SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

IMAREM 100, 100 mg film-coated tablet

IMAREM 400, 400 mg film-coated tablet

2. QUALITATIVE AND QUANTITAVIE COMPOSITION:

IMAREM 100: Each film-coated tablet contains 119.5 mg imatinib mesilate equivalent to 100 mg imatinib base

IMAREM 400: Each film-coated tablet contains 478, 00 mg imatinib mesilate equivalent to 400 mg imatinib base

Sugar free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

IMAREM 100: Dark yellow to brownish-orange, round shaped, film-coated tablets with a breakline on one side and ‘100’ on the other side.

IMAREM 400: Dark yellow to brownish-orange, ovaloid shaped film-coated tablets with a breakline on one side and ‘400’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

IMAREM is indicated for:

- Treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML) (for paediatric use, see **sections 4.2**)
- Treatment of adult and paediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy (for paediatric use, (see [**sections 4.2)**
- Treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Treatment of adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Treatment of adult patients with myelodysplastic / myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Treatment of adult patients with systemic mastocytosis (SM) without the D816V c-Kit mutation and eosinophilia.
- Treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1 –PDGFRα rearrangement.
- Treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

The effectiveness of **IMAREM** is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological arid cytogenetic response rates in Ph + ALL, MDS/MPD, on haematological response rates in SM,

HES/CEL, and on objective response rates in DFSP (see **section 5**). Increased survival has been demonstrated only in newly diagnosed chronic phase CML.

4.2 Posology and method of administration

Therapy should be initiated by a medical practitioner experienced in the treatment of patients with malignancies.

The prescribed dose should be administered orally with a meal and a large glass of water. 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).

Dosage in CML:

The recommended dosage of **IMAREM** is 400 mg/day for patients in chronic phase CML and 600 mg/day 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 daily in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse medicine reaction and severe non-leukaemia related neutropaenia or thrombocytopaenia 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 of treatment; or loss of a previously achieved haematological and /or cytogenic response.

Dosing in children should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with chronic phase and advanced phase CML (not to exceed the total dose of 600mg 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 imatinib as in **IMAREM** in children under 2 years of age.

Dosage in Ph+ ALL:

The recommended dose of **IMAREM** is 600 mg./day for patients with Ph+ ALL.

***Dosage In MDS/MPD*:**

The recommended dose of **IMAREM** is 400 mg/day for patients with MDS/MPD

Dosage in SM*:*

For patients with SM associated with eosinophilia, a clonal haematological disease related to the fusion kinase FIPlL1-PDGFRα, a starting dose of 100 mg/day is recommended. A dose increase from 100 mg: to 400 mg for these patients may be considered in the absence of adverse medicine reactions if assessments demonstrate an insufficient response to therapy.

Dosage in HES/CEL

For HES/CEL patients with demonstrated FIPlL1 -PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. A dose increase from 100 mg to 400 mg for these

patients may be considered in the absence of adverse medicine reactions if assessments demonstrate an insufficient response to therapy.

Dosage in DFSP

The recommended dose of **IMAREM** is 800 mg/day for patients with DFSP.

Dose adjustments for adverse reactions*:*

Non-haematological adverse reactions:

If a severe non-haematological adverse reaction develops with **IMAREM** 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, **IMAREM** should be withheld until bilirubin levels have returned to a < l ,5 x IULN and transaminase levels to < 2.5 x IULN.

Treatment with **IMAREM** 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/day.

Haematological adverse reactions**:**

Dose reduction or treatment interruption for severe neutropaenia and thrombocytopaenia are recommended as indicated in the table below.

Dose adjustments for neutropaenia and thrombocytopaenia:

SM associated with eosinophilia and HES/CEL with FIP1L1-PDGFR α fusion kinase (starting dose 100 mg)	ANC < 1,0 x 10^9 /L and/ or platelets < 50 x 10^9 /L	1. Stop **IMAREM** until ANC ≥ 1,5 x 10^9 /L and platelets ≥ 75 x 10^9 /L 2. Resume treatment with **IMAREM** at previous dose (i.e. before severe adverse reaction)
Chronic phase CML, MDS/MPD, SM, HES/CEL (starting dose 400 mg	ANC < 1,0 x 10^9 /L and/ or platelets < 50 x 10^9 /L	1. Stop **IMAREM** until ANC ≥ 1,5 x 10^9 /L and platelets ≥ 75 x 10^9 /L 2. Resume treatment with **IMAREM** at previous dose (i.e. before severe adverse reaction) 3. In the event of a recurrence of ANC < 1,0 x 10^9 /L and /or platelets < 50 x 10^9 /L repeat step 1 and

