Glimatinib® Benta

Imatinib

FORMS AND PRESENTATION
Glimatinib® Benta 100 mg: Film coated tablets: Box of 120 or 60.
Glimatinib® Benta 400 mg: Film coated tablets: Box of 30.

COMPOSITION
Glimatinib® Benta: Each film coated tablet contains Imatinib Mesylate equivalent to Imatinib 100mg.
Glimatinib® Benta: Each film coated tablet contains Imatinib Mesylate equivalent to Imatinib 400mg.
Excipients: microcrystalline cellulose, hydroxypropyl methylcellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, talc, yellow iron oxide, polyethylene glycol, titanium dioxide, methacrylic acid copolymer, red iron oxide, sodium bicarbonate.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Therapeutic class: Antineoplastic agents.
ATC code: L01XE01.
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.
Pharmacokinetic properties
Absorption
Mean absolute bioavailability for Imatinib is 98%. There was high between- patient variability in plasma Imatinib AUC levels 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 h), with a small reduction in AUC (7.4%) compared to fasting conditions. The effect of prior gastrointestinal surgery on drug absorption has not been investigated.
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 catalyzing the biotransformation of Imatinib. Of a panel of potential comedications (acetaminophen, aciclovir, allopurinol, amphotericin, cytarabine, erythromycin, fluconazole, hydroxyurea, norfloxacin, penicillin V) only erythromycin (IC_{50} 50 µM) and fluconazole (IC_{50} 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. K_i 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 (K_i = 34.7 µM). This K_i value is far higher than the expected plasma levels of Imatinib in patients, consequently no interaction is expected upon co-administration of either 5-fluorouracil or paclitaxel and Imatinib.
Elimination
Based on the recovery of compound(s) after an oral ^{14}C-labelled dose of Imatinib, approximately 81% of the dose was recovered within 7 days in feces (68% of dose) and urine (13% of dose). Unchanged Imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

INDICATIONS
Glimatinib® Benta is indicated for the treatment of:
- Adult and pediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- Adult and pediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- Adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (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 advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement.

The effect of Glimatinib® Benta on the outcome of bone marrow transplantation has not been determined.
Glimatinib® Benta is indicated for:
- The treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- The adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- The treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and pediatric patients, the effectiveness of Glimatinib® Benta is based on overall hematological and cytogenetic response rates and progression-free survival in CML, on hematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on hematological response rates in HES/CEL and on objective response rates in adult patients with unresectable and/or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST. The experience with Glimatinib® Benta in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited. Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS
- When Imatinib is co-administered with other medicinal products, there is a potential for drug interactions. Caution should be used when taking Imatinib with protease inhibitors, azole antifungals, certain macrolides, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives.
- Concomitant use of Imatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imatinib, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and Imatinib should be avoided.
- Hypothyroidism: Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Imatinib. Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.
- Hepatotoxicity: Metabolism of Imatinib 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. 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 Imatinib is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions has been detected. Hepatic function should be carefully monitored in circumstances where Imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction.
- Fluid retention: Occurrences of severe fluid retention (pleural effusion, edema, pulmonary edema, ascites, superficial edema) have been reported in approximately 2.5% of newly diagnosed CML patients taking Imatinib. 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 patients and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.
- 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 Imatinib. As cardiac adverse events have been reported uncommonly with Imatinib, a careful assessment of the benefit/risk of Imatinib therapy should be considered in the HES/CEL population before treatment initiation. Myelodysplastic/myeloproliferative diseases with PDGFR gene re-arrangements could be associated with high eosinophil levels. Evaluation by a cardiology specialist, performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD 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 Imatinib should be considered at the initiation of therapy.
- Gastrointestinal hemorrhage: In the study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoral hemorrhages were reported. Based on the available data, no predisposing factors (e.g. tumor size, tumor location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of hemorrhage. 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 hemorrhage in all patients should be applied.
- Tumor lysis syndrome: Due to the possible occurrence of tumor lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Imatinib.
- Laboratory tests: Complete blood counts must be performed regularly during therapy with Imatinib. Treatment of CML patients with Imatinib 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 Imatinib may be interrupted or the dose may be reduced, as recommended.

Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving Imatinib.
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.
- Pediatric 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.

Ability to drive and use machines
Patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with Imatinib. Therefore, caution should be recommended when driving a car or operating machinery.

PREGNANCY AND LACTATION
There are limited data on the use of Imatinib in pregnant women. Studies in animals have however shown reproductive toxicity and the potential risk for the fetus is unknown. Imatinib should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus.
Women of childbearing potential must be advised to use effective contraception during treatment.
There is limited information on Imatinib distribution on human milk. Studies in two breast-feeding women revealed that both Imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio studied in a single patient was determined to be 0.5 for Imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of Imatinib and the metabolite and the maximum daily milk intake by infants, the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to Imatinib are unknown, women taking Imatinib should not breast-feed.

DRUG INTERACTIONS
Active substances that may increase Imatinib 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 Imatinib concentrations. There was a significant increase in exposure to Imatinib (the mean C_{max} and AUC of Imatinib 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 Imatinib with inhibitors of the CYP3A4 family.
Active substances that may decrease Imatinib plasma concentrations
Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or *Hypericum perforatum*, also known as St. John's Wort) may significantly reduce exposure to Imatinib, potentially increasing the risk of therapeutic failure. Pretreatment with multiple doses of rifampicin 600 mg followed by a single 400 mg dose of Imatinib resulted in decrease in C_{max} and $AUC_{0-\infty}$ by at least 54% and 74%, of the respective values without rifampicin treatment. Similar results were observed in patients with malignant gliomas treated with Imatinib while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbazepine, oxcarbazepine and phenytoin. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. Concomitant use of rifampicin or other strong CYP3A4 inducers and Imatinib should be avoided.
Active substances that may have their plasma concentration altered by Imatinib
Imatinib increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, indicating an inhibition of the CYP3A4 by Imatinib. Therefore, caution is recommended when administering Imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). Imatinib may increase plasma concentration of other CYP3A4 metabolized drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).
Because of known increased risks of bleeding in conjunction with the use of Imatinib (e.g. hemorrhage), patients who require anticoagulation should receive low-molecular-weight or standard heparin instead of coumarin derivatives such as warfarin.
In vitro Imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had an inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23% (90%CI [1.16–1.30]). 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 K_i 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 Imatinib and paracetamol concomitantly.
In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be decreased when Imatinib is co-administered. 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, but drug-drug interactions between Imatinib and chemotherapy regimens are not well characterized. 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. Therefore, the use of Imatinib in combination requires special precaution.

ADVERSE EFFECTS
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.
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequency categories are defined using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of frequency, the most frequent first.
- Infections and infestations: Herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1], sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis (uncommon); fungal infection (rare).
- Neoplasm benign, malignant and unspecified (including cysts and polyps): Tumor lysis syndrome (rare).
- Blood and lymphatic system disorders: Neutropenia, thrombocytopenia, anemia (very common); pancytopenia, febrile neutropenia (common); Thrombocythemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy (uncommon); hemolytic anemia (rare).
- Metabolism and nutrition disorders: Anorexia (common); hypokalemia, increased appetite, hypophosphatemia, decreased appetite, dehydration, gout, hyperuricemia, hypercalcemia, hyperglycemia, hyponatremia (uncommon); hyperkalemia, hypomagnesemia (rare).
- Psychiatric disorders: Insomnia (Common); depression, decreased libido, anxiety (uncommon); confusional state (rare).
- Nervous system disorders: Headache[2] (very common); dizziness, paraesthesia, taste disturbance, hypoesthesia (common); migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral hemorrhage (uncommon); increased intracranial pressure, convulsions, optic neuritis (rare).
- Eye disorders: Eyelid edema, increased lacrimation, conjunctival hemorrhage, conjunctivitis, dry eye, blurred vision (common); eye irritation, eye pain, orbital edema, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema (uncommon); Cataract, glaucoma, papilloedema (rare).
- Ear and labyrinth disorders: Vertigo, tinnitus, hearing loss (uncommon).
- Cardiac disorders: Palpitations, tachycardia, congestive cardiac failure[3], pulmonary edema (uncommon); arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion (rare).
- Vascular disorders[4]: Flushing, hemorrhage (common); hypertension, hematoma, peripheral coldness, hypotension, Raynaud's phenomenon (uncommon).
- Respiratory, thoracic and mediastinal disorders: Dyspnea, epistaxis, cough (common); pleural effusion[5], pharyngolaryngeal pain, pharyngitis (uncommon); pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary hemorrhage (rare).
- Gastrointestinal disorders: Nausea, diarrhea, vomiting, dyspepsia, abdominal pain[6] (very common); flatulence, abdominal distension, gastro-esophageal reflux, constipation, dry mouth, gastritis (common); stomatitis, mouth ulceration, gastrointestinal hemorrhage[7], eructation, melena, esophagitis, ascites, gastric ulcer, hematemesis, cheilitis, dysphagia, pancreatitis (uncommon); colitis, ileus, inflammatory bowel disease (rare).

