02-09-0408

ERTUVIA-M

(Ertugliflozin and Metformin HCl) Tablets

Product Specifications: Innovator

Ertuvia-M 2.5 mg / 500 mg Tablets: Each film coated tablet contains:

Ertugliflozin L-pyroglutamic acid eq. to Ertugliflozin	2.5 mg
Metformin HCl U.S.P.	500 mg

Ertuvia-M 2.5 mg / 1000 mg Tablets: Each film coated tablet contains:

Ertugliflozin L-pyroglutamic acid eq. to Ertugliflozin	2.5 mg
Metformin HCl U.S.P.	1000 mg

Ertuvia-M 7.5 mg / 500 mg Tablets: Each film coated tablet contains:

Ertugliflozin L-pyroglutamic acid eq. to Ertugliflozin	7.5 mg
Metformin HCl U.S.P.	500 mg

Ertuvia-M 7.5 mg / 1000 mg Tablets: Each film coated tablet contains:

Ertugliflozin L-pyroglutamic acid eq. to Ertugliflozin	7.5 mg
Metformin HCl U.S.P.	1000 mg

WARNING: LACTIC ACIDOSIS

Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), 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 the Full Prescribing Information [see Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, and Use in Specific Populations.

If metformin-associated lactic acidosis is suspected, immediately discontinue ERTUVIA-M and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

DESCRIPTION

ERTUVIA-M (ertugliflozin and metformin hydrochloride) tablet for oral use contains ertugliflozin Lpyroglutamic acid, a SGLT2 inhibitor, and metformin HCl, a member of the biguanide class.

Ertugliflozin:

The chemical name of ertugliflozin l-pyroglutamic acid is (1s,2s,3s,4r,5s)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2s)-5-oxopyrrolidine-2-carboxylic acid. the molecular formula is c27h32clno10 and the molecular weight is 566.00.

Metformin HCl:

Metformin hydrochloride (n, n-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

CLINICAL PARTICULARS

Therapeutic indications

ERTUVIA-M is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Limitations of Use

Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients**.**

Posology and method of administration

Recommended Dose:

- Take ERTUVIA-M (Ertugliflozin and metformin) twice daily with meals, with gradual dose escalation for those initiating metformin HCl to reduce the gastrointestinal side effects due to metformin
- Dosing may be adjusted based on effectiveness and tolerability
- Individualize the starting dose of ERTUVIA-M, ertugliflozin and metformin hydrochloride (HCl), based on the patient's current regimen, while not exceeding the maximum recommended daily dose of 15 mg ertugliflozin and 2,000 mg metformin HCl:
- In patients on metformin HCl, switch to ERTUVIA-M tablets containing 2.5 mg ertugliflozin, with a similar total daily dose of metformin HCL.
- In patients on ertugliflozin, switch to ERTUVIA-M tablets containing 500 mg metformin HCl, with a similar total daily dose of ertugliflozin.
- In patients already treated with ertugliflozin and metformin HCl, switch to ERTUVIA-M tablets containing the same total daily dose of ertugliflozin and a similar daily dose of metformin HCl
- When ERTUVIA-M is used in combination with insulin or an insulin secretagogue, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia
- Assess renal function prior to initiation of ERTUVIA-M (Ertugliflozin and metformin) and as clinically indicated [see Warnings and Precautions]
- In patients with volume depletion, correct this condition before initiating ERTUVIA-M (Ertugliflozin and metformin)

Recommended Dosage in Patients with Renal Impairment:

- Use of ERTUVIA-M (Ertugliflozin and metformin) is not recommended in patients with an eGFR less than 45 mL/min/1.73 m2.
- Use of ERTUVIA-M (Ertugliflozin and metformin) is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2), end stage-renal disease (ESRD), or on dialysis [see Contraindications]

Recommended Dosage in Patients with Hepatic impairment:

- ERTUVIA-M (Ertugliflozin and metformin) is contraindicated in patients with hepatic impairment

Recommended Dosage in Pediatric Use:

- Safety and effectiveness of Ertugliflozin and metformin tablets in pediatric patients under 18 years of age have not been established.

Recommended Dosage in Geriatric Use:

- No dosage adjustment of ERTUVIA-M (Ertugliflozin and metformin) is recommended based on age. Elderly patients are more likely to have decreased renal function. Assess renal function in elderly patients prior to initiating dosing and periodically thereafter.

Contraindication

- Hypersensitivity to the active substances or to any of the excipients listed in Section 1;
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis [DKA]);
- diabetic pre coma;
- severe renal failure (GFR less than 30 ml/min), end-stage renal disease (ESRD), or patients on dialysis
- acute condition with the potential to alter renal function, such as: dehydration, severe infection, shock
- acute or chronic disease that may cause tissue hypoxia, such as: cardiac or respiratory failure, recent myocardial infarction, shock
- hepatic impairment
- acute alcohol intoxication, alcoholism.