		resume **IMAREM** 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 **IMAREM** until ANC ≥ 1,5 x 10^9 /L and platelets ≥ 75 x 10^9 /L 2. Resume treatment with **IMAREM** at previous dose (i.e. before severe adverse reaction) 3. In the event of a recurrence of ANC < 1,0 x 10^9 /L and /or platelets < 50 x 10^9 /L repeat step 1 and resume **IMAREM** at reduced dose of 260 mg/m^2
Accelerated phase CML and blast crisis and	ANC < 0, 5 x 10^9 /L and/ or platelets < 10 x	1.Check whether cytopaenia is related to

Ph + ALL (starting dose 600 mg or 340 mg/m^2 in children)	10^9 /L. (occurring after at least 1 month of treatment)	leukaemia (marrow aspirate or biopsy) 2.If cytopaenia is unrelated to leukaemia, reduce the dose of **IMAREM** to 400 mg (or 260 mg/m^2 in children) 3.If Cytopaenia persists for 2 weeks, reduce further to 300 mg (or 200 mg/m^2 in children) 4.If cytopaenia persists for 4 weeks and is still unrelated to leukaemia, stop **IMAREM** until ANC is 1 x 10^9 /L and / or platelets ≥ 20 x 10^9 /L then resume treatment at 300 mg (or 200 mg/m^2 in children)
DFSP (starting dose 800 mg)	ANC < 1,0 x 10^9 /L and/ or	1. Stop **IMAREM** until ANC ≥ 1,5 x 10^9 /L and platelets ≥ 75 x 10^9 /L

	platelets < 50 x 10^9 /L	2. Resume treatment with **IMAREM** at 600 mg 3. In the event of a recurrence of ANC < 1,0 x 10^9 /L and /or platelets < 50 x 10^9 /L repeat step 1 and resume **IMAREM** at reduced dose of 400 mg

ANC = absolute neutrophil count.

Paediatric Use

There is no experience with the use of imatinib as in **IMAREM** in children with CML below 2 years of age. There is very limited experience with the use of imatinib as in **IMAREM** in children below 3 years of age in other indications.

Hepatic insufficiency

Imatinib as in **IMAREM** 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 not tolerated (see **Sections 4.4, 4.8 and 5.2**).

Renal insufficiency

Imatinib as in **IMAREM** and its metabolites are not significantly excreted via the kidney. Since the renal clearance of imatinib as in **IMAREM** is negligible, a decrease in free drug clearance is not expected in patients with renal insufficiency. Patients with mild or moderate renal dysfunction should be given the minimum recommended dose of 400 mg daily as starting dose. The dose can be reduced if not tolerated or increased for lack of efficacy (see **Section 4.4**). There are insufficient data on patients with chronic renal failure or on dialysis to make a dose recommendation.

Elderly

No significant age-related pharmacokinetic differences have been observed in adult patients in clinical trials, which included over 20 % of patients age 65 and older. No specific dose recommendation is necessary in the elderly.

Method of administration

IMAREM should be taken orally with food and a large glass of water to minimise the risk of gastrointestinal disturbances (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active ingredient, imatinib, or to any of the excipients of **IMAREM** listed in **section 6.1**.

Safety in pregnancy and lactation has not been established. (see section 4.6)

4.4 Special warnings and precautions for use

Cerebrovascular adverse events identified as class related adverse events have occurred in patients treated with TKI containing medicines such as **IMAREM**. These adverse events include cerebrovascular accident (CA), transient ischaemic attack (TIA), ischaemic stroke (IS), and cerebral infarct (CI). These events may occur in patients on treatment, with or without risk factors and may occur at any time during treatment. Patients on treatment should be carefully monitored and relevant risk factors managed to reduce the risk of these cerebrovascular adverse events. Treatment with **IMAREM** should be discontinued, and alternative treatment options be considered in patients who develop these class related adverse events.

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

When imatinib as in **IMAREM** is co-administered with other medications, there is a potential for medicine interactions (see section 4.5)

Special caution should be exercised when using paracetamol, as it may increase the risk of liver damage. (see section 4.5).

