Erdanib

Erdafitinib INN 4mg & 5mg Tablet

Composition: Erdanib-4: Each film coated tablet contains Erdafitinib INN 4.00 mg.
Erdanib-5: Each film coated tablet contains Erdafitinib INN 5.00 mg.

Pharmacology: Erdafitinib is a kinase inhibitor that binds to and inhibits enzymatic activity of FGFR1, FGFR2, FGFR3 and FGFR4 based on in vitro data. Erdafitinib also binds to RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2. Erdafitinib inhibited FGFR phosphorylation and signaling and decreased cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplification, and fusions. Erdafitinib demonstrated antitumor activity in FGFR-expressing cell lines and xenograft models derived from tumor types, including bladder cancer.
Pharmacokinetics: Following administration of 8 mg once daily, the mean (coefficient of variation [CV%]) Erdafitinib steady-state maximum observed plasma concentration (Cmax), area under the curve (AUCtau), and minimum observed plasma concentration (Cmin) were 1,399 ng/mL (51%), 29,268 ng•h/mL (60%), and 936 ng/mL (65%), respectively. Following single and repeat once daily dosing, Erdafitinib exposure (maximum observed plasma concentration [Cmax] and area under the plasma concentration time curve [AUC]) increased proportionally across the dose range of 0.5 to 12 mg (0.06 to 1.3 times the maximum approved recommended dose). Steady state was achieved after 2 weeks with once daily dosing and the mean accumulation ratio was 4-fold. **Absorption:** Median time to achieve peak plasma concentration (tmax) was 2.5 hours (range: 2 to 6 hours). **Effect of Food:** No clinically meaningful differences with Erdafitinib pharmacokinetics were observed following administration of a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50% of total caloric content of the meal from fat) in healthy subjects. **Distribution:** The mean apparent volume of distribution of Erdafitinib was 29 L in patients. Erdafitinib protein binding was 99.8% in patients, primarily to alpha-1-acid glycoprotein. **Elimination:** The mean total apparent clearance (CL/F) of Erdafitinib was 0.362 L/h in patients. The mean effective half-life of Erdafitinib was 59 hours in patients. **Metabolism:** Erdafitinib is primarily metabolized by CYP2C9 and CYP3A4. The contribution of CYP2C9 and CYP3A4 in the total clearance of Erdafitinib is estimated to be 39% and 20% respectively. Unchanged Erdafitinib was the major drug-related moiety in plasma, there were no circulating metabolites. **Excretion:** Following a single oral dose of radiolabeled Erdafitinib, approximately 69% of the dose was recovered in feces (19% as unchanged) and 19% in urine (13% as unchanged).

Indications: It is indicated for the treatment of adult patients with locally advanced or metastatic Urothelial Carcinoma (mUC), that has-

- Susceptible FGFR3 or FGFR2 genetic alterations, and
- Progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Dosage & Administration: The recommended starting dose of Erdafitinib is 8 mg (two 4 mg tablets) orally once daily, with a dose increase to 9 mg (three 3 mg tablets) once daily based on serum phosphate (PO4) levels and tolerability at 14 to 21 days. Whole tablets should be swallowed with or without food. If vomiting occurs any time after taking Erdafitinib, the next dose should be taken the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs. If a dose is missed, it can be taken as soon as possible on the same day. The regular daily dose schedule for Erdafitinib should be resumed the next day. Extra tablets should not be taken to make up for the missed dose. Or, as directed by the registered physicians.

Dose Modification:

Dose	1st Dose Reduction	2nd Dose Reduction	3nd Dose Reduction	4nd Dose Reduction	5nd Dose Reduction
9mg (three 3mg tablets)	8mg (two 4mg tablets)	6mg (two 3mg tablets)	5mg (one 5mg tablet)	4mg (one 4mg tablet)	Stop
8mg (two 4mg tablets)	6mg (two 3mg tablets)	5mg (one 5mg tablet)	4mg (one 4mg tablet)	Stop	

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

Precautions:
•**Ocular Disorders:** Erdafitinib can cause ocular disorders, including central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) resulting in visual field defect. Monthly ophthalmological examinations should be performed during the first four months of treatment, every 3 months afterwards, and at any time for visual symptoms. Ophthalmological examination should include assessment of visual acuity, slit lamp examination, fundoscopy, and optical coherence tomography. Erdafitinib should withhold when CSR/RPED occurs and permanently discontinue if it does not resolve within 4 weeks or if Grade 4 in severity.
•**Hyperphosphatemia:** Increases in phosphate levels are a pharmacodynamic effect of Erdafitinib. Hyperphosphatemia should be monitored and dose modifications should be managed when required.
•**Embryo-Fetal Toxicity:** Erdafitinib can cause fetal harm. Patients should be advised of the potential risk to the fetus and to use effective contraception.

Side Effects: The most common side effects of Erdafitinib include: •mouth sores, •feeling tired, •change in kidney function, •diarrhea, •dry mouth, •nails separate from the bed or poor formation of the nail, •change in liver function, •low salt (sodium) levels, •decreased appetite, •change in sense of taste, •low red blood cells (anemia), •dry skin, •dry eyes, •hair loss, •redness, •swelling, •peeling or •tenderness, •mainly on the hands or feet (hand-foot syndrome), •constipation, •stomach (abdominal) pain, •nausea, •muscle pain, •Ocular Disorders, and •Hyperphosphatemia.

