1.6.1.1 Name of the medicinal Product

Metformin Tablets BP 500 mg

1.6.1.1.1 strength

500 mg/tablet

1.6.1.1.2 Pharmaceutical Form

Oral tablet

1.6.1.2 Qualitative and Quantitative Composition

1.6.1.2.1 Qualitative declaration

Metformin Hydrochloride BP

1.6.1.2.2 Quantitative declaration

Sr. No	Ingredients Chemical Name	Specification	Quantity (mg/tablet)	Reason for Inclusion
1	Metformin Hydrochloride (A)	BP	500.00	Anti-diabetics agent
2	Povidone (PVPK-90)	BP	5.00	Binder
3	Crosscarmellose Sodium	USP-NF	5.00	Disintegrant
4	Povidone (PVPK-90)	BP	5.00	Binder
5	Colloidal Anhydrous Silica (Aerosil)	BP	10.00	Glidant
6	Crosscarmellose Sodium	USP-NF	12.00	Disintegrant
7	Purified Talc	BP	10.00	Glidant
8	Microcrystalline Cellulose (pH 102) (C)	BP	28.00	Diluent
9	Magnesium Stearate	BP	5.00	Lubricant
10	Colour White SC-SP- 3180 (Spraycel)	In-house	18.0	Colouring agent
11	Purified water #	BP	Q.S	Solvent

Note:

(A) = Quantity to be calculated on the basis of its potency.

= This will not remain in final product.

(C) = Quantity of Microcrystalline Cellulose (pH 102) BP to be reduced against incremental increase in quantity of Metformin Hydrochloride BP due to assay compensation.

Q.S. = Quantity of Sufficient

1.6.1.3 Pharmaceutical Form

Oral Tablet

White to off-white coloured, round shaped, biconvex, film coated tablets, plain on both side.

1.6.1.4 Clinical Particulars

1.6.1.4.1 Therapeutic Indications

Metformin hydrochloride tablets are indicated for the management of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as monotherapy when hyperglycemia cannot be managed with diet and exercise alone. In adults, may be used concomitantly with a sulfonylurea or insulin to improve glycaemic control.

1.6.1.4.2 Posology and Method of Administration

There is no fixed dosage regimen for the management of hyperglycemia in patient with type 2 diabetes with Metformin hydrochloride tablets. Dosage of Metformin hydrochloride tablets should be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily doses. The maximum recommended daily dose for Metformin hydrochloride tablet is 3000 mg for adult and 2000mg for children (10-16 years of age).

Adult:

Initial 500 mg twice daily or 850 mg once daily; titrate in increments of 500 mg weekly or 850 mg every other week; may also titrate from 500 mg twice a day to 850 mg twice a day after 2 weeks with breakfast or first main meal of the day and gradual increased dosage as directed by physician.

Children 10-16 years:

Initial: 500 mg twice daily; increases in daily dosage should be made in increments of 500 mg at weekly intervals, given in divided doses, up to a maximum of 2000 mg/day.

1.6.1.4.3 Contraindications

Metformin hydrochloride tablets are contraindicated for patient with

• Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels 1.5 mg/dL [males], 1.4 mg/dL [females] or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.

• Known hypersensitivity to Metformin, or any of the ingredients of the Metformin Hydrochloride tablets.

• Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

• Temporarily discontinue in patients undergoing radiologic studies in which intravascular iodinated contrast media are utilized, because use of such products may result in acute alteration of renal function.

1.6.1.4.4 Special Warnings and Special Precautions for Use

Use Metformin hydrochloride with caution in patients with

• Cardiovascular mortality as oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

• Lactic acidosis is a rare, but potentially severe consequence of therapy with Metformin.

• Hepatic impairment: Avoid use in patients with impaired liver function due to potential for lactic acidosis.

• Renal impairment: Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy.

• Elderly: Metformin should not be initiated in patient ≥80 years of age unless normal renal function is confirmed.

• Stress-related states: It may be necessary to discontinue Metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

• Pregnancy: Available information suggests that Metformin use during pregnancy may be safe as long as good glycaemic control is maintained. Metformin Hydrochloride is prescribed unlabeled for the treatment of Gestational Diabetes Mellitus (GDM); Polycystic Ovary Syndrome (PCOS). However the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Metformin

hydrochloride tablets should not be used unless the potential benefit outweighs the potential risk to fetus.

• Lactation: Metformin Hydrochloride tablets are not recommended for use in lactating mothers as it excretes into breast milk.

