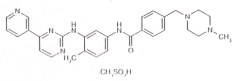
RITOR
Imatinib 100 mg / 400 mg
Coated Tablets
Route of administration: Oral

Made in Argentina | Under prescription only

QUALITATIVE-CUANTITATIVE FORMULA
Each coated tablet of RITOR 100 mg contains:
Imatinib mesylate (equivalent to 100 mg of imatinib base) 119.50 mg, Magnesium Stearate 10.00 mg, Talc 12.50 mg, Microcrystalline Cellulose 26.25 mg, Direct Compression Mannitol 75.50 mg, Colloidal Silicon Dioxide 5.00 mg, Crospovidone 12.50 mg, Opadry II White 85F28751 6.61 mg (Polyvinyl Alcohol 2.65 mg, Titanium Dioxide 1.65 mg, Polyethylene Glycol 1.32 mg, Talc 0.99 mg), Red Iron Oxide 0.10 mg, Yellow Iron Oxide 0.79 mg.
Each coated tablet of RITOR 400 mg contains:
Imatinib mesylate (equivalent to 400 mg of imatinib base) 478.0 mg, Magnesium Stearate 10.00 mg, Talc 50.00 mg, Microcrystalline Cellulose 105.00 mg, Direct Compression Mannitol 302.00 mg, Colloidal Silicon Dioxide 5.00 mg, Crospovidone 50.00 mg, Opadry II White 85F28751 26.43 mg (Polyvinyl Alcohol 10.57 mg, Titanium Dioxide 6.61 mg, Polyethylene Glycol 5.29 mg, Talc 3.96 mg), Red Iron Oxide 0.40 mg, Yellow Iron Oxide 3.17 mg.

DESCRIPTION



THERAPEUTIC ACTION
Tyrosine kinase inhibitor.
ATC code: L01XE01.

PHARMACOLOGY
Pharmacological action
Imatinib mesylate is a tyrosine kinase protein inhibitor that inhibits bcr-abl tyrosine kinase, the constitutively abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in bcr-abl-positive cell lines, as well as fresh leukemic cells in Philadelphia chromosome-positive chronic myeloid leukemia. In colony-forming assays using peripheral blood and ex vivo bone marrow samples, imatinib shows inhibition of bcr-abl-positive colonies in patients with CML. In vivo, it inhibits tumor growth of murine bcr-abl-transfected myeloid cells, as well as bcr-abl-positive leukemia cell lines derived from patients with blast crisis CML. Imatinib is also a receptor tyrosine kinase inhibitor for platelet-derived growth factor (PDGF), 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 tumor (GIST) cells expressing activating c-kit mutation.
Pharmacokinetics
Imatinib is well absorbed after oral administration, reaching peak plasma concentration (Cmax) within 2-4 hours post-dose. The mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its main active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. The mean area under the concentration-time curve (AUC) of imatinib increases proportionally with dose escalation, ranging from 25 mg to 1,000 mg. There is no significant change in the pharmacokinetics of imatinib upon repeated dosing, and accumulation is 1.5 to 2.5-fold at steady state when imatinib is administered once daily. At clinically relevant concentrations, approximately 95% of imatinib is bound to plasma proteins. The pharmacokinetics of imatinib is similar in patients with chronic myeloid leukemia or gastrointestinal stromal tumor. Metabolism and Elimination: CYP3A4 is the primary enzyme responsible for the metabolism of imatinib.
Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, and CYP2C19, play a minor role in its metabolism. The most important circulating active metabolite in humans is the N-desmethyl piperazine derivative, predominantly formed by CYP3A4. It exhibits similar potency to the imatinib precursor in vitro. The plasma AUC for this metabolite is approximately 15% of the AUC for imatinib. The plasma protein binding of the N-desmethyl metabolite CGP71588 is similar to that of the parent compound. Elimination is primarily through the feces, mostly as metabolites. Approximately 80% of the dose was eliminated within 7 days, mainly in the feces, with a smaller proportion excreted in the urine. Unmetabolized imatinib was found in 25% of the dose, with the remaining portion being metabolites. While interpatient variability in clearance has been observed, this does not warrant initial dose adjustments based on body weight and/or age but indicates the need for monitoring to avoid treatment-related toxicity.

