

Meteor

(Metformin HCl)

میتور

COMPOSITION

Each **Meteor** 250 mg film-coated tablet contains metformin hydrochloride 250 mg.
Each **Meteor** 500 mg film-coated tablet contains metformin hydrochloride 500 mg.
Each **Meteor** 850 mg film-coated tablet contains metformin hydrochloride 850 mg.
Each **Meteor** 1000 mg film-coated tablet contains metformin hydrochloride 1000 mg.

DESCRIPTION

Metformin is an oral antihyperglycemic drug used in the management of type 2 diabetes.

CLINICAL PHARMACOLOGY

Mechanism of Action: Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, Metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS

Absorption and Bioavailability: The absolute bioavailability of a metformin tablet given under fasting conditions is approximately 50% to 60%. Food decreases the extent of and slightly delays the absorption of metformin.

Distribution: Metformin is negligibly bound to plasma proteins. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24 to 48 hours.

Metabolism and Elimination: Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. 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.

Special Populations:

Patients with Type 2 Diabetes

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Insufficiency: In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Insufficiency: No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics: Total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. The change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Pediatrics: After administration of a single oral metformin tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

Gender: In controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

INDICATIONS

Meteor tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus.

DOSEAGE AND ADMINISTRATION

Dosage of **Meteor** must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily doses.

The maximum recommended daily dose of **Meteor** is 2550 mg in adults and 2000 mg in pediatric patients (10-16 years of age).

Meteor should be given in divided doses with meals. **Meteor** should be started at a low dose, with gradual dose escalation. During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to **Meteor** and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of **Meteor**, either when used as monotherapy or in combination with sulfonylurea or insulin.

Short-term administration of **Meteor** may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

RECOMMENDED DOSING SCHEDULE

In general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms. The usual starting dose of **Meteor** is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg per day, given in divided doses. Patients can also be titrated from 500 mg twice a day to 850 mg twice a day after 2 weeks. For those patients requiring additional glycemic control, **Meteor** may be given to a maximum daily dose of 2550 mg per day. Doses above 2000 mg may be better tolerated given 3 times a day with meals.

Pediatric: The usual starting dose of **Meteor** is 500 mg twice a day, given with meals. Dosage increases should be made in increments of 500 mg weekly up to a maximum of 2000 mg per day, given in divided doses.

Transfer From Other Antidiabetic Therapy: When Transferring patients from standard oral hypoglycemic agents other than chlorpropamide to **Meteor**, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant Meteor and Oral Sulfonylurea Therapy in Adult Patients: If patients have not responded to four weeks of the maximum dose of **Meteor** monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing **Meteor** at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. With concomitant **Meteor** and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased.. Appropriate precautions should be taken.

If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of **Meteor** and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without **Meteor**.

Concomitant METEOR and Insulin Therapy in Adult Patients: The current insulin dose should be continued upon initiation of **METEOR** or therapy. **Meteor** should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of **Meteor** should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved. The maximum recommended daily dose is 2500 mg for **Meteor**. It is recommended that the insulin dose can be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and **Meteor**. Further adjustment should be individualized based on glucose-lowering response.

Specific Patient Populations: **Meteor** is not recommended for use in pregnancy.

Meteor is not recommended in patients below the age of 10 years.

The initial and maintenance dosing of **Meteor** should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of **Meteor**. Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly.

UNDESIRABLE EFFECTS:

The following undesirable effects may occur under treatment with metformin. Frequencies are defined as follows: very common: > 1/10; common: > 1/100, < 1/10; uncommon: > 1/1,000, < 1/100; rare: > 1/10,000, < 1/1,000; very rare < 1/10,000 and isolated reports.

Metabolism and nutrition disorders: Very rare: Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Very rare: Lactic acidosis.

Nervous system disorders: Common: Taste disturbance.

Gastrointestinal disorders: Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders: Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders: Very rare: Skin reactions such as erythema, pruritus, urticaria. In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

DRUG INTERACTIONS

Nifedipine: Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of **Meteor** and/or the interfering drug is recommended.

- Other**
- 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 such drugs are administered to a patient receiving **Meteor**, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving **Meteor**, the patient should be observed closely for hypoglycemia.
 - In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.
 - Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lactic acidosis: Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Renal function: As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter.

- At least annually in patients with normal renal function,
- At least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects. Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent: As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery: Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

Children and adolescents: No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended.

Children aged between 10 and 12 years: Although metformin efficacy and safety in children below 12 did not differ from efficacy and safety in older children, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other precautions:

- All patients should continue their diet with a regular distribution of carbohydrate intake during the day.
- Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulphonylureas.

Hypoxic states: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued.

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving metformin.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 levels: Decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin and any apparent abnormalities should be appropriately investigated and managed.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold metformin and temporarily administer insulin. metformin may be reinstituted after the acute episode is resolved.

PREGNANCY

Pregnancy Category B: Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin should be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, metformin should not be used during pregnancy unless clearly needed.

NURSING MOTHERS

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If metformin is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

The safety and effectiveness of metformin for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years).

GERIATRIC USE

Generally, elderly patients should not be titrated to the maximum dose of metformin.

OVER DOSAGE

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

CONTRAINDICATIONS

- 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 hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

PRESENTATION:

Meteor 250 mg tablet : 5 x 10's/pack.
Meteor 500 mg tablet : 5 x 10's/pack.
Meteor 850 mg tablet : 5 x 10's/pack.
Meteor 1000 mg tablet : 5 x 10's/pack.

Dosage:

As directed by the physician.

Instructions:

Store below 30°C.
Protect from sunlight & moisture.
Keep out of reach of children.

Issued : 11/2012

Detailed prescribing information is available on request.

Manufactured by:
AsianContinental (Pvt.) Ltd.
D-32, S.I.T.E. II, Super Highway,
Karachi-Pakistan.



An ISO Certified Company

LFT/036/00

خوراک:
ڈاکٹر کی ہدایت کے مطابق۔

ہدایات:
دوا کو 30 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