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Metsa™

Metformin Hydrochloride BP / USP

50062

Presentation
Metsa 500mg tablet: Each coated tablet contains 500mg Metformin Hydrochloride BP.
Metsa 850mg tablet: Each coated tablet contains 850mg Metformin Hydrochloride BP.
Metsa XR 500mg tablet: Each XR tablet contains 500mg Metformin Hydrochloride USP.
Metsa XR 1000mg tablet: Each XR tablet contains 1000mg Metformin Hydrochloride USP.

Pharmacokinetics
Metformin Hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500mg dose is reported to be about 50% to 60%, although this is reduced somewhat if taken with food. Following absorption plasma protein binding is negligible, and it is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours oral administration.

Description and Mechanism of Action
Metformin hydrochloride tablets and metformin hydrochloride XR tablets are oral antihyperglycemic drugs used in the management of type 2 diabetes.

Mechanism of Action
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. 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.

Indications
The main use for metformin is in the treatment of diabetes mellitus type 2, especially when this accompanies obesity and insulin resistance. Metformin is the only anti-diabetic drug that has been proven to protect against the cardiovascular complications of diabetes. Unlike the other most-commonly prescribed class of oral diabetes drugs, the sulfonylureas, metformin (taken alone) does not induce hypoglycemia. Hypoglycemia during intense exercise has been documented, but is extremely rare. It also does not cause weight gain, and may indeed produce minor weight loss. Metformin also modestly reduces LDL and triglyceride levels.

It is also being used increasingly in polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD) and premature puberty, three other diseases that feature insulin resistance; these indications are still[update] considered experimental.

Contra-indications
Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (creatinine levels over 150 µmol/l, although this is an arbitrary limit), lung disease and liver disease. Heart failure has long been considered a contraindication for metformin use, although a 2007 systematic review showed metformin to be the only anti-diabetic drug not associated with harm in people with heart failure.

It is recommended that metformin be temporarily discontinued before any radiographic study involving iodinated contrast (such as a contrast-enhanced CT scan or angiogram), as contrast dye may temporarily impair kidney function, indirectly leading to lactic acidosis by causing retention of metformin in the body. It is recommended that metformin be resumed after two days, assuming kidney function is normal.

Side-Effects
Lactic acidosis
The most serious potential side effect of metformin is lactic acidosis; this complication is very rare, and seems limited to those with impaired liver or kidney function. Phenformin, another biguanide, was withdrawn because of an increased risk of lactic acidosis (up to 60 cases per million patient-years). However, metformin is safer than phenformin, and the risk of developing lactic acidosis is not increased by the medication so long as it is not prescribed to known high-risk groups.

Gastrointestinal
The most common adverse effect of metformin is gastrointestinal upset, including diarrhea, cramps, nausea, vomiting and increased flatulence; metformin is more commonly associated with gastrointestinal side effects than most other anti-diabetic drugs. In a clinical trial of 286 subjects, 53.2% of the 141 who were given immediate-release metformin (as opposed to placebo) reported diarrhea, versus 11.7% for placebo, and 25.5% reported nausea/vomiting, versus 8.3% for those on placebo.

Gastrointestinal upset can cause severe discomfort for patients; it is most common when metformin is first administered, or when the dose is increased. The discomfort can often be avoided by beginning at a low dose (1 to 1.7 grams per day) and increasing the dose gradually. Gastrointestinal upset after prolonged, steady use is less common.

Long-term use of metformin has been associated with increased homocysteine levels and malabsorption of vitamin B_{12}. Higher doses and prolonged use are associated with increased incidence of B_{12} deficiency, and some researchers recommend screening or prevention strategies.

Hormonal
There is an initial report; involving four patients with impaired thyroid function, that metformin can suppress the TSH level with no accompanying symptoms of hyperthyroidism or changes in measured thyroid hormone levels. The mechanism is currently unknown.

