INFORMATION FOR THE USER

CEMIVIL®

Imatinib (as mesylate)

Read all of this leaflet carefully before you start this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them.
- If any of the side effects gets serious, or if you notice any side effects, please tell your doctor immediately.

INDICATIONS

Cemivil is indicated for the treatment of patients with newly diagnosed chronic myeloid leukaemia (CML), as well as for the treatment of patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

DOSAGE AMD ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with CML

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 Cemivil 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 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 drug reaction and severe non-leukaemia-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.

Dosing in children should be on the basis of body surface area (mg/m²).

Doses of 260 mg/m² and 340 mg/m² daily are recommended for children with chronic phase CML and advanced phase CML, respectively. However, the total daily dose in children should not exceed adult equivalent doses of 400 and 600 mg, respectively. Treatments 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 Cemivil in children below 3 years of age.

CONTRAINDICATIONS

Hypersensitivity to the active substance or ta any of the excipients.

PRECAUTION

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

When Imatinib is co-administered with other medications, there is a potential far drug interactions Complete blood counts must be performed regularly during therapy with Imatinib.

DOSE ADJUSTMENTS FOR ADVERSE REACTIONS IN CML

Non-hematological adverse reactions

If a severe non-hematological adverse reaction develops with Imatinib 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.

Hematological adverse reactions

Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended

Children

There is no experience with the use of Imatinib in children below 3 years of age.

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.

Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidney. Since the renal clearance of Imatinib is negligible, a decrease in free drug clearance is not expected in patients with renal insufficiency. The dose can be reduced if not tolerated, or increased for lack of efficacy.

Elderly patients

No significant age related pharmacokinetic differences have been observed in adult patients. No specific dose recommendation is necessary in the elderly.

INTERACTIONS

Drugs that may alter Imatinib plasma concentrations

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Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) could decrease metabolism and increase imatinib concentrations.

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Substances 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, phenobarbital or hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imatinib.

Drugs that may have their plasma concentration altered by Imatinib

Imatinib increases the mean C_{max} and AUC of simvastatin caution is recommended when administering Imatinib with cyclosporin or pimozide. Imatinib may increase plasma concentration e.g. triazolo- benzodiazepines-dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, eic.). 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 Imatinib therapy and when altering the dosage. Alternatively, the use of low-molecular weight heparin should be considered.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate data on the use of imatinib in pregnant women. 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 foetus.

Women of child-bearing potential

Women of childbearing potential must be advised to use effective contraception during treatment.

Lactation

It is not known whether imatinib is excreted in human milk. In animals, imatinib and/or its metabolites were extensively excreted in milk. Women who are taking Imatinib should therefore not breast-feed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHIENS

While no specific reports have been received, patients should be advised that they may experience undesirable effects such as dizziness or blurred vision during treatment with imatinib. Therefore, caution should be recommended when driving a car or operating machinery.

SIDE EFFECTS

Imatinib was generally well tolerated with chronic oral daily dosing in patients with CML. The majority of patients experienced adverse events at some point in time, but most were of mild to moderate grade,

The most frequently reported drug related adverse events were mild nausea, vomiting, diarrhoea, myalgia, muscle cramps and rash, which were easily manageable. Superficial oedemas were a common finding in all studies and were described primarily as periorbital or lower limb oedemas. However, these oedemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Imatinib.

Miscellaneous adverse events such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as "fluid retention". These events can usually be managed by withholding Imatinib temporarily and/or with diuretics and/or other appropriate supportive care measures.

LABORATORY TEST ABNORMALITIES

Haematology

In CML cytopenias, particularly neutropenia and thrombocytopenia have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses > 750 mg (phase I study). However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients.

Biochemistry

Severe elevation of transaminases (<5%) or bilirubin(<1%) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week).

OVERDOSAGE

Experience with doses greater than 800 mg is limited. Isolated cases of Imatinib overdosage have been reported. In the event of overdosage, the patient should be observed and appropriate supportive treatment given.

PHARMACODYNAIMICS

Imatinib is a protein-tyrosine kinase inhibitor, which potently inhibits the breakpoint cluster region-Abelson (Bcr-Abl) tyrosine kinase at the in vitro, cellular, in vivo levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive 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.

PHARMACOKINETICS

Pharmacokinetics of Imatinib

The pharmacokinetics of imatinib have been evaluated over a dosage range of 25 to 1,000 mg. Plasma pharmacokinetics profiles were analysed on day 1 and on either day 7 or day 28, by which time plasma concentrations had reached Steady state.

Absorption

Mean absolute bioavailability for imatinib is 98 % 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.

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.

Metabolism

The main circulating metabolite in humans is the N-demethylated pipera-zine derivative (CGP71588), which shows similar in vitro patency as the parent compound.

Elimination

Based on the recovery of compound(s) after an *oral ^{14}C labeled dose of imatinib*, approximately 81% of the dose was eliminated within 7 days in faeces (68% of dose) and urine (13 % of dose), unchanged Imatinib accounted for 25 % of the dose (5% urine, 20% faeces), the remainder being metabolites.

Plasma pharmacokinetics

Following oral administration in healthy volunteers, the $t_{1/2}$ was approximately 18 h, suggesting that once-daily dosing is appropriate. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25 to 1,000 mg imatinib after oral administration.

Pharmacokinetics in children

As in adult patients, Imatinib was rapidly absorbed after oral administration in paeditric patients in a phase I study.

STORAGE

Store below 30°C. Store in original container.

PRESENTATIONS

Film-Coated Tablets

CEMIVIL 100 MG: Imatinib (as mesylate) 100 mg/tablet

CEMIVIL 400 MG: Imatinib (as mesylate) 400 mg/tablet

Excipients: Microcrystalline cellulose, hydroxypropylmethylcellulose, crospovidone, colloidal silicon dioxide, magnesium stearate.

Film coating: Opadry II orange.

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, 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 by yourself repeat the same prescription without consulting your doctor.

Manufactured by:
The Arab Pharmaceutical Manufacturing Co. Ltd., Sahab - Jordan
For HIKMA Pharmaceuticals, Amman - Jordan

Keep medicament out of the reach of children

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