatinib adverse events, i.e. hepatotoxicity, myelosuppression or others, may increase and it has been reported that concomitant use with L-asparaginase could be associated with increased hepatotoxicity (see section 4.8). Therefore, the use of **MIVESTA** in combination requires special precaution.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must be advised to use highly effective contraception during treatment and for at least 15 days after stopping treatment with **MIVESTA** to avoid pregnancy. Use in pregnancy may lead to foetal abortion or malformation.

Pregnancy

MIVESTA should not be taken during pregnancy (see section 4.3).

Breast-feeding

MIVESTA should not be taken when breastfeeding (see section 4.3)

Patients should not breast-feed during treatment and for at least 15 days after stopping treatment with **MIVESTA**. Both imatinib and its active metabolite can be distributed into human milk.

Fertility

Studies on patients receiving imatinib and its effect on fertility and gametogenesis have not been performed. Patients concerned about their fertility on **MIVESTA** treatment should consult with their medical practitioner.

4.7 Effects on ability to drive and use machines

Patients should be advised that they may experience undesirable effects such as dizziness or blurred vision during treatment with **MIVESTA**. Therefore, caution should be recommended when driving a car or operating machinery

4.8 Undesirable effects

a) Summary of the safety profile

Patients with advanced stages of malignancies may have numerous confounding medical conditions that make causality of adverse reactions difficult to assess due to the variety of symptoms related to the underlying disease, its progression, and the co-administration of numerous medicinal products.

More myelosuppression can be seen in CML patients than in GIST, which is probably due to the underlying disease. In patients with unresectable and/or metastatic GIST, CTC grade 3/4 GI bleeds were experienced, intra-tumoural bleeds or both. GI tumour sites may be the source of the GI bleeds (see section 4.4). GI and tumoural bleeding may be serious and sometimes fatal. The most frequently reported medicine-related adverse reactions are mild nausea, vomiting, diarrhoea, abdominal pain, fatigue, myalgia, muscle cramps and rash. Superficial oedemas are a frequent finding and are described primarily as periorbital or lower limb oedemas. However, these oedemas are rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of **MIVESTA**.

When imatinib is combined with high dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of transaminase elevation and hyper bilirubinaemia are observed.

Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as “fluid retention”. These reactions can usually be managed by withholding **MIVESTA** temporarily and with diuretics and other appropriate supportive care measures. However, some of these reactions may be serious or life-threatening, as several patients with blast crisis have died with a complex clinical history of pleural effusion, congestive heart failure and renal failure.

b) Tabulated summary of adverse reactions

System organ class	**All ADRs/Frequency**		
	Frequent	**Less frequent**	**Frequency not known**
Infections and infestations		Sepsis, pneumonia[1], herpes simplex, nasopharyngitis, herpes zoster, upper respiratory tract infection, gastroenteritis,	Hepatitis B reactivation*

		sinusitis, cellulitis, influenza, urinary tract infections, fungal infection	
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Tumour lysis syndrome	Tumour haemorrhage/ tumour necrosis*
Blood and lymphatic system disorders	Neutropenia, thrombocytopenia, anaemia, pancytopenia, febrile neutropenia	Bone marrow depression, eosinophilia, lymphadenopathy, thrombocythaemia, lymphopenia, haemolytic anaemia, thrombotic microangiopathy	
Immune system disorders		Anaphylactic shock	
Metabolism and nutrition disorders	Anorexia	Dehydration, hyperuricaemia, hypokalaemia, increased appetite, decreased appetite, gout, hypophosphataemia, hyperkalaemia, hyponatraemia, hyperglycaemia, hypercalcaemia, hypomagnesaemia	
Psychiatric disorders	Insomnia	Depression, anxiety, decreased libido, confusion	
Nervous system disorders	Headache[2], dizziness, paraesthesia, taste disturbances, hypoaesthesia	Cerebral haemorrhage, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, cerebral oedema, increased intracranial pressure, convulsions, sciatica, restless leg syndrome, tremor, optic neuritis	
Eye disorders	Conjunctivitis, increased	Eye irritation, orbital oedema, macular	

	lacrimation, blurred vision, eyelid oedema, conjunctival haemorrhage, dry eye	oedema, papilloedema, retinal and scleral haemorrhage, vitreous haemorrhage, glaucoma, blepharitis, cataract, eye pain	
Ear and labyrinth disorders		Vertigo, tinnitus, hearing loss	
Cardiac disorders		Congestive cardiac failure[3]/arrest, pulmonary oedema, tachycardia, pericardial effusion, pericarditis, cardiac tamponade, angina pectoris, myocardial infarction, atrial fibrillation, palpitations, arrhythmia	
Vascular disorders[4]	Flushing, haemorrhage	Haematoma, subdural haematoma, hypertension, hypotension, peripheral coldness, thrombosis/ embolism, Raynaud's phenomenon,	
Respiratory system, thoracic and mediastinal disorders	Epistaxis, dyspnoea, cough	Pleural effusion[5], pharyngolaryngeal pain, acute respiratory failure[11], pulmonary fibrosis, interstitial pneumonitis/ lung disease, pharyngitis, pleuritic pain, pulmonary hypertension	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain[6], abdominal distension, flatulence, constipation, gastro-	Gastrointestinal haemorrhage[7], melaena, ascites, gastric ulcer, eructation, colitis, diverticulitis, ileus/ intestinal obstruction, gastrointestinal	