Hypothyroidism:

Hypothyroidism may occur in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib as in IMAREM. Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients (see section 4.5).

Hepatotoxicity:

Metabolism of IMAREM occurs mainly via the liver. Patients with hepatic dysfunction (mild, moderate, or severe) must have their peripheral blood counts and liver enzymes carefully monitored (see sections 4.2, 4.8 and 5.2).

Cases of liver injury, including liver failure and liver necrosis, have been reported with imatinib as in **IMAREM**.

It has been reported that when imatinib as in **IMAREM** is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia has been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended in circumstances where imatinib as in **IMAREM** 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, ascites, and superficial oedema) have been reported in newly diagnosed CML patients taking imatinib as in **IMAREM**. Therefore, it is 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. It has been reported that there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease.

Patients with cardiac disease:

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

In patients with hypereosinophilicsyndrome(HES) and cardiac involvement isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib as in **IMAREM** therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib as in **IMAREM.**

Myelodysplastic/myeloproliferative diseases 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/GEL, and in patients with MDS/MPD or SM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with imatinib as in IMAREM should be considered at the initiation of therapy.

Gastrointestinal haemorrhage:

Gastric antral vascular ectasia (GAVE), a cause of gastrointestinal haemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases (see section 4.8). When needed, discontinuation of **IMAREM** treatment may be considered.

Laboratory tests:

- Complete blood counts must be performed regularly during therapy with **IMAREM**. Treatment of CML patients with **IMAREM** has been associated

with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is likely to be related to 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 IMAREM 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 **IMAREM.** These laboratory abnormalities should be managed with Interruption and/or dose reduction of the treatment with imatinib as in **IMAREM**.
- Imatinib as in **IMAREM** and its metabolites are excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect imatinib kinetics (see section 5).
- Renal impairment: 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 and 5.2).

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.

Tumour lysis syndrome

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

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. An increase in the viral load or positive serology occurred upon HBV reactivation.

Patients should be tested for HBV infection before initiating treatment with imatinib as in **IMAREM**. Patients already on treatment with **IMAREM** should be tested for hepatitis B infection in order to identify chronic carriers of the virus.

Expert medical practitioners experienced in oncology and hepatology 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 **IMAREM** should be counselled and 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 as in **IMAREM** 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), including individual case reports for imatinib as in **IMAREM** (see **section 4.8**). If laboratory or clinical findings associated with TMA occur in a patient receiving **IMAREM,** 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 **IMAREM** should not be resumed.

Paediatric population

There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib as in **IMAREM**. Close monitoring of growth in children under imatinib treatment is recommended (see **section 4.8**).

4.5 Interaction with other medicines and other forms of interaction

*The following medicines may increase **imatinib as in IMAREM** plasma concentrations:*

Medicines that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. azole antifungals such as ketoconazole, itraconazole, macrolides such as erythromycin, clarithromycin and protease inhibitors such as indinavir, lopinavir/ritonavir, ritonavir, telaprevir, nelfinavir, boceprevir) could decrease metabolism and increase imatinib concentrations. Caution should be taken when administering **IMAREM** with inhibitors of the CYP3A4 family.

*The following medicines that may decrease imatinib as in **IMAREM** plasma concentrations:*

Medicines that are inducers of CYP3A4 activity could increase metabolism and decrease imatinib plasma concentrations. Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine. rifampicin, phenobarbitone or hypericum perforatum (also known as St. John's Wort) may significantly reduce exposure to imatinib as in **IMAREM.** Patients with malignant gliomas treated with IMAREM while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenyloin, phenobarbital, and primidone may experience a decrease in concentration levels of imatinib as in **IMAREM**, compared to patients not on (EIAEDs). In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

*Medicines that may have their plasma concentration altered by imatinib as in **IMAREM*****:***

Imatinib as in **IMAREM** increases the mean Cmax and AUC of CYP3A4 substrates.

Therefore, caution is recommended when administering imatinib as in **IMAREM** with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin, simvastatin or pimozide).

Imatinib as in **IMAREM** may increase plasma concentration of other CYP3A4 metabolised medicines (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.)

Imatinib as in **IMAREM** also inhibits CYP2C9 and CYP2Cl9 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 **IMAREM** therapy and when altering the dosage. Alternatively, the use of low - molecular weight heparin should be considered.