- Hepatobiliary disorders: Increased hepatic enzymes (common); Hyperbilirubinemia, hepatitis, jaundice (uncommon); hepatic failure[8], hepatic necrosis (rare).
- Skin and subcutaneous tissue disorders: Periorbital edema, dermatitis/eczema/rash (very common); pruritus, face edema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction (common) pustular rash, contusion, increased sweating, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis
purpura, skin hyperpigmentation, bullous eruptions (uncommon); acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discoloration, angioneurotic edema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP) (rare).
- Musculoskeletal and connective tissue disorders: Muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain[9] (very common); joint swelling (common); joint and muscle stiffness (uncommon); muscular weakness, arthritis, rhabdomyolysis/myopathy (rare).
- Renal and urinary disorders: Renal pain, hematuria, acute renal failure, increased urinary frequency (uncommon).
- Reproductive system and breast disorders: Gynecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal edema (uncommon); hemorrhagic corpus luteum/hemorrhagic ovarian cyst (rare).
- General disorders and administration site conditions: Fluid retention and edema, fatigue (very common); weakness, pyrexia, anasarca, chills, rigors (common); chest pain, malaise (uncommon).
- Investigations: Increased weight (very common); decreased weight (common); increased blood creatinine, increased blood creatine phosphokinase, increased blood lactate dehydrogenase, increased blood alkaline phosphatase (uncommon); increased blood amylase (rare).

[1]Pneumonia was reported most commonly in patients with transformed CML and in patients with GIST.
[2] Headache was the most common in GIST patients.
[3] On a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML.
[4] Flushing was most common in GIST patients and bleeding (hematoma, hemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC).
[5] Pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML.
[6-7] Abdominal pain and gastrointestinal hemorrhage were most commonly observed in GIST patients.
[8] Some fatal cases of hepatic failure and of hepatic necrosis have been reported.
[9] Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.

The following types of reactions have been reported mainly from post-marketing experience with Imatinib. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Imatinib exposure.
- Neoplasm benign, malignant and unspecified (including cysts and polyps): Tumour hemorrhage/tumor necrosis.
- Immune system disorders: Anaphylactic shock.
- Nervous system disorders: Cerebral edema.
- Eye disorders: Vitreous hemorrhage.
- Cardiac disorders: Pericarditis, cardiac tamponade.
- Vascular disorders: Thrombosis/embolism.
- Respiratory, thoracic and mediastinal disorders: Acute respiratory failure (fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions), interstitial lung disease.
- Gastrointestinal disorders: Ileus/intestinal obstruction, gastrointestinal perforation, diverticulitis.
- Skin and subcutaneous tissue disorders: Palmoplantar erythrodysesthesia syndrome, lichenoid keratosis, lichen planus, toxic epidermal necrolysis.
- Musculoskeletal and connective tissue disorders: Avascular necrosis/hip necrosis, growth retardation in children.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies and malignant sarcomas, as appropriate.
For doses of 400 mg and above (see dosage recommendation below) a 400 mg tablet (not divisible) is available.
For doses other than 400 mg and 800 mg (see dosage recommendation below) a 100 mg divisible tablet is available.
The prescribed dose should be administered orally with a meal and a large glass of water to minimize the risk of gastrointestinal irritations. 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 mineral 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).