WARNINGS AND PRECAUTIONS

General: Ertugliflozin/Metformin should not be used in patients with type 1 diabetes mellitus.

Lactic Acidosis:

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate

blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Ertugliflozin/Metformin. In Ertugliflozin/Metformin-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Ertugliflozin/Metformin and report these symptoms to their healthcare provider.

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Stop Ertugliflozin/Metformin at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Ertugliflozin/Metformin if renal function is stable.

Renal Impairment

The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney.

- Before initiating Ertugliflozin/Metformin, obtain an eGFR
- Use of Ertugliflozin/Metformin is not recommended in patients with an eGFR less than 45 mL/min/1.73 m2
- Ertugliflozin/Metformin is contraindicated in patients with severe renal impairment (an eGFR less than 30 mL/min/1.73 m2), end stage-renal disease (ESRD), or on dialysis
- Obtain an eGFR at least annually in all patients taking Ertugliflozin/Metformin. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently

Age 65 or Greater

The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Surgery and Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Ertugliflozin/Metformin should be temporarily discontinued while patients have restricted food and fluid intake. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Hypoxic States

Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur, discontinue Ertugliflozin/Metformin tablets.

Excessive Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Ertugliflozin/Metformin.

Hepatic Impairment

Patients with hepatic impairment have developed metformin-associated lactic acidosis. Therefore, avoid use of Ertugliflozin/Metformin tablets in patients with clinical or laboratory evidence of hepatic disease.

Diabetic ketoacidosis:

- Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors including ertugliflozin.
- In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Ertugliflozin/Metformin tablets are not indicated for the treatment of patients with type 1 diabetes mellitus.
- In patients where DKA is suspected or diagnosed, treatment with Ertugliflozin/Metformin should be discontinued immediately.
- Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with Ertugliflozin/Metformin tablets may be restarted when the ketone values are normal and the patient's condition has stabilised.
- Before initiating Ertugliflozin/Metformin tablets, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.
- Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved

Lower limb amputations:

In a long-term cardiovascular outcomes study, in patients with type 2 diabetes and established cardiovascular disease, the occurrence of non-traumatic lower limb amputations was reported. Amputation of the toe and foot were most frequent. Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation.

Across seven ertugliflozin clinical trials, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the ertugliflozin 5 mg group, and 8 (0.5%) patients in the ertugliflozin 15 mg group.

Before initiating Ertugliflozin/Metformin tablets, consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care.

Volume Depletion

Before initiating Ertugliflozin/Metformin tablets in patients assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Ertugliflozin/Metformin. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

In case of conditions that may lead to fluid loss (e.g., gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving ertugliflozin. Temporary interruption of treatment with Ertugliflozin/Metformin tablets should be considered until the fluid loss is corrected.

Urosepsis and Pyelonephritis

Treatment with medicines containing SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Ertugliflozin/Metformin tablets may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Ertugliflozin/Metformin.
Genital Mycotic Infections
Ertugliflozin increases the risk of genital mycotic infections. Patients who have a history of genital mycotic infections or who are uncircumcised are more likely to develop genital mycotic infections. Monitor and treat appropriately.
Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Post-marketing cases of necrotizing fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment. Patients treated with Ertugliflozin/Metformin tablets presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Ertugliflozin/Metformin tablets, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.
Vitamin B12 Deficiency
In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed
to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals in patients on metformin and manage any abnormalities
Urine laboratory assessments
Due to the mechanism of action of ertugliflozin, patients taking ERTUVIA-M (Ertugliflozin/Metformin) will test positive for glucose in their urine. Alternative methods should be used to monitor glycaemic control.
FERTILITY, PREGNANCY AND LACTATION:
Pregnancy: Based on animal data showing adverse renal effects, from ertugliflozin, this drug is not recommended during the second and third trimesters of pregnancy. The limited available data with Ertugliflozin/Metformin tablets in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage.
Lactaion: There is no information regarding the presence of ertugliflozin in human milk, the effects on the breast-fed infant, or the effects on milk production. Metformin is present in human breast milk.
Fertility: The effect of Ertugliflozin/Metformin tablets on fertility in humans has not been studied.
USE IN SPECIFIC POPULATIONS
Patients with Renal Impairment
Ertugliflozin
In a clinical pharmacology study in patients with type 2 diabetes mellitus and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15 mg ertugliflozin, the mean increases in AUC of ertugliflozin were 1.6-, 1.7-, and 1.6-fold, respectively, for mild, moderate, and severe renally-impaired patients compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically meaningful. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment.
Metformin
In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased.
Patients with Hepatic Impairment
Ertugliflozin
Moderate hepatic impairment (based on the Child-Pugh classification) did not result in an increase in exposure of ertugliflozin. The AUC of ertugliflozin decreased by approximately 13%, and Cmax decreased by approximately 21% compared to subjects with normal hepatic function. This decrease in ertugliflozin exposure is not considered clinically meaningful. There is no clinical experience in patients with Child-Pugh
class C (severe) hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment.
Metformin
No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.
Effects of Age, Body Weight, Gender, and Race
Ertugliflozin
Based on a population pharmacokinetic analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin.
Metformin
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females. No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24)
DRUG INTERACTIONS
Carbonic Anhydrase Inhibitors
The risk of lactic acidosis may increase due to concomitant use of Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) with metformin. These drugs frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis.
Drugs that Reduce Metformin Clearance
The risk of lactic acidosis may increase due to concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) which increase systemic exposure to metformin.
Alcohol
Potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving ERTUVIA-M (Ertugliflozin/Metformin).
Concomitant Use with Insulin and Insulin Secretagogues
Ertugliflozin/Metformin tablets may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Ertugliflozin/Metformin.
Positive Urine Glucose Test
Due to the mechanism of action of ertugliflozin, patients taking Ertugliflozin/Metformin tablets will test positive for glucose in their urine. Alternative methods should be used to monitor glycaemic control
Interference with 1,5-anhydroglucitol (1,5-AG) Assay
Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Drugs that Affect Glycemic Control
Certain drugs tend to produce hyperglycemia and may lead to loss of 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. When patient receiving Ertugliflozin/Metformin tablets along with such drugs, the patient should be closely observed to maintain adequate glycemic control.
Diuretics
Ertugliflozin may add to the diuretic effect of diuretics and may increase the risk of dehydration and hypotension.