In vitro, Imatinib as in **IMAREM** inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. **IMAREM** at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol GI metabolism. with metoprolol C_{max} and AUC being increased by approximately 23%. Co-administration of imatinib as in **IMAREM** with CYP2D6 substrates, such as metoprolol, does not seem to be a risk factor for drug-drug interactions and dose adjustment may not be necessary.

In vitro, imatinib as in **IMAREM** inhibits paracetamol 0-glucuronidation (Ki value of 58, 5 micromol/I at therapeutic levels) see **section 4.5**).

Concomitant use of levothyroxine and **IMAREM** may result in plasma exposure to levothyroxine being decreased in thyroidectomy patients, therefore caution is recommended (see section 4.4).

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential/Contraception in males and females

Women of child- bearing potential must be advised to use effective contraception during treatment. (see **section 4.3**).

Contraceptive measures must be taken during treatment and for at least three months after cessation of **IMAREM t**herapy for men and at least six months after cessation of **IMAREM** therapy for women.

Pregnancy

Safety in pregnancy has not been established (See **Section 4.3**). Studies in animals have shown reproductive toxicity.

Breastfeeding

Safety in lactation has not been established (See **Section 4.6**).

Women taking **IMAREM** should not breastfeed.

Fertility

In non-clinical studies in rats, the fertility of male and female species was not affected (see section 5.3). Studies on patients receiving imatinib and its effect on fertility and gametogenesis have not been performed. Patients concerned about their fertility on **IMAREM** 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, somnolence, or blurred vision during treatment with **IMAREM**. Therefore, patients should not drive or operate machines, until they know how treatment with **IMAREM** affects them (see section 4.8).

4.8 Undesirable effects

a) CNS effects associated with tyrosine kinase inhibitors.

Cerebrovascular adverse events identified as class related adverse events have occurred in patients treated with TKI containing medicines. These class related cerebrovascular adverse events, shared to a variable degree by all TKIs, 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 TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

Table 1: Ischaemic Central Nervous System Vascular Condition Associated with Imatinib- a tyrosine kinase inhibitor

Drug	Period	Cases	Cerebro-vascular accident	Transient ischaemic attack	Cerebral infarction	Ischaemic stroke
Imatinib	2002 till 6/3/2020	464	277	44	71	18

- Cerebrovascular adverse events (mentioned in table above) may occur in patients on treatment with TKI containing medicines with or without risk factors for these events and may occur at any time during treatment with TKIs.
- Patients on treatment with TKI containing medicine should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.
- Treatment with TKI containing medicines should be discontinued, and alternative treatment options be considered in patients who develop these class related cerebrovascular adverse events.

Tabulated summary of Adverse reactions:

MedDRA System organ classification	**Frequent**	**Less Frequent**
Infections and infestations:		Sepsis, pneumonia, herpes simplex, herpes zoster, nasopharyngitis, upper respiratory tract infection, gastroenteritis, sinusitis, cellulitis influenza urinary tract infection, fungal infection
Neoplasm benign, malignant and		Tumour lysis syndrome

unspecified (including cysts and polyps)		
Blood and lymphatic system disorders:	Neutropenia, thrombocytopaenia, anaemia, febrile neutropenia, pancytopenia	Thrombocythemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy, haemolytic anaemia, thrombotic microangiopathy
Metabolism and nutrition disorders:	Anorexia	Dehydration, hyperuricaemia, hypokalaemia, increased appetite, decreased appetite, gout, hypophosphatemia, hypercalcaemia, hyperglycaemia, hyponatraemia, hyperkalaemia, hypomagnesaemia
Psychiatric disorders	Insomnia	Depression, anxiety, decreased libido, confusion
Nervous system disorders:	Headache***,*** dizziness, taste disturbances, paraesthesia, hypoaesthesia	Cerebral haemorrhage, syncope, peripheral neuropathy, somnolence, migraines, memory

		impairment, sciatica, restless leg syndrome, tremor. optic neuritis, increased intracranial pressure, convulsions
Eye disorders:	Conjunctivitis, increased lacrimation, blurred vision, eyelid oedema, conjunctival haemorrhage, dry eye	Eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema, cataract, papilloedema, glaucoma
Ear and Labyrinth disorders:		Vertigo, tinnitus, hearing loss
Cardiac disorders:		Cardiac failure, congestive pulmonary oedema, palpitations, tachycardia, pericardial effusion, dysrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris

Vascular disorder:	Flushing haemorrhage	Haematoma, subdural haematoma, hypertension, hypotension, peripheral coldness, Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders:	Epistaxis, dyspnoea, cough	Pleural effusion, pharyngo-laryngeal pain, pharyngitis, pulmonary fibrosis, pleuritic pain, pulmonary hypertension, pulmonary haemorrhage
Gastrointestinal disorders:	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, abdominal distension, flatulence, constipation, gastro-oesophageal reflux, dry mouth, gastritis	Gastrointestinal haemorrhage, eructation. melaena, oesophagitis, ascites, gastric ulcer, mouth ulceration, stomatitis, haematemesis, cheilitis, dysphagia, pancreatitis, colitis, ileus. inflammatory bowel disease

Hepato- biliary disorders	Increased hepatic enzymes	Jaundice, hepatitis, hyperbilirubinemia, hepatic failure, hepatic necrosis.
Skin and subcutaneous tissue disorders:	Periorbital oedema, dermatitis/ eczema/rash, face oedema, pruritus, erythema, dry skin, alopecia, night sweats, photosensitivity reaction.	Rash pustular, petechiae, contusion, increased sweating, urticarial, ecchymosis, increased tendency to bruise, onychoclasis, folliculitis, purpura, hypotrichosis, skin hyperpigmentation, psoriasis, exfoliative dermatitis and bullous eruptions, nail discolouration, vesicular rash, Stevens-Johnson syndrome, acute febrile neutrophilic dermatosis (Sweets Syndrome), erythema multiforme, leucocytoclastic vasculitis. acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, connective tissue and bone disorders:	Muscle spasm and cramps, musculoskeletal pain, including myalgia,	Joint and muscle stiffness, muscular weakness, arthritis. rhabdomyolysis/myopathy.

	arthralgia, bone pain, joint swelling	
Renal and urinary disorders		Renal failure, renal pain increased urinary frequency, haematuria
Reproductive system and breast disorders		Gynaecomastia, erectile dysfunction, breast enlargement, scrotal oedema, menorrhagia, menstruation irregular, nipple pain, sexual dysfunction. haemorrhagic corpus luteum/haemorrhagic ovarian cyst
General Disorders and administration site conditions	Fluid retention and oedema, fatigue, pyrexia, weakness, rigors, anasarca, chills	Malaise, chest pain
Investigations:	Increased weight, weight decreased	Increased blood alkaline phosphatase, increased blood creatine, increased blood creatine

	phosphokinase, increased blood lactate dehydrogenase, Blood amylase increased

Tabulated results from undesirable effects from post-marketing reports

Infections and infestations	Hepatitis B reactivation
Neoplasm benign, malignant and unspecified (including cysts and polyps)	Tumour haemorrhage/tumour necrosis
Nervous system disorders	Cerebral oedema
Immune system disorders	anaphylactic shock
Eye disorders	Vitreous haemorrhage
Cardiac disorders	Pericarditis, cardiac tamponade
Vascular disorders	Thrombosis/embolism,
Respiratory, thoracic and mediastina/ disorders	Acute respiratory failure, interstitial lung disease.

Gastrointestinal disorders	Ileus/intestinal obstruction, tumour haemorrhage/tumour necrosis, gastrointestinal perforation, diverticulitis, gastric antral vascular ectasia (GAVE)
Musculoskeletal and connective tissue disorders	Avascular necrosis/hip osteonecrosis, growth retardation in children
Renal and urinary disorders	Chronic renal failure
Skin and subcutaneous tissue disorders	Lichenoid keratosis, lichen planus, toxic epidermal necrolysis. palmoplantar erythrodysesthesia syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), pseudoporphyria.

Laboratory test abnormalities:

In CML cytopenias, particularly neutropaenia and thrombocytopaenia, is a consistent finding, with the suggestion of a higher frequency at high doses ≥ 750mg. The occurrence of cytopenias is dependent on the stage of the disease. In patients, in newly diagnosed CML, cytopenias are less frequent than in the other CML patients. The median duration of the neutropenic and thrombocytopenic episodes usually ranges 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 interruptions of treatment with **IMAREM** but can in rare cases lead to permanent discontinuation of treatment. In paediatric CML patients the most frequent toxicities are Grade 3 or 4 cytopenias involving neutropaenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

Biochemistry

It was reported that severe elevation of transaminases or bilirubin was seen in CML patients and is managed with dose reduction or interruption.