Special Populations
Pediatrics:
Similar to adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients, with a Cmax of 2-4 hours. The apparent oral clearance was similar to values in adults, as well as the half-life. Doses in children achieved a similar AUC to the 400mg dose in adults. Comparison of the AUC(0-24) on the day of treatment initiation with that observed days after once-daily drug administration revealed drug accumulation. The mean AUC of imatinib did not increase proportionally to the dose escalation.
Hepatic Impairment:
Patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite compared to patients with normal hepatic function.
Renal Impairment:
There is no evidence of the use of imatinib in patients with decreased renal function. Imatinib and its metabolites were not significantly excreted via the kidneys.

INDICATIONS
RITOR is indicated for the treatment of patients with the following:
- Newly diagnosed chronic myeloid leukemia.
- Chronic-phase chronic myeloid leukemia when treatment with interferon-alpha fails.
- Blastic phase chronic myeloid leukemia and accelerated phase chronic myeloid leukemia.
- Unresectable and/or metastatic CD117-positive gastrointestinal stromal tumor (GIST) in adult patients.
- RITOR is indicated for the treatment of newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia patients for whom bone marrow transplantation is not considered as first-line treatment.
- RITOR is also indicated for the treatment of Ph+ chronic myeloid leukemia in chronic phase after failure of interferon-alpha treatment, or in accelerated phase or blastic crisis.
- The effect of RITOR on bone marrow transplantation outcome has not been determined.
- RITOR is also indicated for the treatment of adult patients with unresectable and/or metastatic CD117-positive malignant gastrointestinal stromal tumors.
- In adult patients, the effectiveness of imatinib is based on overall hematological and cytogenetic response rates and progression-free survival in chronic myeloid leukemia, and objective response rates in gastrointestinal stromal tumors. Experience with imatinib in children with chronic myeloid leukemia is very limited. There are no controlled trials demonstrating clinical benefit or increased survival for either of the two diseases.