1.6.1.4.5 Interaction with other medicinal products and other forms of interaction

Drug	Interaction
Amiloride, Digoxin, Morphine, Procainamide, Quinidine, Quinine, Ranitidine, Triamterene, Vancomycin	Compete with Metformin hydrochloride for substantial tubular secretion
ACE inhibitors	Potential risk of hypoglycemia/hyperglycemia when ACE inhibitor therapy is initiated/withdrawn
Calcium-channel blocking agents, corticosteroids, thiazide diuretics, estrogens and progestins (e.g., oral contraceptives), isoniazid, niacin, phenothiazines, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline)	Antagonize Hypoglycemic Effects of Metformin hydrochloride
Alcohol	Increased risk of hypoglycemia and lactic acidosis
Cimetidine	Possible decreased excretion of Metformin hydrochloride
Clomiphene	Possible resumption of ovulation in premenopausal patients with polycystic ovary syndrome
Furosemide	Increased plasma concentrations of Metformin hydrochloride and furosemide

1.6.1.4.6 Fertility, Pregnancy and Lactation

Pregnancy: Available information suggests that Metformin use during pregnancy may be safe as long as good glycaemic control is maintained. Metformin Hydrochloride is prescribed unlabelled for the treatment of Gestational Diabetes Mellitus (GDM); Polycystic Ovary Syndrome (PCOS). However the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Metformin hydrochloride tablets should not be used unless the potential benefit outweighs the potential risk to fetus.

Lactation: Metformin Hydrochloride tablets are not recommended for use in lactating mothers as it excretes into breast milk.

1.6.1.4.7 Effects on ability to Drive and use Machines

Not Applicable.

1.6.1.4.8 Undesirable Effects

Gastrointestinal: Diarrhea, nausea, vomiting, flatulence Indigestion, abdominal discomfort, abdominal distention, abnormal stools, constipation, dyspepsia/ heartburn, taste disorder

Neuromuscular & skeletal: Weakness, Myalgia

Cardiovascular: Chest discomfort, flushing, palpitation

Central nervous system: Headache , chills, dizziness, lightheadedness

Dermatologic: Rash

Endocrine & metabolic: Hypoglycemia

Respiratory: Dyspnea, upper respiratory tract infection

Miscellaneous: Diaphoresis increased, vitamin B12 levels decreased, flu-like syndrome, nail disorder.

1.6.1.4.9 Overdose

Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns.

Close monitoring should continue until the physician is assured that the patient is out of danger.

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

Lactic acidosis is a rare, but serious, metabolic complication that can occur if Metformin accumulates during treatment due to overdosing. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

1.6.1.5 Pharmacological Properties

1.6.1.5.1 Pharmacodynamics Properties

Metformin hydrochloride decreases hepatic glucose production, decreasing intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization).

1.6.1.5.2 Pharmacokinetic Properties

- Onset of action: Within days; maximum effects up to 2 weeks
- Distribution: Vd: 654 ± 358 L; partitions into erythrocytes
- Protein binding: Negligible
- Metabolism: Not metabolized by the liver
- Bioavailability: Absolute: Fasting: 50% to 60%
- Half-life elimination: Plasma: 4-9 hours
- Time to peak, serum: Extended release: 7 hours (range: 4-8 hours)
- Excretion: Urine (90% as unchanged drug; active secretion)

1.6.1.5.3 Preclinical Safety Data

Not Applicable.

1.6.1.6 Pharmaceutical Particulars

1.6.1.6.1 List of Excipients

Povidone (PVPK-90) BP

Croscarmellose Sodium

Colloidal Anhydrous Silica (Aerosil)

Purified Talc

Microcrystalline Cellulose (pH 102)

Magnesium Stearate

Colour White SC-SP-3180 (Spraycel)

Purified Water

1.6.1.6.2 Incompatibilities

Not applicable.

1.6.1.6.3 Shelf Life

36 months

1.6.1.6.4 Special Precautions for Storage

Store below 30°C. Protect from light.

1.6.1.6.5 Nature and Contents of Container

10 tablets are in blister pack, Such 10 blisters are packed in printed carton with packing insert.

1.6.1.6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

1.6.1.7 Marketing Authorization Holder And Manufacturing Site Addresses

1.6.1.7.1 Name and Address of Marketing Authorization Holder

Name : **LINCOLN PHARMACEUTICALS LTD.**
Address : Trimul Estate, Khatraj, Tal. Kalol,
Dist. Gandhinagar,
Gujarat, India.
Phone : +91-2764-665000
Fax : +91-2764-281809
E-mail : info@lincolnpharma.com
Website : www.lincolnpharma.com

1.6.1.7.2 Name and Address of manufacturing site(s)

Name : **LINCOLN PHARMACEUTICALS LTD.**
Address : Trimul Estate, Khatraj, Tal. Kalol,
Dist. Gandhinagar,
Gujarat, India.
Phone : +91-2764-665000
Fax : +91-2764-281809

E-mail : info@lincolnpharma.com

Website : www.lincolnpharma.com

1.6.1.8 Marketing Authorization Number

To be included after obtaining first registration.

1.6.1.9 Date of First <Registration> / Renewal of The <Registration>

It will be applicable after registration of this product.

1.6.1.10 Date of Revision of the Text

1.6.1.11 Dosimetry (If Applicable)

Not Applicable

1.6.1.12 Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable