# ITAGLIP Plus Tablets

(Sitagliptin Phosphate + Metformin HCl)

**WARNING: LACTIC ACIDOSIS**

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5mcg/ml.
- Risk factors include renal impairment, concomitant use of certain drugs, age • 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in WARNINGS AND PRECAUTIONS section.
- If lactic acidosis is suspected, discontinue ITAGLIP® Plus and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

## COMPOSITION

**ITAGLIP® Plus 50mg/500mg Tablets:**
Each film coated tablet contains:
Sitagliptin Phosphate USP eq. to Sitagliptin……50mg
Metformin HCl BP ……500mg

**ITAGLIP® Plus 50mg/850mg Tablets:**
Each film coated tablet contains:
Sitagliptin phosphate monohydrate USP eq. to Sitagliptin……50mg
Metformin HCl BP ……850mg

**ITAGLIP® Plus 50mg/1000mg Tablets:**
Each film coated tablet contains:
Sitagliptin phosphate monohydrate USP eq. Sitagliptin……50mg
Metformin HCl BP ……1000mg

## DRUG DESCRIPTION

**ITAGLIP® Plus** tablets contain two oral antihyperglycemic drugs; sitagliptin and metformin HCl, used in the management of type 2 diabetes.

Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. It is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5 trifluorophenyl) butyl]-5,6,7,8 tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a] pyrazine phosphate (1:1) monohydrate with an empirical formula of $C_{16}H_{15}F_6N_5OH_3PO_4H_2O$ and a molecular weight of 523.32. Metformin hydrochloride (N, N-dimethylimido dicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents with a molecular formula of $C_4H_{11}N_5HCl$ and a molecular weight of 165.63.

## CLINICAL PHARMACOLOGY

PHARMACODYNAMICS: Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD07.

**ITAGLIP® Plus** combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: Sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Mechanism of action:

Sitagliptin: It is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4.

Metformin: It is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.

Metformin may act via three mechanisms: - By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis; - In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization; - By delaying intestinal glucose absorption.

PHARMACOKINETICS:

Sitagliptin: Absorption: Rapid; Distribution: ~198 L; Protein binding: 38%; Metabolism: Not extensively metabolized; minor metabolism via CYP3A4 and 2C8 to metabolites (inactive) suggested by in vitro studies; Bioavailability: ~87%; Half-life elimination: 12.4 hours; Time to peak, plasma: 1 to 4 hours; Excretion: Urine 87% (~79% as unchanged drug, 16% as metabolites); feces 13%; Renal function impairment: Plasma AUC levels of sitagliptin were increased approximately 2- and 4-fold in patients with moderate and severe renal impairment, including patients with ESRD on hemodialysis, respectively; Geriatric: Elderly patients had ~19% higher plasma concentration.

Metformin: Onset of action: Within days; maximum effects up to 2 weeks; Distribution: Vd: 654 ± 358 L; partitions into erythrocytes; concentrates in liver, kidney, and GI tract; Protein binding: Negligible; Metabolism: Not metabolized by the liver. Bioavailability: Absolute: Fasting: 50% to 60%; Half-life elimination: Plasma: 4 to 9 hours; Blood ~17.6 hours; Time to peak conc. in serum: 2 to 3 hours; Excretion: Urine (90% as unchanged drug; active secretion); Renal function impairment: Peak and systemic exposure is increased and oral and renal clearance is decreased; Geriatric: Total plasma clearance is decreased, half-life is prolonged, and Cmax is increased.

## INDICATIONS AND DOSAGE

INDICATIONS AND USAGE:

**ITAGLIP® Plus** is indicated in adult patients with type 2 diabetes mellitus:

- It is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.
- **ITAGLIP® Plus** is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.
- **ITAGLIP® Plus** is indicated as triple combination therapy with a PPAR• agonist (i.e. a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPAR• agonist.
- **ITAGLIP® Plus** is also indicated as add-on to insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

DOSAGE AND ADMINISTRATION:

Method of Administration: **ITAGLIP® Plus** should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. It must not be split or divided before swallowing.