DOSAGE
The treatment should be initiated by an experienced physician in the treatment of patients with chronic myeloid leukemia or gastrointestinal stromal tumors. For doses other than 400 mg and 800 mg (see the following dosage recommendation). The prescribed dose should be taken orally, with food and a large glass of water, to minimize the risk of gastrointestinal irritation. The daily dose can be taken once a day or divided into two administrations, one in the morning and one in the evening. For patients unable to swallow, the tablets can be dispersed in a glass of mineral water or apple juice. The required number of tablets should be placed in an 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.
Dosage for chronic myeloid leukemia: The recommended dose of imatinib for patients with chronic-phase chronic myeloid leukemia is 400 mg/day. The recommended dose of imatinib for patients in accelerated phase is 600 mg/day. The recommended dose of imatinib for patients in blast crisis is 600 mg/day.
Duration of treatment: It is advised to continue treatment with imatinib until disease progression. The effect of discontinuing treatment after achieving a complete cytogenetic response is unknown. Dose increases from 400 mg to 600 mg in patients in the chronic phase of the disease, or from 600 mg to a maximum of 800 mg (administered as 400 mg twice daily) in patients in accelerated phase or blast crisis, may be considered in the absence of severe adverse reactions and non-leukemia-related severe neutropenia or thrombocytopenia, under the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; loss of previously achieved hematologic response. Due to the possibility of increased incidence of adverse effects at higher doses, patients should be closely monitored following dose escalation. Dosage in children should be based on body surface area (mg/m²). Daily doses of 260 mg/m² and 340 mg/m² are recommended in children with chronic-phase chronic myeloid leukemia and advanced-phase chronic myeloid leukemia, respectively. However, the total daily dose in children should not exceed the equivalent adult dose of 400 mg and 600 mg, respectively. The treatment can be administered once a day or, alternatively, the dose can be split into two administrations, one in the morning and one in the evening.
The dosage recommendation is currently based on a small number of pediatric patients. There is no experience in treating children under 3 years of age.
Dosage for gastrointestinal stromal tumors: The recommended dose of imatinib for patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors is 400 mg/day. Limited data exist on the effect of increasing the dose from 400 mg to 600 mg in patients who show progression with the initial dose. Currently, there are no data based on previous gastrointestinal resection supporting specific dosage recommendations for patients with gastrointestinal stromal tumors. Duration of treatment: It is recommended to continue treatment with imatinib until disease progression. The effect of discontinuing treatment after achieving a response has not been investigated.
Dose adjustment for adverse reactions in patients with chronic myeloid leukemia and gastrointestinal stromal tumors:
- *Non-hematological adverse reactions:* If a severe non-hematological adverse reaction occurs with the use of imatinib, treatment should be interrupted until the reaction resolves. Afterward, treatment may be resumed as appropriate depending on the initial severity of the reaction. If bilirubin levels increase >3 times the upper limit of normal or liver transaminases increase >5 times the upper limit of normal, imatinib should be interrupted until bilirubin levels normalize or are expressed as <1.5 times. Treatment with imatinib can then be continued at a reduced daily dose. In adults, the dose should be reduced from 400 mg to 300 mg or from 600 mg to 400 mg, and in children, from 260 to 200 mg/m²/day or from 340 to 260 mg/m²/day.
- *Hematological adverse reactions:* Dose reduction or treatment interruption is recommended in cases of severe neutropenia and thrombocytopenia, as indicated below.
Dose adjustment for neutropenia and thrombocytopenia:
Chronic myeloid leukemia in chronic phase and gastrointestinal stromal tumors (initial dose 400 mg) or 260 mg/m² in children; absolute neutrophil count <1.0 x 10⁹/L and/or platelets <50 x 10⁹/L:
1. Interrupt imatinib until the absolute neutrophil count is >1.5 x 10⁹/L and platelets >75 x 10⁹/L.
2. Resume imatinib treatment at a dose of 400 mg or 260 mg/m² in children.
3. If there is a recurrence of an absolute neutrophil count <1.0 x 10⁹/L and/or platelets <50 x 10⁹/L, repeat step 1 and resume imatinib at the reduced dose of 300 mg or 200 mg/m² in children.
Accelerated phase and blast crisis of chronic myeloid leukemia (initial dose 600 mg) or 340 mg/m² in children; occurring at least after one month of treatment. Absolute neutrophil count <0.5 x 10⁹/L and/or platelets <10 x 10⁹/L:
1. Determine if the cytopenia is leukemia-related (bone marrow aspirate or biopsy).
2. If the cytopenia is not leukemia-related, reduce the imatinib dose to 400 mg or 260 mg/m² in children.
3. If the cytopenia persists for 2 weeks, reduce to 300 mg or 200 mg/m² in children.
4. If the cytopenia persists for 4 weeks and remains unrelated to leukemia, interrupt imatinib until the absolute neutrophil count is >1 x 10⁹/L and platelets >20 x 10⁹/L, then resume treatment with 300 mg or 200 mg/m² in children.
Use in pediatrics: There is no experience with the use of imatinib in children under 3 years of age. Experience with imatinib in the pediatric population with both conditions is limited to a few cases. Chronic myeloid leukemia in blast crisis: There is no experience in children or adolescents with gastrointestinal stromal tumors.
Hepatic impairment: Since no clinical trials have been conducted in patients with reduced hepatic function, no specific dose adjustment recommendation can be given. As imatinib is primarily metabolized by the liver, exposure to imatinib is expected to increase if hepatic function is impaired. Imatinib should be used with caution in patients with hepatic dysfunction.
Renal impairment: No clinical trials have been conducted with imatinib in patients with reduced renal function (the trials excluded patients with serum creatinine concentration more than two times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidneys. A decrease in total body clearance is not expected in patients with renal impairment since renal clearance of imatinib is negligible. However, caution is advised in cases of severe renal impairment.
Elderly patients: The pharmacokinetics of imatinib specifically in elderly individuals have not been studied. In clinical trials in adult patients, which included over 20% of patients aged 65 years or older, no significant age-related differences in pharmacokinetics were observed. No specific dose recommendation is necessary for elderly patients.

CONTRAINDICATIONS
Hypersensitivity to the active ingredient or any of its excipients.

ADVERSE REACTIONS
Patients in advanced stages of chronic myeloid leukemia or malignant gastrointestinal stromal tumors may have multiple clinical symptoms that can make it difficult to attribute causality to adverse effects, given the variety of symptoms related to the underlying disease, its progression, and the concomitant administration of numerous medications. Adverse reactions were similar in patients with chronic myeloid leukemia and gastrointestinal stromal tumors; less myelosuppression was observed in gastrointestinal stromal tumors, and intraneoplastic hemorrhage was only observed in the gastrointestinal stromal tumor population. Treatment discontinuation due to drug-related adverse reactions was observed in only 1% of patients in the chronic phase, 2% of patients in the accelerated phase, and 5% of patients in the blast crisis phase. In gastrointestinal stromal tumors, 3% of patients discontinued study medication due to drug-related adverse reactions. The most commonly reported adverse reactions were nausea, vomiting, diarrhea,