Use in Pregnancy and Lactation: Erdafitinib can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with Erdafitinib. Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Males and females of reproductive potential are advised to use effective contraception during treatment with Erdafitinib and for one month after the last dose. Based on findings from animal studies, Erdafitinib may impair fertility in females of reproductive potential.
Lactation: Because of the potential for serious adverse reactions from Erdafitinib in a breastfed child, lactating women should not to breastfeed during treatment with Erdafitinib and for one month following the last dose.
Pediatric Use: The safety and effectiveness of Erdafitinib in pediatric patients have not been established.

Drug Interactions:

•Effect of Other Drugs on Erdafitinib

Strong CYP2C9 or CYP3A4 Inhibitors	
Clinical Impact	• Co-administration of Erdafitinib with strong inhibitors of CYP2C9 or CYP3A4 can increase Erdafitinib plasma concentrations. • Increased Erdafitinib plasma concentrations may lead to increased drug-related toxicity.
Clinical Management	• Alternative therapies should consider that are not strong inhibitors of CYP2C9 or CYP3A4 during treatment with Erdafitinib. • If co-administration of a strong inhibitor of CYP2C9 or CYP3A4 is unavoidable, adverse reactions should closely monitor and dose modifications should consider accordingly. If the strong inhibitor is discontinued, Erdafitinib dose may be increased in the absence of drug-related toxicity.
Strong CYP2C9 or CYP3A4 Inducers	
Clinical Impact	• Co-administration of Erdafitinib with strong inducers of CYP2C9 or CYP3A4 may decrease Erdafitinib plasma concentrations significantly. • Decreased Erdafitinib plasma concentrations may lead to decreased activity.
Clinical Management	• Co-administration of strong inducers of CYP2C9 or CYP3A4 should avoid with Erdafitinib.
Moderate CYP2C9 or CYP3A4 Inducers	
Clinical Impact	• Co-administration of Erdafitinib with moderate inducers of CYP2C9 or CYP3A4 may decrease Erdafitinib plasma concentrations. • Decreased Erdafitinib plasma concentrations may lead to decreased activity.
Clinical Management	• If a moderate CYP2C9 or CYP3A4 inducer must be co-administered at the start of Erdafitinib treatment, Erdafitinib dose should be administered as recommended (8 mg once daily with potential to increase to 9 mg once daily based on serum phosphate levels on Days 14 to 21 and tolerability). • If a moderate CYP2C9 or CYP3A4 inducer must be co-administered after the initial dose increase period based on serum phosphate levels and tolerability, Erdafitinib dose should be increased up to 9 mg. • When a moderate inducer of CYP2C9 or CYP3A4 is discontinued, continue Erdafitinib at the same dose, in the absence of drug-related toxicity.
Serum Phosphate Level-Altering Agents	
Clinical Impact	• Co-administration of Erdafitinib with other serum phosphate level-altering agents may increase or decrease serum phosphate levels. • Changes in serum phosphate levels due to serum phosphate level-altering agents (other than Erdafitinib) may interfere with serum phosphate levels needed for the determination of initial dose increased based on serum phosphate levels.
Clinical Management	• Co-administration of serum phosphate level-altering agents with Erdafitinib should avoid before initial dose increase period based on serum phosphate levels (Days 14 to 21).

•Effect of Erdafitinib on Other Drugs

CYP3A4 Substrates	
Clinical Impact	• Co-administration of Erdafitinib with CYP3A4 substrates may alter the plasma concentrations of CYP3A4 substrates. • Altered plasma concentrations of CYP3A4 substrates may lead to loss of activity or increased toxicity of the CYP3A4 substrates.
Clinical Management	• Co-administration of Erdafitinib should avoid with sensitive substrates of CYP3A4 with narrow therapeutic indices.
OCT2 Substrates	
Clinical Impact	• Co-administration of Erdafitinib with OCT2 substrates may increase the plasma concentrations of OCT2 substrates. • Increased plasma concentrations of OCT2 substrates may lead to increased toxicity of the OCT2 substrates.
Clinical Management	• Alternative therapies should consider that are not OCT2 substrates or consider reducing the dose of OCT2 substrates (e.g., metformin) based on tolerability.
P-glycoprotein (P-gp) Substrates	
Clinical Impact	• Co-administration of Erdafitinib with P-gp substrates may increase the plasma concentrations of P-gp substrates. • Increased plasma concentrations of P-gp substrates may lead to increased toxicity of the P-gp substrates.
Clinical Management	• If co-administration of Erdafitinib with P-gp substrates is unavoidable, Erdafitinib administrationshould be separated by at least 6 hours before or after administration of P-gp substrates with narrows therapeutic index.

Overdose: There is no data available.

Storage: Store below 30^{o} C in a cool & dry place, away from sunlight. Keep out of reach of children.

Packaging: Erdanib-4: Each box contains 60 tablets in a container.
Erdanib-5: Each box contains 30 tablets in a container.

DRUG INTERNATIONAL LTD.
UNIT-2
Tongi, Gazipur, Bangladesh