Dosage: The dose of antihyperglycemic therapy with **ITAGLIP® Plus** should be individualized while not exceeding the maximum recommended daily dose of 100mg Sitagliptin and 2000mg of metformin.

- Patients already on metformin: Initial: Sitagliptin 100mg/day plus current daily dose of metformin. Patients currently on metformin 1,700mg/day (e.g. 850mg twice daily) may receive an initial dose of sitagliptin 100mg/metformin 2,000mg per day.
- Patients not on metformin: Initial: Sitagliptin 100mg/metformin 1,000mg per day. Gradual dose escalation is recommended to reduce gastrointestinal side effects associated with metformin.
- Dosage adjustment for concomitant therapy: Patients receiving concomitant insulin and/or insulin secretagogues (e.g. sulfonylureas) may require dosage adjustments of these agents. All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.

Important Limitations of Use: **ITAGLIP® Plus** should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. The combination has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis during its use.

SPECIAL POPULATIONS:

Paediatric population: No studies are performed in paediatric population under 18 years of age.

Geriatric population: As metformin and sitagliptin are excreted by the kidney, **ITAGLIP® Plus** should be used with caution as age increases. No dose adjustment is recommended but monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

Renal impairment: eGFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR < 60mL/min. - eGFR >45mL/minute/1.73 m²: No dosage adjustment necessary; monitor renal function at least annually. - eGFR 30 to 45mL/minute/1.73 m²: Use is not recommended for initiation of therapy; if eGFR falls to <45mL/minute/1.73m² during therapy, consider benefits/risks of continuing therapy and limit sitagliptin dose to 50mg once daily. - eGFR <30mL/minute/1.73m²: Use is contraindicated. If no adequate strength of **ITAGLIP® Plus** is available, individual monocomponents should be used instead of the fixed-dose combination.

Hepatic Impairment: **ITAGLIP® Plus** must not be used in patients with hepatic impairment.

OVERDOSAGE:

There is no experience with doses above 800mg in clinical studies for sitagliptin. A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. It is not known if sitagliptin is dialysable by peritoneal dialysis.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

## CONTRAINDICATIONS

**ITAGLIP® Plus** (Sitagliptin and metformin HCl) is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²)
- History of a serious hypersensitivity reaction to sitagliptin such as anaphylaxis or angioedema
- Diabetic pre-coma
- Intravascular administration of iodinated contrast agents
- Hepatic impairment
- Breast-feeding
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin
- Acute conditions with the potential to alter renal function such as; dehydration, severe infection, shock etc.
- Acute or chronic disease which may cause tissue hypoxia such as; cardiac or respiratory failure, recent myocardial infarction, shock etc.
- Acute alcohol intoxication, alcoholism

## WARNINGS AND PRECAUTIONS

CONCERNS RELATED TO ADVERSE EFFECTS:

Lactic acidosis: [Boxed Warning]: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset is often subtle, accompanied by nonspecific symptoms (e.g., malaise, myalgias, respiratory distress, somnolence, abdominal pain); elevated blood lactate levels (>5mmol/L); anion gap acidosis (without evidence of ketonuria or ketonemia); increased lactate:pyruvate ratio; metformin plasma levels generally > 5mcg/mL. Risk factors for lactic acidosis include patients with renal impairment, concomitant use of certain drugs (e.g., NSAIDS, diuretics, carbonic anhydrase inhibitors such as topiramate),• 65 years, having a radiologic study with contrast, surgery and other procedures, hypoxic states (e.g., acute heart failure or other cardiorespiratory illness) or sepsis, excessive alcohol intake, hepatic impairment, inadequately controlled diabetes, ketosis, prolonged fasting, or concomitant use of medicines causing lactic acidosis. Discontinue immediately if acidosis is suspected; prompt hemodialysis is recommended. Discontinue metformin in patients with conditions associated with dehydration, hypoperfusion, sepsis,or hypoxemia. Temporarily discontinue therapy in patients with restricted food and fluid intake.