Posology for CML in adult patients

The recommended dosage of Glimatinib® Benta is 400 mg/day for adult patients in chronic phase CML. Chronic phase CML is defined when all of the following criteria are met: blasts < 15% in blood and bone marrow, peripheral blood basophils < 20%, platelets > 100 x 109/l.
The recommended dosage of Glimatinib® Benta is 600 mg/day for adult patients in accelerated phase. Accelerated phase is defined by the presence of any of the following: blasts ≥ 15% but < 30% in blood or bone marrow, blasts plus promyelocytes ≥ 30% in blood or bone marrow (providing < 30% blasts), peripheral blood basophils ≥ 20%, platelets < 100 x 109/l unrelated to therapy.
The recommended dose of Glimatinib® Benta is 600 mg/day for adult patients in blast crisis. Blast crisis is defined as blasts ≥ 30% in blood or bone marrow or extramedullary disease other than hepatosplenomegaly.
Treatment duration: In clinical trials, treatment with Imatininb was continued until disease progression. The effect of stopping treatment after the achievement of a complete cytogenetic response has not been investigated.
Dose increases from 400 mg to 600 mg or 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 with accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved hematological and/or cytogenetic response. Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

Posology for CML in children

Dosing for children should be on the basis of body surface area (mg/m^2). The doses of 340 mg/m^2 daily is recommended for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 800 mg). 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. The dose recommendation is currently based on a small number of pediatric patients. There is no experience with the treatment of children below 2 years of age.
Dose increases from 340 mg/m^2 daily to 570 mg/m^2 daily (not to exceed the total dose of 800 mg) may be considered in children in the absence of severe adverse drug reaction and severe non-leukemia-related neutropenia or thrombocytopenia in the following irrucmstances: disease progression (at any time); failure to achieve a satisfactory hematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved hematological and/or cytogenetic response. Patients should be monitored losely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

Posology for Ph+ ALL

The recommended dose of Glimatinib® Benta is 600 mg/day for adult patients with Ph+ ALL. Hematological experts in the management of this disease should supervise the therapy throughout all phases of care.
Treatment schedule: On the basis of the existing data, Glimatinib® Benta has been shown to be effective and safe when administered at 600 mg/day in combination with chemotherapy in the induction phase, the consolidation and maintenance phases of chemotherapy for adult patients with newly diagnosed Ph+ ALL. The duration of Glimatinib® Benta therapy can vary with the treatment program selected, but generally longer exposures to Glimatinib® Benta have yielded better results.
For adult patients with relapsed or refractory Ph+ALL Glimatinib® Benta monotherapy at 600 mg/day is safe, effective and can be given until disease progression occurs.

Posology for MDS/MPD

The recommended dose of Glimatinib® Benta is 400 mg/day for adult patients with MDS/MPD.
Treatment duration: In the only clinical trial performed up to now, treatment with Glimatinib® Benta was continued until disease progression. At the time of analysis, the treatment duration was a median of 47 months (24 days - 60 months).

Posology for HES/CEL

The recommended dose of Glimatinib® Benta is 100 mg/day for adult patients with HES/CEL.
Dose increase from 100 mg to 400 mg may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.
Treatment should be continued as long as the patient continues to benefit.

Posology for GIST

The recommended dose of Glimatinib® Benta is 400 mg/day for adult patients with unresectable and/or metastatic malignant GIST.
Limited data exist on the effect of dose increases from 400 mg to 600 mg or 800 mg in patients progressing at the lower dose.
Treatment duration: In clinical trials in GIST patients, treatment with Glimatinib® Benta was continued until disease progression. At the time of analysis, the treatment duration was a median of 7 months (7 days to 13 months). The effect of stopping treatment after achieving a response has not been investigated.
The recommended dose of Glimatinib® Benta is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. Optimal treatment duration is not yet established. Length of treatment in the clinical trial supporting this indication was 36 months.

Posology for DFSP

The recommended dose of Glimatinib® Benta is 800 mg/day for adult patients with DFSP.

Dose adjustment for adverse reactions

- Non-hematological adverse reactions: If a severe non-hematological adverse reaction develops with Glimatinib® Benta 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, Glimatinib® Benta should be withheld until bilirubin levels have returned to < 1.5 x IULN and transaminase levels to < 2.5 x IULN. Treatment with Glimatinib® Benta 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.
- Hematological adverse reactions: Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.

Dose adjustments for neutropenia and thrombocytopenia:

EL (starting dose 100 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Glimatinib® Benta until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75x 10^9/l. 2. Resume treatment with Glimatinib® Benta at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, MDS/MPD and GIST (starting dose 400 mg) HES/CEL (at dose 400 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Glimatinib® Benta until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75x 10^9/l. 2. Resume treatment with Glimatinib® Benta at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume Glimatinib® Benta at reduced dose of 300 mg.
Pediatric 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 Glimatinib® Benta until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75x 10^9/l. 2. Resume treatment with Glimatinib® Benta at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume Glimatinib® Benta at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check wether cytopenia is related to leukemia (marrow aspirate or biopsy). 2. if Cytopenia is unrelatedto leukemia, reduce dose of Glimatinib® Benta to 400 mg. 3. If cytopenia presists for 2 weeks, reduce further to 300 mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop Glimatinib® Benta until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 300 mg.
Pediatric accelerated phase CML and blast crisis (starting dose 340 mg/m^2)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check wether cytopenia is related to leukemia (marrow aspirate or biopsy). 2. if Cytopenia is unrelatedto leukemia, reduce dose of Glimatinib® Benta to 260 mg/m^2. 3. If cytopenia presists for 2 weeks, reduce further to 200 mg/m^2. 4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop Glimatinib® Benta until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 200 mg/m^2.
DFSP (at dose 800 mg)	[a]ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Glimatinib® Benta until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75x 10^9/l. 2. Resume treatment with Glimatinib® Benta at 600 mg. 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume Glimatinib® Benta at reduced dose of 400 mg.

ANC = absolute neutrophil count
[a]occuring after at least 1 month of treatment

Special populations

- Pediatric use: There is no experience in children with CML below 2 years of age. There is limited experience in children with Ph+ ALL and very limited experience in children with MDS/MPD and DFSP. There is no experience in children or adolescents with GIST and HES/CEL.
- Hepatic insufficiency: Imatinib is mainly metabolized 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.

Liver dysfunction classification:

Liver dysfunction	Liver function tests
Mild	Total bilirubin: = 1.5 ULN AST: > ULN (can be normal or < ULN if total bilirubin is > ULN)
Moderate	Total bilirubin: = 1.5 - 3.0 ULN AST: any
Severe	Total bilirubin: > 3 - 10 ULN AST: any

ULN = upper limit of normal for the institution
AST = aspartate aminotransferase

- Renal insufficiency: Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy.
- Elderly patients: Imatinib pharmacokinetics have not been specifically studied in the 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.

OVERDOSAGE

In the event of overdose the patient should be observed and appropriate symptomatic treatment given. Generally the reported outcome in these cases was “improved” or “recovered”.

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.

Pediatric population

One 3-year-old male exposed to a single dose of 400 mg experienced vomiting, diarrhea and anorexia and another 3-year-old male exposed to a single dose of 980 mg dose experienced decreased white blood cell count and diarrhea.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: April 2014-.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor’s prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L
Dbayeh - Lebanon