For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Pioglitazone Hydrochloride Tablets IP

(Brand Name: K-PIO™ 15 Tablets/ K-PIO™ 30 Tablets)

BOX WARNING

1. **The drug should not be used as first line therapy for diabetes.**
2. **Advice for healthcare professionals:**

- **Pioglitazone should not be used as first line of therapy for diabetes. Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should *not* receive pioglitazone.**
- **Prescribers should review the safety and efficacy of pioglitazone in individuals after 3 to 6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do *not* respond adequately to treatment (e.g., reduction in glycosylated haemoglobin, HbA1c).**
- **Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals: age; current or past history of smoking; exposure to some occupational or chemotherapy agents such as cyclophosphamide; or previous irradiation of the pelvic region.**
- **Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.**

2. Qualitative and Quantitative Composition

Each Uncoated Tablet Contains:

Pioglitazone Hydrochloride IP equivalent to Pioglitazone ……..… 15 mg

Excipients …… q.s.

Each Uncoated Tablet Contains:

Pioglitazone Hydrochloride IP equivalent to Pioglitazone ……..… 30 mg.

Excipients …… q.s.

Colour: Sunset Yellow FCF.

3. Dosage Form and Strength

Dosage Form: Tablet.
Dosage Strength: Pioglitazone 15 mg and 30 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

K-PIO Tablets are indicated as second line therapy in adults with type 2 diabetes mellitus when diet, exercise, and other antidiabetic drugs do not result in adequate glycemic control. Pioglitazone may be used alone or in combination with metformin or sulfonylureas. Pioglitazone exerts its antihyperglycemic effect only in the presence of endogenous insulin. Therefore, pioglitazone should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. The use of pioglitazone in combination with insulin is not indicated.

4.2Posology and Method of Administration

For oral administration in adults.
The recommended starting dose for patients without congestive heart failure is 15 mg or 30 mg once daily. The recommended starting dose for patients with congestive heart failure (NYHA Class I or II) is 15 mg once daily. Based on glycemic response, the dose may be up-titrated in increments of 15 mg up to a maximum of 45 mg once daily.
Dosage should be individualized on the basis of both efficacy and tolerance.
K-PIO Tablets can be administered without regard to meals. Swallow the tablets whole and never crush, cut or chew.
Or, as prescribed by the physician.

4.3Contraindications

K-PIO Tablets are contraindicated in the following:

- Hypersensitivity to pioglitazone or to any component of the formulation.
- Patients with established NYHA Class III or IV heart failure.
- Severe hepatic impairment.
- Pregnancy.
- Diabetic ketoacidosis.
- Current bladder cancer or a history of bladder cancer.
- Uninvestigated macroscopic haematuria.

4.4Special Warnings and Precautions for Use

Congestive Heart Failure (CHF): Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of pioglitazone, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive and rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed

according to current standards of care and discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.

Edema: In controlled clinical trials, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose-related. In post-marketing experience, reports of new onset or worsening edema have been received. Pioglitazone should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, pioglitazone should be used with caution in patients at risk for congestive heart failure. Patients treated with pioglitazone should be monitored for signs and symptoms of congestive heart failure.

Bladder Cancer: Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone than in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded. Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g., cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic hematuria should be investigated before starting pioglitazone therapy. Patients should be advised to promptly seek the attention of their physician if macroscopic hematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Monitoring of Liver Function/ Hepatic Effects: There have been rare reports of hepatocellular dysfunction during post-marketing studies with pioglitazone. Therefore, it is recommended that patients treated with pioglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with pioglitazone in all patients. Therapy with pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 times of ULN) or with any other evidence of liver disease.

Following initiation of therapy with pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgment. If ALT levels are increased to 3 times of ULN during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 times of ULN, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be evaluated. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgment and laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Weight Gain: In clinical trials with pioglitazone there was evidence of dose-related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure. Therefore, weight should be closely

monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Hematology: There was a small reduction in mean hemoglobin (4% relative reduction) and hematocrit (4.1% relative reduction) during therapy with pioglitazone, consistent with hemodilution. Similar changes were seen in metformin (hemoglobin 3 to 4% and hematocrit 3.6 to 4.1% relative reductions) and to a lesser extent sulphonylurea and insulin (hemoglobin 1 to 2% and hematocrit 1 to 3.2% relative reductions)-treated patients in comparative controlled trials with pioglitazone.

