Upadinum ER

(Upadacitinib)

15mg Tablets

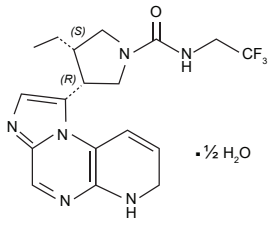
اوپاڈینم ایی آر

(اوپاڈیسیٹینِب)

۱۵ ملی گرام ٹیبلیٹس

COMPOSITION
Each film coated extended release tablet contains:
Upadacitinib Hemihydrate eq. to Upadacitinib ...15 mg
Product complies Innovator's Specs.

DESCRIPTION
Upadinum ER contains Upadacitinib a Janus kinase (JAK) inhibitor. The chemical name of Upadacitinib is (3S, 4R)-3-Ethyl-4-(3H-imidazo[1, 2- a]pyrrolo[2, 3-e]pyrazin-8-yl)-N-(2, 2, 2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1). Its molecular formula is $C_{17}H_{19}F_3N_8O \cdot ½\ H_2O$ and the structural formula is:



Upadacitinib Hemihydrate

CLINICAL PHARMACOLOGY
Mechanism of Action
Upadacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). In a cell-free isolated enzyme assay, Upadacitinib had greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2. In human leukocyte cellular assays, Upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1 and JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation.

Pharmacokinetics
Absorption
Following oral administration of Upadacitinib extended-release tablets, Upadacitinib is absorbed with a median T_{max} of 2 to 4 hours. Following oral administration of 6mg Upadacitinib, Upadacitinib is absorbed with a median T_{max} of 1 hour. Coadministration of Upadacitinib tablets with a high-fat/high-calorie meal had no clinically relevant effect on Upadacitinib exposures (increased AUC_{inf} by 29% and C_{max} by 39% to 60%). Coadministration of Upadacitinib with food is not expected to have a clinically relevant effect on Upadacitinib exposure.

Distribution
Upadacitinib is 52% bound to plasma proteins. Upadacitinib partitions similarly between plasma and blood cellular components with a blood to plasma ratio of 1.0.

Metabolism
Upadacitinib metabolism is mediated by mainly CYP3A4 with a potential minor contribution from CYP2D6. The pharmacologic activity of Upadacitinib is attributed to the parent molecule. In a human radiolabeled study, unchanged Upadacitinib accounted for 79% of the total radioactivity in plasma while the main metabolite detected (product of monooxidation followed by glucuronidation) accounted for 13% of the total plasma radioactivity.

Elimination
Following single dose administration of [^{14}C]-Upadacitinib immediate-release solution, Upadacitinib was eliminated predominantly as the unchanged parent drug in urine (24%) and feces (38%). Approximately 34% of Upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 8 to 14 hours.

Special Population
Patients with Renal Impairment
Mild or moderate renal impairment has no clinically relevant effect on Upadacitinib exposure. Upadacitinib AUC_{inf} was 18%, 33%, and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib C_{max} was similar in subjects with normal and impaired renal function.

Patients with Hepatic Impairment
Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment has no clinically relevant effect on Upadacitinib exposure. Upadacitinib AUC_{inf} was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal liver function. Upadacitinib C_{max} was unchanged in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal liver function. Upadacitinib was not studied in patients with severe hepatic impairment (Child-Pugh C).

THERAPEUTIC INDICATIONS
Upadinum ER (Upadacitinib) is indicated for the treatment of:
- Adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers.
- Adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
- Adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.
- Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers.
- Adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.
- Adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers.
- Adults with active non-radiographic axial spondyloarthritis having objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal Anti-inflammatory drugs (NSAIDs).

DOSAGE AND ADMINISTRATION
Recommended Evaluations and Immunizations Prior to Treatment Initiation
Prior to Upadinum ER (Upadacitinib) treatment initiation, consider performing the following evaluations:
- Active and latent tuberculosis (TB) infection evaluation - If positive, treat for TB prior to Upadinum ER (Upadacitinib) use.
- Viral hepatitis screening in accordance with clinical guidelines - Upadinum ER (Upadacitinib) initiation is not recommended in patients with active hepatitis B or hepatitis C.
- A complete blood count - Upadinum ER (Upadacitinib) initiation is not recommended in patients with an absolute lymphocyte count less than 500 cells/mm^3, absolute neutrophil count less than 1000 cells/mm^3, or hemoglobin level less than 8g/dL.
- Baseline hepatic function: Upadinum ER (Upadacitinib) initiation is not recommended for patients with severe hepatic impairment (Child-Pugh C).
- Pregnancy Status: Verify the pregnancy status of females of reproductive potential prior to starting treatment.
- Update immunizations according to current immunization guidelines.
- Treatment with Upadinum ER (Upadacitinib) should be initiated and supervised by physicians experienced in the diagnosis and treatment of conditions for which Upadinum ER (Upadacitinib) is indicated.

Rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis
The recommended dose of Upadinum ER (Upadacitinib) is 15mg once daily.

Consideration should be given to discontinuing treatment in patients with axial spondyloarthritis who have shown no clinical response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Atopic dermatitis
Adults
The recommended dose of Upadinum ER (Upadacitinib) is 15mg or 30mg once daily based on individual patient presentation.

- A dose of 15mg is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy.
- A dose of 30mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy or patients with an inadequate response to 15mg once daily.
- The lowest effective dose to maintain response should be used.

Elderly
For patients 65 years of age and older, the recommended dose is 15mg once daily.

Adolescents (from 12 to 17 years of age)
The recommended dose of Upadinum ER (Upadacitinib) is 15mg once daily for adolescents weighing at least 30 kg.

Concomitant topical therapies
Upadinum ER (Upadacitinib) can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas. Consideration should be given to discontinuing Upadinum ER (Upadacitinib) treatment in any patient who shows no evidence of therapeutic benefit after 12 weeks of treatment.

Ulcerative colitis
Adults
Induction
The recommended induction dose of Upadinum ER (Upadacitinib) is 45mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, Upadinum ER (Upadacitinib) 45mg once daily may be continued for an additional 8 week. Upadinum ER (Upadacitinib) should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance
The recommended maintenance dose of Upadinum ER (Upadacitinib) is 15mg or 30mg once daily based on individual patient presentation:
- A dose of 15mg is recommended for patients at higher risk of VTE, MACE and malignancy.
- A dose of 30mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment who are not at higher risk of VTE, MACE and malignancy or who do not show adequate therapeutic benefit to 15mg once daily.
- The lowest effective dose to maintain response should be used.

Elderly
For patients 65 years of age and older, the recommended dose is 15mg once daily. In patients who have responded to treatment with Upadinum ER (Upadacitinib), corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Crohn's disease
Induction
The recommended induction dose of Upadinum ER (Upadacitinib) is 45mg once daily for 12 weeks.

Maintenance
The recommended maintenance dose of Upadinum ER (Upadacitinib) is 15mg or 30mg once daily based on individual patient presentation.
- A dose of 15mg is recommended for patients at higher risk of VTE, MACE and malignancy.
- A dose of 30mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy or who do not show adequate therapeutic benefit to 15mg once daily.
- A dose of 30mg once daily may be appropriate for patients who have not achieved adequate therapeutic benefit after the initial 12-week induction. For these patients, Upadinum ER (Upadacitinib) should be discontinued if there is no evidence of therapeutic benefit after 24 weeks of treatment.
- The lowest effective dose to maintain response should be used.

Elderly
For patients 65 years of age and older, the recommended maintenance dose is 15mg once daily. In patients who have responded to treatment with Upadinum ER (Upadacitinib), corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Strong Inhibitors of Cytochrome P450
For patients with ulcerative colitis and Crohn's disease receiving strong inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole, clarithromycin), the recommended induction dose is 30mg once daily and the recommended maintenance dose is 15mg once daily.

Dose Interruption
Treatment should be interrupted if a patient develops a serious infection until the infection is controlled. Interruption of dosing may be needed for management of laboratory abnormalities as described in Table below.

Laboratory measures and monitoring guidance

Laboratory measure	Action	Monitoring guidence
Absolute neutrophil Count (ANC)	Treatment should be interrupted if ANC is <1 x 10^9 cells/L and may be restarted once ANC returns above this value	Evaluate at baseline and then no later than 12 weeks after initiation of treatment. Thereafter evaluate according to individual patient management.
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is <0.5 x 10^9 cells/L and may be restarted once ANC returns above this value	
Haemoglobin (Hb)	Treatment should be interrupted if HB is <8 g/dL and may be restarted once HB returns above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	Evaluate at baseline and thereafter according to routine patient management.
Lipids	Patients should be managed according to international guidelines for clinical hyperlipidaemia	Evaluate 12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia

Special Population
Atopic dermatitis
For atopic dermatitis, doses higher than 15mg once daily are not recommended in patients 65 years of age and older.