Acute Pancreatitis: Cases of acute pancreatitis (including hemorrhagic and necrotizing with some fatalities) have been reported with use. Monitor for signs/symptoms of pancreatitis; discontinue use immediately if pancreatitis is suspected and initiate appropriate management. If acute pancreatitis is confirmed, sitagliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Renal effects: Worsening renal function, including acute renal failure, sometimes requiring dialysis has been reported. When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.
Vitamin $B^{12}$ concentrations: Monitor vitamin $B^{12}$ serum concentrations periodically with long-term therapy due to deficiency risk and in particular those with peripheral neuropathy or anemia.
Change in clinical status of patients with previously controlled type 2 diabetes: In case of vague change in clinical status of patients, patient should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, treatment must be stopped immediately and other appropriate corrective measures initiated.
Hypoglycemia when used in combination with other anti-hyperglycemic medicinal products: In clinical trials of sitagliptin as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycemia (i.e. metformin and/or a PPAR• agonist). Hypoglycemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea. Therefore, to reduce the risk of hypoglycemia, a lower dose of sulphonylurea or insulin may be considered.
Hypersensitivity reactions: Serious hypersensitivity reactions, including anaphylaxis, angioedema, and exfoliative skin reactions, such as Stevens-Johnson syndrome, have been reported; discontinue if signs/symptoms of hypersensitivity reactions occur. Events have generally been noted within the first 3 months of therapy, and may occur with the initial dose. Use with caution if patient has experienced angioedema with other dipeptidyl peptidase-4 (DPP-4) inhibitor use.
Severe and Disabling Arthralgia: With DPP-4 inhibitor use, onset may occur within one day to years after treatment initiation and may resolve with discontinuation of therapy. Some patients may experience a recurrence of symptoms if therapy resumed.
Bullous pemphigoid: DPP-4 inhibitor. Advise patients to report development of blisters or erosions. Discontinue therapy if bullous pemphigoid is suspected and consider referral to a dermatologist.
Surgical procedures: Metformin should be withheld the day of surgery (all other oral hypoglycemic agents). Resume only after normal intake resumed and normal renal function is verified.
Iodinated contrast: It is recommended to temporarily discontinue metformin at the time of or before iodinated contrast imaging procedures in patients with an eGFR 30 to 60 mL/minute/1.73 $m^2$; or with a history of hepatic disease, alcoholism, or heart failure; or in patients who will receive intra-arterial iodinated contrast. Reevaluate eGFR 48 hours after imaging procedure; restart if renal function is stable.

DISEASE-RELATED CONCERNS:
Heart Failure: An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. Consider the risks and benefits prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation.
Hepatic impairment: It is recommended to generally avoid metformin use in patients with hepatic impairment due to potential for lactic acidosis. However, continued use of metformin in patients with diabetes with liver dysfunction, including cirrhosis, may be associated with a survival benefit in carefully selected patients.
Renal impairment: The risk of metformin accumulation and lactic acidosis increases with degree of renal impairment. Use of concomitant medications that may affect renal function (i.e. affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.
Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).
Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with sitagliptin.

CONCURRENT DRUG THERAPY ISSUES:
Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions section.

SPECIAL POPULATIONS:
Pregnancy: Sitagliptin/Metformin: Pregnancy Category B
**ITAGLIP® Plus** (Sitagliptin and metformin HCl) should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment should be discontinued and the patient switched to insulin treatment as soon as possible.
Lactation: Not recommended to women who are breast-feeding.
Geriatric Use: Use with caution due to increased risk of lactic acidosis with metformin with increasing age.

OTHER WARNINGS/PRECAUTIONS:
Patient education: Diabetes self-management education is essential to maximize the effectiveness of therapy.
Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism.
Laboratory tests: Response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C levels
Females and Males of Reproductive Potential: Therapy with metformin may result in ovulation in some anovulatory women.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
**ITAGLIP® Plus** has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that dizziness and somnolence have been reported with sitagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when **ITAGLIP® Plus** is used in combination with a sulphonylurea or with insulin.