	oesophageal reflux, mouth ulceration, dry mouth, gastritis	perforation, pancreatitis and oropharyngeal pain, colitis, inflammatory bowel disease, gastric antral vascular ectasia (GAVE), cheilitis, stomatitis, oesophagitis, haematemesis, dysphagia	
Hepatobiliary disorders	Increased hepatic enzymes	Jaundice, hepatitis, hyperbilirubinaemia, hepatic failure[8], hepatic necrosis	
Skin and subcutaneous tissue disorders	Periorbital oedema, dermatitis, eczema, rash, face oedema, pruritus, erythema, dry skin, alopecia, night sweats, photosensitivity reaction	Petechiae, contusion, increased sweating, urticaria, onychoclasis, purpura, hypotrichosis, skin hyperpigmentation, skin hypopigmentation, psoriasis, exfoliative dermatitis and bullous eruptions, angioedema, vesicular rash, Stevens-Johnson syndrome, acute febrile neutrophilic dermatosis (Sweet's syndrome), rash pustular, ecchymosis, increased tendency to bruise, folliculitis, nail discolouration, angioneurotic oedema, erythema multiforme, leucocytoclastic vasculitis, acute generalised exanthematous pustulosis (AGEP)	Palmoplantar erythrodysaesthesia syndrome, lichenoid keratosis, lichen planus, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), pseudoporphyria*
Musculoskeletal and connective tissue disorders	Muscle spasm and cramps, musculoskeletal pain, including	Sciatica, joint and muscle stiffness, avascular necrosis/hip	Growth retardation in children

	myalgia[9], arthralgia, bone pain[10], joint swelling	osteonecrosis, muscular weakness, arthritis, rhabdomyolysis/ myopathy	
Renal and urinary disorders		Renal failure acute, renal pain, increased urinary frequency, haematuria	Renal failure chronic
Reproductive system and breast disorders		Gynaecomastia, breast enlargement, scrotal oedema, menorrhagia, nipple pain, sexual dysfunction, erectile dysfunction, menstruation irregular, haemorrhagic corpus luteum/haemorrhagic ovarian cyst	
General disorders and administration site conditions	Fluid retention and oedema, fatigue, pyrexia, weakness, rigors, anasarca, chills	Malaise, haemorrhage, chest pain	
Investigations	Increased weight, decreased weight	Increased blood alkaline phosphatase, increased blood creatinine, increased blood creatine phosphokinase, increased blood lactate dehydrogenase, blood amylase increased	

* Reported mainly from post-marketing experience with Imatinib. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

1 Pneumonia was reported most frequently in patients with transformed CML and in patients with GIST.

2 Headache was the most frequent in GIST patients.

3 On a patient-year basis, cardiac events including congestive heart failure were more frequently observed in patients with transformed CML than in patients with chronic CML.

4 Flushing was most frequent in GIST patients and bleeding (haematoma, haemorrhage) was most frequent in patients with GIST and with transformed CML (CML-AP and CML-BC).

5 Pleural effusion was reported more frequently in patients with GIST and in patients with transformed CML (CML-APand CML-BC) than in patients with chronic CML.

6+7 Abdominal pain and gastrointestinal haemorrhage were most frequently observed in GIST patients.

8 Some fatal cases of hepatic failure and of hepatic necrosis have been reported.

9 Musculoskeletal pain during treatment with imatinib or after discontinuation has been observed post-marketing.

10 Musculoskeletal pain and related events were more frequently observed in patients with CML than in GIST patients.

11 Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions.

Laboratory test abnormalities

Haematology

In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding, with the suggestion of a higher frequency at high doses ≥ 750 mg. However, the occurrence of cytopenias is also clearly dependent on the stage of the disease, the frequency of grade 3 or 4 neutropenias (ANC < 1.0 x 10^9/l) and thrombocytopenias (platelet count < 50 x 10^9/l) being between 4 and 6 times higher in blast crisis and accelerated phase as compared to newly diagnosed patients in chronic phase CML. In newly diagnosed chronic phase CML grade 4 neutropenia (ANC < 0.5 x 10^9/l) and thrombocytopenia (platelet count < 10 x 10^9/l) were observed. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These

events can usually be managed with either a reduction of the dose or an interruption of treatment with **MIVESTA** but can in rare cases lead to permanent discontinuation of treatment. In paediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

In patients with unresectable and/or metastatic GIST, grade 3 and 4 anaemia was reported and may have been related to gastrointestinal or intra-tumoural bleeding in at least some of these patients. Grade 3 and 4 neutropenia and grade 3 thrombocytopenia was seen in patients. No patient developed grade 4 thrombocytopenia. The decreases in white blood cell (WBC) and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.