Ulcerative colitis and Crohn's disease
For ulcerative colitis and Crohn's disease, doses higher than 15mg once daily for maintenance therapy are not recommended in patients 65 years of age and older.

Patients with Renal Impairment
Upadinum ER (Upadacitinib) should be used with caution in patients with severe renal impairment as described in Table below. The use of Upadinum ER (Upadacitinib) has not been studied in subjects with end stage renal disease and is therefore not recommended for use in these patients.

Recommended dose for severe renal impairment*

Therapeutic indication	Recommended once daily dose
Rheumatoid arthritis, Psoriatic arthritis, Axial spondyloarthritis, Atopic dermatitis	15mg
Ulcerative colitis, Crohn's disease	Induction: 30mg for 8 weeks
	Maintenance: 15mg
*estimated glomerular filtration rate (eGFR) 15 to < 30 ml/min/1.73m^2	

Patients with Hepatic Impairment
Upadinum ER (Upadacitinib) should not be used in patients with severe (Child-Pugh C) hepatic impairment.

Rheumatoid Arthritis, Psoriatic Arthritis, Atopic Dermatitis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis
No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Ulcerative Colitis
For patients with mild to moderate hepatic impairment (Child-Pugh A or B) the recommended dosage is:
Induction: 30mg once daily for 8 weeks
Maintenance: 15mg once daily

Crohn's Disease
For patients with mild to moderate hepatic impairment (Child-Pugh A or B) the recommended dosage is:
Induction: 30mg once daily for 12 weeks
Maintenance: 15mg once daily

Method of Administration
Upadinum ER (Upadacitinib) is to be taken orally once daily with or without food and may be taken at any time of the day. Tablets should be swallowed whole and should not be split, crushed, or chewed in order to ensure the entire dose is delivered correctly. Food or drink containing grapefruit should be avoided during treatment with Upadacitinib.

ADVERSE REACTIONS
Very Common: Upper respiratory tract infections (URTI) and acne.
Common: Bronchitis, Herpes zoster, Herpes simplex, folliculitis, influenza, urinary tract infection, pneumonia, non-melanoma skin cancer, anaemia, neutropaenia, lymphopaenia, urticaria, hypercholesterolaemia, hyperlipidaemia, cough, abdominal pain, nausea, rash, fatigue, pyrexia, blood CPK increased, ALT increased, AST increased, weight increased, headache and dizziness.
Uncommon: Oral candidiasis, diverticulitis, sepsis, serious hypersensitivity reactions, hypertriglyceridaemia and gastrointestinal perforation.

CONTRAINDICATIONS
Upadacitinib is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients of the product.
- Active tuberculosis (TB) or active serious infections.
- Severe hepatic impairment.
- Pregnancy.

PRECAUTIONS

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS SERIOUS INFECTIONS

ELDERLY
Upadacitinib should only be used if no suitable treatment alternatives are available in patients with 65 years of age and older.

SERIOUS INFECTIONS
Patients treated with Upadacitinib are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.
If a serious infection develops, interrupt Upadacitinib until the infection is controlled.
Reported infections include:
- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Upadacitinib use and during therapy. Treatment for latent infection should be considered prior to Upadacitinib use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis.
- Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with Upadacitinib should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.
Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Upadacitinib, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MORTALITY
In a large, randomized, post-marketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with Upadacitinib. In RA patients treated with another JAK inhibitor, a higher rate of malignancies was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk.

MAJOR ADVERSE CARDIOVASCULAR EVENTS
In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue Upadacitinib in patients that have experienced a myocardial infarction or stroke.

THROMBOSIS
Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid Upadacitinib in patients at risk. Patients with symptoms of thrombosis should discontinue Upadacitinib and be promptly evaluated.

Hypersensitivity Reactions
Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving Upadacitinib in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue Upadacitinib and institute appropriate therapy.

Gastrointestinal Perforations
Gastrointestinal perforations have been reported in clinical trials with. Monitor Upadacitinib treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and those taking concomitant medications including NSAIDs or corticosteroids). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.

Laboratory Abnormalities
Neutropenia
Treatment with Upadacitinib was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3). Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid Upadacitinib initiation and interrupt Upadacitinib treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3).