ADVERSE REACTIONS
Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported.
>10%: Endocrine and metabolic: Hypoglycaemia (13.8% combination with sulphonylurea and 10.9% combination with Insulin).
1% TO 10%: Central Nervous System: Headache (6%), Respiratory: Upper respiratory infections (6%), Gastrointestinal: Diarrhea (8%), nausea (5%), abdominal pain (3%), vomiting (2%)
<1%, postmarketing, and/or case reports: Arthralgia, back pain, constipation, hypersensitivity reaction (including anaphylaxis, angioedema, skin rash, urticaria, hypersensitivity angiitis, exfoliative skin conditions [including stevens-johnson syndrome]), thrombocytopenia, somnolence, increased liver enzymes, lactic acidosis, limb pain, myalgia, oral mucosa ulcer, pancreatitis (including hemorrhagic or necrotizing), pemphigoid, pruritus, renal failure, renal insufficiency, severe arthralgia, stomatitis, interstitial lung disease, vasculitis.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
Sitagliptin was not mutagenic or clastogenic with or without metabolic activation. Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking. There was no evidence of a carcinogenic and mutagenic potential of metformin found in rats/ in vitro tests, nor it affects fertility.

REPORTING OF SUSPECTED ADVERSE REACTIONS:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals and patients/carers are asked to report any suspected adverse reactions at safety@samikhi.com or call on +92 (0) 21 34383400 (Office hours and out of office hours). Also, adverse event may be reported via website: www.samipharmapk.com

DRUG INTERACTIONS
Co-administration of sitagliptin (50mg twice daily) and metformin (1000mg twice daily) did not meaningfully alter each other's pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.
CONCOMITANT USE NOT RECOMMENDED:
Alcohol: Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.
Iodinated contrast agents: Sitagliptin and metformin must be discontinued prior to or at the time of the imaging procedure
COMBINATIONS REQUIRING PRECAUTIONS FOR USE:
Carbonic Anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients
Medicines Affect Renal Functions: These medicinal products can adversely affect renal function, which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.
Drugs that Reduce Metformin Clearance: Drugs such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.
Insulin Secretagogues or Insulin: Coadministration with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
ACE-inhibitors: If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted with ACE inhibitors due to potential risk of hypoglycemia
EFFECTS OF OTHER MEDICINAL PRODUCTS ON SITAGLIPTIN:
Due to limited CYP3A4 mediated metabolism, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could only alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD.
Cyclosporin, a potent inhibitor of p-glycoprotein, when combine with sitagliptin may alter the pharmacokinetics of sitagliptin but that were not considered to be clinically meaningful.
EFFECTS OF SITAGLIPTIN ON OTHER MEDICINAL PRODUCTS:
Digoxin: No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.
Sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives
USE OF METFORMIN WITH OTHER DRUGS:
Certain drugs tend to produce hyperglycemia and may require close observation to maintain adequate glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

STABILITY
See expiry on the pack.

AVAILABILITY
**ITAGLIP® Plus** 50mg/500mg tablets in a pack of 14's.
**ITAGLIP® Plus** 50mg/850mg tablets in a pack of 14's
**ITAGLIP® Plus** 50mg/1000mg tablets in a pack of 14's

INSTRUCTIONS
Dosage as advised by physician. To be sold on the prescription of registered medical practitioner.
Keep out of reach of children. Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine. Store in the original package in order to protect from moisture.

Please read the contents carefully before use.
This package insert is regularly reviewed and updated.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

## ایٹاگلپ® پلس ٹیبلٹ
(سیٹاگلپٹن فاسفیٹ + میٹ فورمن ہائیڈروکلورائیڈ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں
ورنہ دوا خراب ہو جائیگی۔
دوا کو نمی سے محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔

R.N-08/HA/04/19