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

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 34 Other

Mechanism of action

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1 and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.

Pharmacodynamic effects

Imatinib is a protein-tyrosine kinase inhibitor, which potently inhibits the breakpoint cluster region-Abelson {Bcr-Abl} 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 leukaemia 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.

In vivo the compound shows anti-tumour activity as a single agent in animal models using Bcr-Abl positive tumour cells.

Imatinib is also 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.

In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumour (GIST) cells, which express an activating kit mutation. Constitutive activation of the platelet-derived growth factor receptor (PDGFR) or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGFR have been implicated in the pathogenesis of myelodysplastic syndrome / myeloproliferative disorder (MDS/MPD), hypereosinophilic syndrome/ chronic eosinophilic leukemia (HES/CEL) and dermatofibrosarcoma protuberans (DFSP). In addition, constitutive activation of c-Kit or the PDGFR has been implicated in the pathogenesis of SM. Imatinib inhibits signaling and proliferation of cells driven by dysregulated PDGFR, Kit and Abl kinase activity.

5.2 Pharmacokinetic properties

The main circulating active metabolite of imanitib in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. The elimination half-life of imatinib and its major active metabolite, the N-desmethyl derivative, are 18 and 40 hours, respectively. Mean Imatinib area under the curve (AUC) increases proportionally with increasing dose in the range 25-1000 mg. Food does not change the pharmacokinetic profile of imatinib.

Absorption

Mean absolute bioavailability is 98 %. The coefficient of variation for plasma imatinib AUC 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 Cmax and prolongation of tmax by 1,5 h), 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

The main circulating metabolite in humans is the N-demethylated piperazine derivative, which shows similar *in vitro* potency to the parent. The plasma AUC for this metabolite was found to be only 16% of the AUC for imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the parent compound.

Imatinib and the N-demethyl metabolite together accounted for about 65% of the circulating radioactivity (AUC(0-48h)). The remaining circulating radioactivity consisted of a number of minor metabolites.

The *in vitro* results showed that CYP3A4 was the major human P450 enzyme catalysing the biotransformation of imatinib. Of a panel of potential comedications (acetaminophen, aciclovir, allopurinol, amphotericin, cytarabine, erythromycin, fluconazole, hydroxyurea, norfloxacin, penicillin V) only erythromycin (IC50 50 µM) and fluconazole (IC50 118 µM) showed inhibition of imatinib metabolism which could have clinical relevance.

Imatinib was shown *in vitro* to be a competitive inhibitor of marker substrates for CYP2C9, CYP2D6 and CYP3A4/5. Ki values in human liver microsomes were 27, 7.5 and 7.9 µmol/l, respectively.

Maximal plasma concentrations of imatinib in patients are 2–4 µmol/l, consequently an inhibition of CYP2D6 and/or CYP3A4/5-mediated metabolism of co-administered drugs is possible. Imatinib did not interfere with the biotransformation of 5-fluorouracil, but it inhibited paclitaxel metabolism as a result of competitive inhibition of CYP2C8 (Ki = 34.7 µM). This Ki value is far higher than the expected plasma levels of imatinib in patients, consequently no interaction is expected upon coadministration of either 5-fluorouracil or paclitaxel and imatinib.

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.

Paediatric population:

As in adult patients, imatinib was rapidly absorbed after oral administration in paediatric patients in both phase I and phase II studies. 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. The comparison of $AUC_{(0-24)}$ on Day 8 and Day 1at340 mf/m2 dose level revealed a 1,7-fold drug accumulation after repealed once daily dosing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The list of excipients for **IMAREM** is microcrystalline cellulose, low substituted hydroxypropyl cellulose, povidone, crospovidone, silica colloidal anhydrous, magnesium stearate, hypromellose, macrogol 400, talc, red iron oxide, yellow iron oxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months (see **section 6.4** for storage instructions)

6.4 Special Precautions for storage

Store at or below 25 ° C in the original pack

Protect from moisture. The blisters should not be removed from the carton until required for use.

6.5 Nature and contents of container

30 or 60 film-coated tablets are packed in PVC/PE/PVDC (polyvinylchloride/polyethylene/polyvinylchloride) blisters with an aluminium foil backing.

The outer carton is a printed cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7.HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. REGISTRATION NUMBERS

IMAREM 100 51/34/0842

IMAREM 400 51/34/0843

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/03/2021

10. DATE OF REVISION OF THETEXT

29/04/2024