Lymphopenia
ALC less than 500 cells/mm^3 were reported in Upadacitinib treated patients in clinical trials. Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid Upadacitinib initiation or interrupt Upadacitinib treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3).

Anemia
Decreases in hemoglobin levels to less than 8g/dL were reported in Upadacitinib treated patients in clinical trials. Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid Upadacitinib initiation or interrupt Upadacitinib treatment in patients with a low hemoglobin level (i.e., less than 8g/dL).

Lipids
Treatment with Upadacitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.

Liver Enzyme Elevations
Treatment with Upadacitinib was associated with increased incidence of liver enzyme elevations compared to treatment with placebo. Evaluate liver enzymes at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, Upadacitinib should be interrupted until this diagnosis is excluded.

Embryo-Fetal Toxicity
Upadacitinib may cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with Upadacitinib and for 4 weeks following completion of therapy.

Vaccinations
Avoid use of live vaccines during or immediately prior to Upadacitinib therapy initiation. Prior to initiating Upadacitinib treatment, it is recommended that patients be brought up to date with all immunizations, including prophylactic *Varicella zoster* or *Herpes zoster* vaccinations, in agreement with current immunization guidelines.

Medication Residue in Stool
Reports of medication residue in stool or ostomy output have occurred in patients taking Upadacitinib. Most reports described anatomic (e.g., ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions with shortened gastrointestinal transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly.
Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

Immunosuppressive Medicinal Products
Combination with other potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporin, tacrolimus, and biologic DMARDs or other JAK inhibitors has not been evaluated in clinical studies and is not recommended as a risk of additive immunosuppression cannot be excluded.

Hypoglycaemia in patients treated for Diabetes
There have been reports of hypoglycaemia following initiation of JAK inhibitors, including Upadacitinib, in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.

Non-Melanoma Skin Cancer (NMSC)
NMSCs have been reported in patients treated with Upadacitinib. A higher rate of NMSC was observed with Upadacitinb 30mg compared to Upadacitinib 15mg. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Effects on ability to drive and use machines
Upadacitinib may have a minor influence on the ability to drive and use machines because dizziness and vertigo may occur during treatment with updacitinib.

Pregnancy
Upadacitinib is contraindicated during pregnancy. If a patient becomes pregnant while taking Upadacitinib the parents should be informed of the potential risk to the foetus.

Nursing Mothers
Upadacitinib should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue Upadacitinib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

DRUG INTERACTIONS
Strong CYP3A4 Inhibitors
Upadacitinib exposure is increased when it is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole, clarithromycin, and grapefruit), which may increase the risk of Upadacitinib adverse reactions.
Monitor patients closely for adverse reactions when co-administering Upadacitinib once daily with strong CYP3A4 inhibitors. Food or drink containing grapefruit should be avoided during treatment with Upadacitinib.

Strong CYP3A4 Inducers
Upadacitinib exposure is decreased when Upadacitinib is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of Upadacitinib. Coadministration of Upadacitinib with strong CYP3A4 inducers is not recommended.

Potential for Upadacitinib to affect the pharmacokinetics of other medicinal products
Administration of multiple 30mg or 45mg once daily doses of Upadacitinib to healthy subjects had a limited effect on midazolam (sensitive substrate for CYP3A) plasma exposures (24-26% decrease in midazolam AUC and C_{max}), indicating that Upadacitinib 30mg or 45mg once daily may have a weak induction effect on CYP3A. In a clinical study, rosuvastatin and atorvastatin AUC were decreased by 33% and 23%, respectively, and rosuvastatin C_{max} was decreased by 23% following the administration of multiple 30mg once daily doses of Upadacitinib to healthy subjects. Administration of multiple 45mg once daily doses of Upadacitinib to healthy subjects led to a limited increase in AUC and C_{max} of dextromethorphan (sensitive CYP2D6 substrate) by 30% and 35%, respectively, indicating that Upadacitinib 45mg once daily has a weak inhibitory effect on CYP2D6.

OVERDOSAGE
In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

STORAGE
Store below 30°C in a dry place, protect from light. To be dispensed on the prescription of a registered medical practitioner only. Keep out of the reach of children.

PRESENTATION
Upadinum ER 15mg tablets are available in 1x10's blister in a carton.

ہدایات:

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر خشک جگہ پر رکھیں،
روشنی سے بچائیں۔ صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دُور رکھیں۔

Manufactured by:
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Mfg. Lic No. 000415

QAR No. AW23-1433-01