Coadministration of metformin with
- Inhibitors of Organic cation transporters 1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

ADVERSE REACTIONS
Common: Hypoglycaemia, Thirst, Taste disturbance, Volume depletion, Gastrointestinal symptoms, Increased urination, Vulvovaginal pruritus, Vulvovaginal mycotic infection, Balanitis candida and other male genital mycotic infections, Serum lipids changed, Haemoglobin increased, BUN Increased.
Uncommon: Dysuria, Blood creatinine increased/Glomerular filtration rate decreased,
Rare: Necrotizing fasciitis of the perineum (Fournier's gangrene), Diabetic ketoacidosis, Lactic acidosis, Vitamin B12 deficiency, Erythema, Pruritus, Urticaria, Liver function test abnormal, Hepatitis, Lower Limb amputation.
OVERDOSAGE
In the event of an overdose with Ertugliflozin/Metformin tablets, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status.
CLINICAL PHARMACOLOGY
Mechanism Of Action
SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Ertugliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.
Absorption: The effects of a high-fat meal on the pharmacokinetics of ertugliflozin and metformin tablets when administered are comparable to those reported for the individual tablets. Food had no meaningful effect on AUC-¬-inf of ertugliflozin and metformin, but reduced mean ertugliflozin Cmax by approximately 41% and metformin Cmax by approximately 29% compared to the fasted condition.
Distribution:
Ertugliflozin
The mean steady-state volume of distribution of ertugliflozin following an intravenous dose is 85.5 L. Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.
Metformin
The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound.
Biotransformation:
Ertugliflozin
Metabolism is the primary clearance mechanism for ertugliflozin. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation to two glucuronides that are pharmacologically inactive at clinically relevant concentrations. CYP-mediated (oxidative) metabolism of ertugliflozin is minimal (12%).
Metformin
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.
Elimination:
Ertugliflozin
The mean systemic plasma clearance following an intravenous 100 µg dose was 11.2 L/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 16.6 hours based on the population pharmacokinetic analysis. Following administration of an oral [14C]-ertugliflozin solution to healthy subjects, approximately 40.9% and 50.2% of the drug-related radioactivity was eliminated in feces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 33.8% as unchanged ertugliflozin in feces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent. Metformin
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours,
suggesting that the erythrocyte mass may be a compartment of distribution.

HOW SUPPLIED:

Ertuvia-M 2.5 mg / 500 mg Tablets:	Pack of 14 Tablets
Ertuvia-M 2.5 mg / 1000 mg Tablets:	Pack of 14 Tablets
Ertuvia-M 7.5 mg / 500 mg Tablets:	Pack of 14 Tablets
Ertuvia-M 7.5 mg / 1000 mg Tablets:	Pack of 14 Tablets

STORAGE
Do not store above 25°C.
The expiration date refers to the product correctly stored at the required condition.

INSTRUCTIONS
Keep away from moisture, light and reach of children.
To be sold on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:
FEROZSONS LABORATORIES LIMITED
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