Hypoglycaemia: As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary. The use of pioglitazone in combination with insulin is not indicated.

Eye Disorders/Macular Edema: Post-marketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral edema. It is unclear whether or not there is a direct association between pioglitazone and macular edema but prescribers should be alert to the possibility of macular edema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Fractures: An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomized, controlled, double blind clinical trials with treatment for up to 3.5 years. Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women. The risk of fractures should be considered in the long term care of patients treated with pioglitazone.

Ovulation: As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued.

Elderly: Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure. In light of age-related risks (especially bladder cancer, fractures, and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

4.5Drug Interactions

Strong CYP2C8 Inhibitors: An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the serum concentration-time curve or AUC) and half-life (t½) of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors.

CYP2C8 Inducers: An inducer of CYP2C8 (e.g., rifampin) may significantly decrease the exposure (AUC) of pioglitazone. Therefore, if an inducer of CYP2C8 is started or stopped during

treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response without exceeding the maximum recommended daily dose of 45 mg for pioglitazone.

Oral Contraceptives: Administration of thiazolidinediones with oral contraceptives containing ethinyl oestradiol and norethindrone may reduce the plasma concentrations of both hormones by approximately 30%. This could result in loss of contraception. Therefore, a higher dose of oral contraceptive or an alternative method of contraception should be considered.

Topiramate: A decrease in the exposure of pioglitazone and its active metabolites were noted with concomitant administration of pioglitazone and topiramate. The clinical relevance of this decrease is unknown; however, when pioglitazone and topiramate are used concomitantly, monitor patients for adequate glycemic control.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category C. There are no adequate and well-controlled studies of pioglitazone in pregnant women. Animal studies show increased rates of post-implantation loss, delayed development, reduced fetal weight, and delayed parturition at doses 10 to 40 times the maximum recommended human dose. The relevance of such a mechanism in humans is unclear. Pioglitazone is contraindicated during pregnancy.

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. It also increases the fetal risk for major birth defects, still birth, and macrosomia-related morbidity. Thus, when the patient plans to become pregnant and during pregnancy, it is recommended that insulin be used to maintain blood glucose levels as close to normal as possible.

Lactating Women

It is not known whether pioglitazone is secreted in human milk. Pioglitazone is secreted in the milk of lactating rats. Pioglitazone should not be administered to breast-feeding women. Accordingly, a decision should be made whether to discontinue nursing or discontinue pioglitazone, taking into account the importance of drug to the mother.

Paediatric Patients

Safety and effectiveness of pioglitazone in paediatric patients have not been established. Thus, K-PIO Tablets are not recommended for use in children.

Geriatric Patients

With pioglitazone, no significant differences were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Thus, no dose adjustment is necessary for elderly patients. Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin or other antidiabetic agents.

Renal Impairment Patients

No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min). No information is available from dialyzed patients therefore pioglitazone should not be used in such patients.

Hepatic Impairment Patients

Pioglitazone should be used with caution in patients with hepatic disease. Pioglitazone is contraindicated in patients with severe hepatic impairment. Therapy with pioglitazone should not be initiated if a patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5 times upper limit of normal - ULN) at baseline. In cases where therapy is to be initiated, dose adjustment in patients with hepatic disease is not required.

4.7Effect on Ability to Drive and Use Machines

Pioglitazone has no or negligible influence on the ability to drive and use machines. However patients who experience visual disturbance should be cautious when driving a vehicle or using machines.

4.8Undesirable Effects

Commonly reported adverse events with pioglitazone include edema, cardiac failure, pain in extremity, back pain, chest pain, upper respiratory tract infection, headache, sinusitis, myalgia, pharyngitis, and rarely hypoglycemia.