myalgia, muscle cramps, and rash; they were easily treatable. Peripheral edema, primarily periorbital or in the lower limbs, was also observed. Pleural effusion, ascites, pulmonary edema, and rapid weight gain with or without peripheral edema (collectively described as fluid overload) were also observed. They are treated by discontinuing imatinib treatment, administering diuretics, or other appropriate therapeutic measures. Neutropenia, thrombocytopenia, and anemia were observed as well. Severe elevation of transaminases or bilirubin was infrequent. The most commonly reported treatment-related adverse reactions (>10%) in both pathologies were mild: nausea, vomiting, diarrhea, abdominal pain, fatigue, myalgia, muscle cramps, and rash. A common finding in all studies was superficial edema, primarily described as periorbital or lower limb edema. However, these edemas were rarely severe and could be treated with diuretics, other supportive measures, or by reducing the dose of imatinib. Various adverse reactions such as pleural effusion, ascites, pulmonary edema, and rapid weight gain with or without superficial edema can be collectively described as fluid retention. These reactions can usually be treated by temporarily discontinuing imatinib treatment and administering diuretics and other supportive therapeutic measures. However, some of these reactions can be severe or life-threatening. Several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure, and renal failure. In pediatric clinical trials, no special safety findings were observed.

Adverse reactions: The reported adverse reactions, except for isolated cases, are detailed below, categorized by organ systems and frequency. Frequencies are defined as follows: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (<1/1,000).

- Infections and infestations: uncommon: sepsis, pneumonia, herpes simplex, herpes zoster, upper respiratory tract infections, gastroenteritis.
- Lymphatic and blood disorders: very common: neutropenia, thrombocytopenia, anemia. Common: febrile neutropenia. Uncommon: pancytopenia, bone marrow depression.
- Metabolism and nutrition disorders: common: anorexia. Uncommon: dehydration, hyperuricemia, hypokalemia, increased appetite, decreased appetite, gout, hypophosphatemia. Rare: hypokalemia, hyponatremia.
- Psychiatric disorders: uncommon: depression, anxiety, decreased libido. Rare: confusion.
- Nervous system disorders: very common: headache. Common: dizziness, taste alterations, paresthesia, insomnia. Uncommon: cerebral hemorrhage, syncope, peripheral neuropathy, hypoesthesia, drowsiness, migraine, memory impairment. Rare: cerebral edema, increased intracranial pressure, seizures.
- Eye disorders: common: conjunctivitis, increased tearing, blurred vision. Uncommon: eye irritation, conjunctival hemorrhage, dry eye, orbital edema. Rare: macular edema, papilledema, retinal hemorrhage, vitreous hemorrhage, glaucoma.
- Ear and labyrinth disorders: uncommon: vertigo, tinnitus.
- Cardiac disorders: uncommon: heart failure, pulmonary edema, tachycardia. Rare: pericardial effusion, pericarditis.
- Vascular disorders: uncommon: hematomas, hypertension, hypotension, hot flushes, peripheral cooling. Rare: thrombosis, embolism.
- Respiratory, thoracic, and mediastinal disorders: common: epistaxis, dyspnea. Uncommon: pleural effusion, cough, pharyngolaryngeal pain. Rare: pulmonary fibrosis, interstitial pneumonitis.
- Gastrointestinal disorders: very common: nausea, vomiting, diarrhea, dyspepsia, abdominal pain. Common: abdominal distension, flatulence, constipation, gastroesophageal reflux, mouth ulceration. Uncommon: gastrointestinal bleeding, melena, ascites, gastric ulcer, gastritis, eructation, dry mouth. Rare: colitis, ileus, intestinal obstruction, pancreatitis. Hepatobiliary disorders: common: elevated liver enzymes. Uncommon: jaundice, hepatitis, hyperbilirubinemia. Rare: hepatic failure.
- Skin and subcutaneous tissue disorders: very common: periorbital edema, dermatitis/eczema/rash. Common: facial edema, eyelid edema, pruritus, erythema, dry skin, alopecia, night sweats. Uncommon: petechiae, bruising, increased sweating, urticaria, onychoclasis, photosensitivity reaction, purpura, hypotrichosis, cheilitis, skin hyperpigmentation, skin hypopigmentation, psoriasis, exfoliative dermatitis, bullous eruptions. Rare: angioedema, vesicular eruptions, Stevens-Johnson syndrome.
- Musculoskeletal, connective tissue, and bone disorders: very common: muscle spasms and cramps, musculoskeletal pain including arthralgia. Common: joint swelling. Uncommon: sciatica, joint and muscle stiffness.
- Renal and urinary disorders: Infrequent: renal failure, renal pain, increased urinary frequency, hematuria.
- Reproductive system and breast disorders: Infrequent: gynecomastia, breast enlargement, scrotal edema, menorrhagia, nipple pain, sexual dysfunction.
- General disorders and administration site conditions: Very common: fluid retention and edema, fatigue. Common: pyrexia, weakness, chills. Infrequent: malaise, hemorrhage. Rare: anasarca, tumor hemorrhage, tumor necrosis.
- Investigations: Common: weight gain. Infrequent: increased blood alkaline phosphatase, increased blood creatinine, weight loss, increased blood creatine phosphokinase, increased blood lactate dehydrogenase.
- Laboratory abnormalities: Hematology: Cytopenias, particularly neutropenia and thrombocytopenia, have been observed, suggesting a higher frequency at doses >750 mg (Phase I study). However, the presence of cytopenias was also clearly dependent on the disease phase, with the frequency of grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L) and thrombocytopenia (platelet count <50 x 10^9/L) being 4 to 6 times higher in accelerated and blast phase (58-62% and 42-58% for neutropenia and thrombocytopenia, respectively) compared to patients with newly diagnosed chronic phase chronic myeloid leukemia (14% neutropenia and 7% thrombocytopenia). Grade 4 neutropenia (ANC <0.5 x 10^9/L) and thrombocytopenia (platelet count <10 x 10^9/L) were observed in 2% and less than 1% of patients, respectively, with newly diagnosed chronic phase chronic myeloid leukemia. The median duration of neutropenia and thrombocytopenia episodes was typically 2 to 3 weeks and 3 to 4 weeks, respectively. These effects can usually be managed by dose reduction or interruption of imatinib treatment, but in rare cases may lead to permanent discontinuation of treatment. In patients with gastrointestinal stromal tumor, grade 3 and 4 anemia was reported in 3.4% and 0.7% of patients, respectively, which may be related to gastrointestinal or intratumoral bleeding in at least some of these cases. Grade 3 neutropenia was observed in 4.1% of patients and grade 3 thrombocytopenia in 0.7% of patients. No patient developed grade 4 thrombocytopenia. Decreases in leukocyte and neutrophil counts occurred mainly during the first six weeks of treatment, with relatively stable values thereafter.
- Biochemistry: Severe elevation of transaminases or bilirubin was infrequent (<4% of patients) and typically managed by dose reduction or treatment interruption (median duration of these episodes was approximately one week). In less than 0.5% of patients, treatment was permanently discontinued due to hepatic test abnormalities. Cases of hepatocellular and cholestatic hepatitis, as well as hepatic failure, have occurred, some of which were fatal.

