Oncology Product

TYROKIN

Imatinib 400mg

COMPOSITION

TYROKIN 400 Tablet: Each film coated tablet contains Imatinib Mesylate INN 478.00mg equivalent to 400 mg Imatinib base.

PHARMACOKINETICS

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

Absorption

Mean absolute bioavailability for **TYROKIN** is 98%. The coefficient of variation for plasma **TYROKIN** AUC is in the range of 40 to 60% after an oral dose. When given with a high fat meal, the rate of absorption of **TYROKIN** was minimally reduced.

Distribution

At clinically relevant concentrations of **TYROKIN**, binding to plasma proteins was approximately 95%.

Metabolism

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

Elimination

Approximately 81% of the dose was eliminated within 7 days in faeces (68% of dose) and urine (13% of dose). Unchanged Tyrokin® accounted for 25% of the dose (5% urine, 20% faeces), the remainder being metabolites.

INDICATIONS

TYROKIN is indicated for the

- Treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+CML).
- Treatment of adult and paediatric patients with Ph+CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- 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 or with c-Kit mutational status unknown.
- Treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL).
- Treatment of adult patients with KIT+ (CD117) unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- Adjuvant treatment of adult patients following resection of KIT+GIST.
- Treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

DOSAGE AND ADMINISTRATION

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. 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 **TYROKIN** is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis.

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.

Dosage in Ph+ ALL

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

Dosage in MDS/MPD

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

Dosage in SM

The recommended dose of **TYROKIN** is 400 mg/day for patients with SM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with **TYROKIN** at dose of 400 mg/day may be considered for patients with SM not responding satisfactorily to other therapies.

For patients with SM associated with eosinophilia, a clonal haematological disease related to the fusion kinase FIP1L1-PDGFR-alpha, a starting dose of 100 mg/day is recommended.

Dosage in HES/CEL

The recommended dose of **TYROKIN** is 400 mg/day for patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFR-alpha 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.

Dosage in GIST

The recommended dose of **TYROKIN** is 400 mg/day for patients with unresectable and/or metastatic, malignant GIST. A dose increase from 400 mg to 600 mg or 800 mg for patients may be considered.

Dosage in DFSP

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

Use in Special population

Pregnancy

TYROKIN should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breast-feeding

The effects of low-dose exposure of the infant to **TYROKIN** are unknown, women taking **TYROKIN** should not breast feed.

Fertility

Male patients concerned about their fertility on **TYROKIN** treatment should consult with their physician.

Children

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

Hepatic insufficiency

TYROKIN is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction n should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated.

Elderly patients

No specific dose recommendation is necessary in the elderly.

CONTRAINDICATIONS

TYROKIN is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

When **TYROKIN** is co-administered with other medications, there is a potential for drug interactions. Caution should be used when taking **TYROKIN** with rifampicin or other strong CYP3A4 inducers, ketoconazole or other strong CYP3A4 inhibitors, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide) or CYP2C9 substrates with a narrow therapeutic window (e.g. warfarin and other coumarin derivatives).

Hypothyroidism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Imatinib. TSH levels should be closely monitored in such patients.

Hepatotoxicity

In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored.

Fluid retention

Occurrences of severe fluid retention have been reported in approximately 2.5% of newly diagnosed CML patients taking Imatinib. Therefore, it is recommended that patients be weighed regularly.

Patients with cardiac disease or renal failure

Patients with cardiac disease, risk factors for cardiac failure or history of renal failure should be monitored carefully.

Gastrointestinal hemorrhage

GI sites of tumour may have contributed to reports of GI bleeding. When needed, **TYROKIN** discontinuation may be considered.

Tumor lysis syndrome

Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of **TYROKIN**.

ADVERSE EFFECTS

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

The adverse reactions were similar in all indications, with two exceptions. There was less myelosuppression in GIST and intra-tumoral haemorrhage was only seen in the GIST population. 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. 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.

When Imatinib was combined with high dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia were observed.

PHARMACEUTICAL INFORMATION

Storage condition

Store in a cool (below 30˚C) and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

TYROKIN 400 Tablet: Each commercial box contains 1×10 tablets in Alu-PVDC blister pack.

Marketed by
Renata Limited
Mirpur, Dhaka, Bangladesh.

Manufactured by
Renata Oncology
Rajendrapur, Gazipur, Bangladesh.

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