- Adverse events when pioglitazone is co-administered with metformin: Upper respiratory tract infection (URTI), headache, edema, and weight gain.
- Adverse events when pioglitazone is co-administered with sulphonylureas: Edema, headache, flatulence, weight gain, urinary tract infections (UTIs,) URTIs, and hypoglycemia.
- Adverse events when pioglitazone is co-administered with insulin: Hypoglycemia, edema, weight gain, UTIs, diarrhea, back pain, blood creatinine phosphokinase increased, sinusitis, and hypertension.

Clinical Trials Experience

Adverse reactions reported in excess (> 0.5%) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies are listed below:

Infections and Infestations: Upper respiratory tract infection, bronchitis, sinusitis.

Neoplasms (benign, malignant, and unspecified): Bladder cancer.

Blood and Lymphatic System Disorders: Anemia.

Immune System Disorders: Hypersensitivity and allergic reactions.

Metabolism and Nutrition Disorders: Hypoglycaemia, increase in appetite.

Nervous System Disorders: Hypo-aesthesia, headache, dizziness, insomnia.

Eye Disorders: Visual disturbance, macular edema.
Ear and Labyrinth Disorders: Vertigo.
Cardiac Disorders: Heart failure.
Respiratory, Thoracic and Mediastinal Disorders: Dyspnoea.
Gastrointestinal Disorders: Flatulence.
Skin and Subcutaneous Tissue Disorders: Sweating.
Musculoskeletal and Connective Tissue Disorders: Bone fractures, arthralgia, back pain.
Renal and Urinary Disorders: Haematuria, glycosuria, proteinuria.
Reproductive System and Breast Disorders: Erectile dysfunction.
General Disorders: Edema, fatigue,
Investigations: Weight gain, increased blood creatine phosphokinase, increased lactic dehydrogenase, increased alanine aminotransferase.

Post-Marketing Experience

The following adverse reactions have been reported during post-marketing use of pioglitazone.

- New onset or worsening diabetic macular edema with decreased visual acuity.
- Fatal and nonfatal hepatic failure.
- Congestive heart failure.
- Unusually rapid increase in weight - Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

4.9Overdose

In clinical studies, patients have taken pioglitazone at higher than the recommended maximum dose of 45 mg daily. The maximum reported dose of 120 mg/day for 4 days, then 180 mg/day for 7 days have not associated with any symptoms. Hypoglycaemia may occur in combination with sulphonylureas or insulin.
In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

5. Pharmacological Properties

5.1 Mechanism of Action

Pioglitazone is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its unique mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPAR-γ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

5.2Pharmacodynamic Properties

Pioglitazone is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Pharmacological studies indicate that pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone improves glycemic control while reducing circulating insulin levels. Fasting and post-prandial glycemic control is improved in patients with type 2 diabetes mellitus. The decreased insulin resistance produced by pioglitazone results in lower blood glucose concentrations, lower plasma insulin levels and lower HbA1c values. Pioglitazone reduces the hyperglycemia, hyperinsulinaemia, and hypertriglyceridaemia which are characteristics of insulin-resistant diabetes mellitus. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues. Pioglitazone enhances the effects of circulating insulin by decreasing insulin resistance. Therefore, it does not cause hypoglycemia.

5.3Pharmacokinetic Properties

Absorption: Following oral administration, pioglitazone is rapidly absorbed, and peak plasma concentrations (T_{max}) of unchanged pioglitazone are usually achieved within 2 hours after administration. Food delays the T_{max} to 3 to 4 hours, but does not alter the extent of absorption (AUC). The absolute bioavailability following oral administration is approximately 83%.

Following once-daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within 7 days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. Repeated dosing does not result in accumulation of the compound or metabolites.

Distribution: The estimated volume of distribution in humans is 0.25 l/kg. Pioglitazone is extensively bound to plasma protein (> 99 %), principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Major metabolite M-III and M-IV are also extensively bound (>98%) to serum albumin.

Metabolism: Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 and 3A4. Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly converted to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans.

Excretion: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Elimination of unchanged pioglitazone is negligible in either urine or feces. Pioglitazone is excreted primarily as metabolites and their conjugates. Most of the oral dose (55%) is excreted into the bile as metabolites and eliminated in the feces. The mean serum half-life ($t^{1/2}$) of pioglitazone and its metabolites (M-III and M-IV) range from 3 to 7 hours and 16 to 24 hours, respectively.