PRECAUTIONS

Pregnancy: There is insufficient data on the use of imatinib in pregnant women. However, animal studies have shown reproductive toxicity, and the potential risk to the fetus is unknown. Imatinib should not be used during pregnancy unless clearly necessary. If used during pregnancy, the patient should be informed about the potential risk to the fetus. Women of childbearing age should be advised to use effective contraception during treatment.

Breastfeeding: It is unknown whether imatinib is excreted in human milk. In animals, imatinib and/or its metabolites were extensively excreted in milk. Therefore, women taking imatinib should not breastfeed their infants. Although no specific reports have been received, patients should be cautioned that they may experience adverse reactions such as dizziness or blurred vision during imatinib treatment. Therefore, caution should be exercised when driving or operating machinery. Occasionally, severe fluid overload (in approximately 1 to 2% of patients treated with imatinib) has been reported, so it is recommended to regularly weigh patients during treatment and investigate any unexpected weight gain. Complete blood counts should be regularly performed, and liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored before initiating treatment and then monthly or as clinically indicated.

Caution should be exercised when administering imatinib with: inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin); substances inducing the activity of CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital); drugs metabolized by CYP3A4 (e.g., triazolobenzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.) with a narrow therapeutic window. Patients should be advised to avoid or restrict the use of medications containing paracetamol, whether by prescription or over-the-counter.

WARNINGS

When administering imatinib with other medications, there is a potential for drug interactions. The concomitant use of imatinib and CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital) may significantly decrease imatinib exposure, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and imatinib should be avoided. Imatinib metabolism is primarily hepatic, and only 13% of excretion occurs through the kidneys. There is no experience in patients with hepatic or renal dysfunction. Imatinib should only be used in patients with severe hepatic dysfunction after a detailed risk/benefit assessment. In such cases, peripheral blood counts and liver enzymes should be carefully monitored. It should be noted that patients with gastrointestinal stromal tumor may have hepatic metastases that can lead to hepatic failure. Cases of severe fluid retention (pleural effusion, edema, pulmonary edema, ascites) have been reported in a low percentage of patients treated with imatinib, so regular weighing of patients is highly recommended. Rapid and unexpected weight gain should be carefully evaluated, and if necessary, therapeutic and supportive measures should be taken. Special caution should be exercised in patients with heart failure. Both gastrointestinal and intratumoral bleeding have been observed in patients with gastrointestinal stromal tumor. No predisposing factors (e.g., tumor size and location, coagulation disorders) that pose a higher risk for any type of bleeding in patients with gastrointestinal stromal tumor have been identified. Since increased vascularity and a propensity for bleeding are part of the nature and clinical course of gastrointestinal stromal tumor, standardized practices and procedures should be applied for the control and management of bleeding in all patients. Laboratory tests: During imatinib treatment, complete blood counts should be regularly performed. Treatment with imatinib in patients with chronic myeloid leukemia has been associated with neutropenia or thrombocytopenia. However, the presence of these cytopenias is likely related to the phase of the disease being treated and is more common in patients in the accelerated phase or blast crisis of chronic myeloid leukemia compared to patients in the chronic phase. Liver function (transaminases, bilirubin, alkaline phosphatase) should be regularly monitored in patients receiving imatinib. The drug and its metabolites are excreted in the urine in a non-significant amount. It is known that creatinine clearance is reduced with age, but it does not significantly affect the kinetics of imatinib.

INTERACTIONS

Drugs that can alter imatinib plasma concentrations: Substances that inhibit the activity of cytochrome P450 isoenzyme CYP3A4 (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin) may reduce the metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib (mean Cmax and AUC of imatinib increased by 26% and 40%, respectively) in healthy subjects when co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be exercised when administering imatinib with inhibitors of the CYP3A4 family.

Drugs that can reduce imatinib plasma concentrations: Substances that induce the activity of CYP3A4 may increase the metabolism and reduce imatinib plasma concentrations. Co-administration of drugs that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, or Hypericum perforatum, also known as St. John's wort) can significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure. Pre-treatment with multiple doses of rifampicin, 600 mg followed by a single dose of 400 mg of imatinib, results in a reduction in Cmax and AUC(0-inf.) of at least 54% and 74% of the respective values without rifampicin treatment. Concurrent use of rifampicin or other potent CYP3A4 inducers should be avoided with imatinib. Drugs whose plasma concentration can be altered by imatinib: Imatinib increases the mean Cmax and AUC of simvastatin (a CYP3A4 substrate) by 2 and 3.5 times, respectively, indicating that imatinib inhibits CYP3A4. Therefore, caution is advised when administering imatinib with CYP3A4 substrates with a narrow therapeutic range (e.g., cyclosporine or pimozide). Imatinib may increase the plasma concentration of other drugs metabolized by CYP3A4 (e.g., triazolo-benzodiazepines, dihydropyridines, calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e., statins, etc.). Patients requiring anticoagulants should receive low molecular weight or standard heparin, as warfarin is metabolized by CYP2C9. In vitro, imatinib inhibits the activity of cytochrome P450 isoenzyme CYP2D6 at concentrations similar to those that affect CYP3A4 activity. Therefore, systemic exposure to CYP2D6 substrates is potentially increased when co-administered with imatinib. However, no specific studies have been conducted, and caution is recommended.

STORAGE

Store at temperatures not exceeding 30°C, in its original container.

OVERDOSAGE

Experience with doses higher than 800 mg is limited. If an overdose occurs, the patient should be observed and appropriate supportive treatment administered. In the event of an overdose, seek medical attention at the nearest hospital or contact poison control centers:
Hospital de Pediatría Ricardo Gutiérrez: Tel. (011) 4962-6666/2247
Hospital A. Posadas: Tel. (011) 4654-6648/4658-7777
Centro Nacional de Intoxicaciones: Tel. 0800-3330160.

PRESENTATION

RITOR 100 mg: Packages containing 30, 48, 60, 96, 100, 120, and 180 coated tablets, with the last three being exclusively for hospital use.
RITOR 400 mg: Packages containing 30, 48, 60, 96, 100, 120, and 180 coated tablets, with the last three being exclusively for hospital use.

KEEP MEDICINES OUT OF THE REACH OF CHILDREN.
IF IN DOUBT, CONSULT A DOCTOR.

MEDICINAL SPECIALTY AUTHORIZED BY THE MINISTRY OF HEALTH
CERTIFICATE No. 57,255
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