Rutinib-10

Ruxolitinib INN
10 mg Tablet

DRUG INTERNATIONAL LTD.

Composition: Each tablet contains Ruxolitinib 10 mg as Ruxolitinib Phosphate INN.

Mechanism of Action: Ruxolitinib, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. Oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen and decreased circulating inflammatory cytokines (eg, TNF-α, IL-6).

Pharmacokinetics:

Absorption: Ruxolitinib is rapidly absorbed after oral Ruxolitinib administration with maximal plasma concentration (Cmax) achieved within 1 to 2 hours post-dose. Oral absorption of ruxolitinib was estimated to be at least 95%. **Distribution:** The mean volume of distribution of ruxolitinib at steady-state is 72 L in patient with MF and PV in myelofibrosis patients. **Half-lives:** the mean half-life of ruxolitinib & metabolites is approximately 5.8 hours. **Elimination half-life:** The mean elimination half-life of ruxolitinib is approximately 3 hours **AUC:** Mean ruxolitinib Cmax and total exposure (AUC) increased proportionally over a single dose range of 5 to 200 mg. **The plasma protein binding:** 97%, mostly to albumin. **Metabolism:** Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. **Excretion:** Following a single oral dose of radio labeled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism with 74% of radioactivity excreted in urine and 22% excretion via feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity.

Indications:

Myelofibrosis: Ruxolitinib is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults.

Polycythemia Vera: Ruxolitinib is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

Acute Graft-Versus-Host Disease: Ruxolitinib is indicated for treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

Dosage & Administration:

Myclofibrosis: The recommended starting dose of Ruxolitinib is based on platelet count. A complete blood count (CBC) and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Doses may be titrated based on safety and efficacy.

Ruxolitinib Starting Doses for Myelofibrosis	
Platelet Count	**Starting Dose**
Greater than 200 X 10^9/L	20 mg orally twice daily
100 X 10^9/L to 200 X 10^9/L	15 mg orally twice daily
50 X 10^9/L to less than 100 X 10^9/L	5 mg orally twice daily

Polycythemia Vera: The recommended starting dose of Ruxolitinib is 10 mg twice daily. Doses may be titrated based on safety and efficacy. Consider decreasing the dose to 5 mg twice daily if the hemoglobin count 8 to less than 12g/dL and the platelet count 50 to less than 75 X 10^9 L.

Acute Graft-Versus- Host Disease: The recommended dose of Ruxolitinib is 5 mg twice daily. Consider increasing the dose to 10 mg twice daily after at least 3 days of treatment if the ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing with ruxolitinib. Or as directed by the registered physician.

Side effects: The most common side effects are-

- Thrombocytopenia, Anemia and Neutropenia
- Risk of Infection, bruising, dizziness, headache
- Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Ruxolitinib
- Non-Melanoma Skin Cancer

Contraindication: It is contraindicated in patients with a history of hypersensitivity to Ruxolitinib or any other components of this product.

Use in pregnancy and Lactation: There are no adequate and well-controlled studies in pregnant women. **Nursing mother:** It is not known whether Ruxolitinib is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding should be discontinued during treatment with Ruxolitinib and for two weeks after the final dose.

Use in children: The safety and effectiveness of Ruxolitinib in pediatric patients have not been established.

Drug Interaction:

Fluconazole: Concomitant administration of Ruxolitinib with f luconazole greater than 200 mg daily may increase ruxolitinib exposure due to inhibition of both the CYP3A4 and CYP2C9 metabolic pathways. Increased exposure may increase the risk of exposure-related adverse reactions. Avoid the concomitant use of Ruxolitinib with f luconazole doses of greater than 200 mg daily except in patients with acute GVHD.

Strong CYP3A4 Inhibitors: Concomitant administration of Ruxolitinib with strong CYP3A4 inhibitors increases ruxolitinib exposure. Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Ruxolitinib with strong CYP3A4 inhibitors. In patients with acute GVHD, reduce Ruxolitinib dose as recommended only when coadministered with ketoconazole, and monitor blood counts more frequently for toxicity and adjust the dose if necessary when coadministered with itraconazole.

Strong CYP3A4 Inducers: Concomitant administration of Ruxolitinib with strong CYP3A4 inducers may decrease ruxolitinib exposure. No dose adjustment is recommended; however, monitor patients frequently and adjust the Ruxolitinib dose based on safety and efficacy.

Precautions:

Thrombocytopenia, Anemia And Neutropenia: Treatment with Ruxolitinib can cause thrombocytopenia, anemia and neutropenia. Manage thrombocytopenia by reducing the dose or temporarily interrupting Ruxolitinib. Platelet transfusions may be necessary.Patients developing anemia may require blood transfusions and/or dose modifications of Ruxolitinib.Severe neutropenia (ANC less than 0.5 X 109/L) was generally reversible by withholding Ruxolitinib until recovery.Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

Risk of Infection: Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Ruxolitinib until active serious infections have resolved. Observe patients receiving Ruxolitinib for signs and symptoms of infection and manage promptly.

Tuberculosis: Tuberculosis infection has been reported in patients receiving Ruxolitinib. Observe patients receiving Ruxolitinib for signs and symptoms of active tuberculosis and manage promptly.Prior to initiating Ruxolitinib, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed.For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Ruxolitinib. The decision to continue Ruxolitinib during treatment of active tuberculosis should be based on the overall risk-benefit determination.

Progressive Multifocal Leukoencephalopathy: Progressive multifocal leukoencephalopathy (PML) has occurred with Ruxolitinib treatment. If PML is suspected, stop Ruxolitinib and evaluate.

Herpes Zoster Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected.

Hepatitis B Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Ruxolitinib. The effect of Ruxolitinib on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Symptom Exacerbation Following Interruption or Discontinuation Of Treatment With Ruxolitinib Following discontinuation of Ruxolitinib, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Ruxolitinib: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Ruxolitinib, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Ruxolitinib. Instruct patients not to interrupt or discontinue Ruxolitinib therapy without consulting their physician. When discontinuing or interrupting therapy with Ruxolitinib for reasons other than thrombocytopenia or neutropenia, consider tapering the dose of Ruxolitinib gradually rather than discontinuing abruptly.

Non-Melanoma Skin Cancer Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Ruxolitinib. Perform periodic skin examinations.

Lipid Elevations Treatment with Ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Ruxolitinib. Assess lipid parameters approximately 8-12 weeks following initiation of Ruxolitinib therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

Overdose: There is no known antidote for overdoses with Ruxolitinib. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Ruxolitinib.

Storage: Store below 30° C in a dry place, away from sunlight. Keep out of reach of children.

Packaging: Each box contains 30 tablets in a container.