Biochemistry

Severe elevation of transaminases or bilirubin was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities. In GIST patients, grade 3 or 4 ALT (alanine aminotransferase) elevations and grade 3 or 4 AST (aspartate aminotransferase) elevations were observed. Bilirubin elevation cases was low.

There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of them the outcome was fatal, including one patient on a high dose of paracetamol.

c) Description of selected adverse reactions

Hepatitis B reactivation

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

Severe muscle cramps, elevations of serum creatinine, ascites and elevated liver transaminase levels, and elevations of bilirubin. A general exacerbation of symptoms listed as side effects may be seen in the event of overdosage (see section 4.8).

Events that have been reported at different dose ranges are as follows:

Adult population

- 1200 to 1600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.
- 1800 to 3200 mg (as high as 3200 mg daily for 6 days): Weakness, myalgia, increased creatine phosphokinase, increased bilirubin, gastrointestinal pain.
- 6400 mg (single dose): One case reported in the literature of one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, decreased neutrophil count, increased transaminases.

- 8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

Paediatric population

- With a single dose of 400 mg, a patient may experience vomiting, diarrhoea and anorexia.
- 980 mg (single dose): decreased white blood cell count and diarrhoea.

Treatment

In the event of overdose, patients should be observed, and appropriate symptomatic and supportive treatment given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, BCR-ABL tyrosine kinase inhibitors, ATC code: L01EA01

Imatinib is a protein-tyrosine kinase inhibitor, which inhibits the BCR-ABL (Breakpoint cluster region-abelson) tyrosine kinase at the in vitro cellular and in vivo levels. In vitro, the compound selectively inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukaemic cell cultures from patients with Philadelphia chromosome positive chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL) patients. In colony transformation assays using ex vivo peripheral blood and bone marrow samples, imatinib shows selective inhibition of BCR-ABL positive colonies from CML patients. Imatinib is an inhibitor of the receptor tyrosine kinases for platelet derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.

5.2 Pharmacokinetic properties

The pharmacokinetics of imatinib have been evaluated over a dosage range of 25 to 1000 mg. Plasma pharmacokinetic profiles were analysed on day 1 and on either day 7 or day 28, by which time plasma concentrations had reached steady state.

Absorption

Mean absolute bioavailability is 98 %. The coefficient of variation for plasma imatinib AUC (area under curve) is in the range of 40 – 60 % after an oral dose. When given with a high fat meal, the rate of absorption of imatinib was minimally reduced (11 % decrease in C_{max} and prolongation of T_{max} by 1,5 hours), with a small reduction in AUC (7,4 %) compared to fasting conditions.

Distribution

At clinically relevant concentrations of imatinib, binding to plasma proteins was approximately 95 % on the basis of in vitro experiments, mostly to albumin and alpha-acid-glycoprotein, with little binding to lipoprotein.

Biotransformation

CYP3A4 is the major enzyme responsible for metabolism for imatinib. Other cytochrome P-450 enzymes, such as CYP1A2, CYP2D6, CYP2C9 and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is a N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows in vitro potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15 % of the AUC of imatinib, and the plasma protein binding is similar to that of the parent compound.

Elimination

Elimination is predominantly in the faeces, mostly as metabolites. Based on the recovery of compound(s) after an oral 14C-labelled dose of imatinib, approximately 81 % of the dose was eliminated within 7 days, in faeces (68 % of dose) and urine (13 % of dose). Unchanged imatinib accounted for 25 % of the dose (5 % urine, 20 % faeces), the remainder being metabolites.

Plasma pharmacokinetics

Following oral administration in healthy volunteers, the t½ was approximately 18 hours. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25 – 1000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1,5 – 2,5 fold at steady state when dosed once daily.

Special Patients populations:

Based on population pharmacokinetic analysis, there was a small effect of age on the volume of distribution (12 % increase in patients > 65 years old). This change is not thought to be clinically significant.

The effect of body weight on the clearance of imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8,5 litres/hour, while for a patient weighing 100 kg the clearance will rise to 11,8 litres/hour. These changes are not considered sufficient to warrant dose adjustment based on kg body weight. There is no effect of gender on the kinetics of imatinib.

Pharmacokinetics in children:

Imatinib is rapidly absorbed after oral administration in paediatric patients. Dosing in children at 260 and 340 mg/m2 achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients.

Organ function impairment:

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Exposure to imatinib may be expected to increase if liver function is impaired. Imatinib should be used with caution in patients with liver impairment (see section 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica,

crospovidone,

hypromellose,

magnesium stearate,

microcrystalline cellulose and

Opadry Yellow 03F520050 containing:

hypromellose,

iron oxide yellow,

iron oxide red,

macrogol and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture. Keep blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

MIVESTA film-coated tablets are packed into clear transparent PVC/PVdC-Alu blisters or plain matt finish Alu-Alu blisters, containing 10 tablets per blister.

Pack size: 20, 30 or 60 film-coated tablets per carton.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBERS

MIVESTA 100: 49/26/0742

MIVESTA 400: 49/26/0743

9 DATE OF FIRST AUTHORISATION

30 September 2016

10 DATE OF REVISION OF TEXT

13 January 2023