6. Nonclinical Properties

6.1 Animal Toxicology

Toxicity: Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone hydrochloride (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately four times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Carcinogenesis: A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder of male rats. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). Urinary calculi with subsequent irritation and hyperplasia were postulated as the mechanism for bladder tumors observed in male rats.

A two-year mechanistic study was conducted in male rats utilizing dietary acidification to reduce calculi formation. Dietary acidification decreased but did not abolish the hyperplastic changes in the bladder. The presence of calculi exacerbated the hyperplastic response to pioglitazone but was not considered the primary cause of the hyperplastic changes. The relevance to humans of the bladder findings in the male rat cannot be excluded.

A two-year carcinogenicity study was also conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

Mutagenesis: Pioglitazone hydrochloride was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

Impairment of Fertility: No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone hydrochloride daily prior to and throughout mating and gestation (approximately nine times the maximum recommended human oral dose based on mg/m^2).

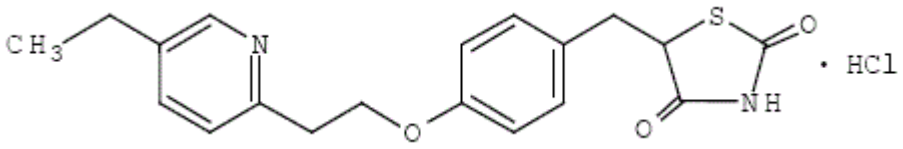
7. Description

K-PIO 15 Tablets are white coloured round beveled shape uncoated tablets having break line on one side and plain on the other side.

K-PIO 30 Tablets are light orange coloured round beveled shape uncoated tablets having break line on one side and plain on the other side.

Each tablet of K-PIO 15 contains 15 mg of pioglitazone for oral administration in adults.
Each tablet of K-PIO 30 contains 30 mg of pioglitazone for oral administration in adults.

Pioglitazone is a thiazolidinedione class of oral antidiabetic drugs. Pioglitazone is an insulin sensitizing agent.
Pioglitazone hydrochloride is an odorless white crystalline powder.
Molecular Weight: 392.9 g/mol.
Molecular Formula: C19H20N2O3S•HCl.
Chemical Name: 5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione;hydrochloride.
Structural Formula:



Inactive ingredients (excipients) of K-PIO 15 Tablet contain Hydroxy Propyl Cellulose, Lactose, Purified Water, Cross Carmellose Sodium, Microcrystalline Cellulose, and Magnesium Stearate.

Inactive ingredients (excipients) of K-PIO 30 Tablet contain Hydroxy Propyl Cellulose, Lactose, Colour Supra Sunset Yellow FCF, Purified Water, Cross Carmellose Sodium, Microcrystalline Cellulose, and Magnesium Stearate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

15 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 25 °C.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting your doctor.
- Pregnant women and breastfeeding mothers should avoid use of this medicine.
- Instruct patients not to take this medicine if they have liver dysfunction.
- Patients are advised not to take this medicine in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- If your body is under stress such as from a fever, infection, accident, or surgery the dose of your diabetes medicines may need to be changed. Consult your doctor.
- This medicine is not recommended for use in children.
- This medicine can cause your body to keep extra fluid (fluid retention) which leads to swelling (edema) especially in the ankles or legs and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure.
- Inform your doctor if you have diabetic eye disease that causes swelling in the back of the eye (macular edema). If you have any changes in your vision, immediately consult your doctor. Your doctor should check your eyes regularly.
- Do not take this medicine if you have severe heart failure or heart failure with symptoms such as shortness of breath, swelling or unusual tiredness.
- Do not take this medicine if you have or have had cancer of the bladder.

10. Details of Manufacturer

MEPROMAX LIFESCIENCES PVT. LTD.
16- Pharmacity, Selaqui, Dehradun – 248 011, Uttarkhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 23/UA/2007; Date of FDA Product Permission: 12/06/2007.

12. Date of Revision

April 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
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