Precautions and Warnings
Metformin should only be prescribed when diet and weight reduction has proven inadequate. During concomitant therapy with other oral hypoglycemic drugs, blood sugar should be monitored carefully because combined therapy may cause hypoglycemia. Patient must be closely monitored in order to identify any factor or condition that may favor the onset of lactic acidosis. The risk lactic acidosis is higher among the patients over 60. Patients should be instructed how to recognize the early symptoms of lactic acidosis. In the event of severe trauma, injuries, infectious diseases and high fever, and surgery, it may be necessary to give insulin to maintain adequate metabolic control. Caution in excess alcohol intake.

Pregnancy & lactation
Metformin is not recommended during pregnancy and breastfeeding, so, a suitable treatment schedule should be prescribed with insulin.

Dose and Administration
There is no fixed dosage regimen for the management of hyperglycemia in patients with type-2 diabetes with metformin or any other pharmacologic agent. Dosage of metformin 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 metformin is 2550mg in adults and 2000mg in pediatric patients (10-16 years of age); the maximum recommended daily dose of metformin in adults is 2000mg.

Metformin should be given in divided doses with meals while metformin should generally be given once daily with the evening meal. Metformin should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration fasting plasma glucose should be used to determine the therapeutic response to metformin 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 metformin, either when used as monotherapy or in combination with sulfonylurea or insulin.

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

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

Metformin tablets must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of metformin will be eliminated in the feces as a soft, hydrated mass.

Recommended Dosing Schedule
Adults - In general, clinically significant responses are not seen at doses below 1500mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

The usual starting dose of metformin hydrochloride tablets is 500mg twice a day or 850mg once a day, given with meals. Dosage increases should be made in increments of 500mg weekly or 850mg every 2 weeks, up to a total of 2000mg per day, given in divided doses. Patients can also be titrated from 500mg twice a day to 850mg twice a day after 2 weeks. For those patients requiring additional glycemic control may be given to a maximum daily dose of 2550mg per day. Doses above 2000mg may be better tolerated given three times a day with meals.

The usual starting dose of metformin hydrochloride extended-release tablets is 500mg once daily with the evening meal. Dosage increases should be made in increments of 500mg weekly, up to a maximum of 2000mg once daily with the evening meal. If glycemic control is not achieved on GLUCOPHAGE XR (metformin hydrochloride) 2000mg once daily, a trial of GLUCOPHAGE XR 1000mg twice daily should be considered. If higher doses of metformin are required, GLUCOPHAGE (metformin hydrochloride) should be used at total daily doses up to 2550mg administered in divided daily doses, as described above.

Pediatrics - The usual starting dose of Metformin is 500mg twice a day, given with meals. Dosage increases should be made in increments of 500mg weekly up to a maximum of 2000mg per day, given in divided doses. Safety and effectiveness of metformin in pediatric patients have not been established.

Transfer from Other Antidiabetic Therapy
When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to metformin, 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 metformin and Oral Sulfonylurea Therapy in Adult Patients
If patients have not responded to four weeks of the maximum dose of metformin monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing metformin at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug- drug interaction data are currently available only for metformin plus glyburide (glibenclamide).

With concomitant metformin and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant metformin and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate pre cautions should be taken If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of metformin and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without metformin.

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

Specific Patient Populations
Metformin is not recommended for use in pregnancy. Metformin is not recommended in patients below the age of 10 years. Metformin is not recommended in pediatric patients (below the age of 17 years).

The initial and maintenance dosing of metformin 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 metformin. Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly.

Overdosages
A review of intentional and accidental metformin overdoses reported to Poison control centers over a 5-year period found that serious adverse events were rare, though elderly patients appeared to be at greater risk. Intentional overdoses with up to 63g of metformin have been reported in the medical literature. The major potentially life-threatening complication of metformin overdose is lactic acidosis. Treatment of metformin overdose is generally supportive, but may include sodium bicarbonate to address acidosis and standard hemodialysis or continuous veno-venous hemofiltration to rapidly remove metformin and correct acidosis.

Drug Interactions
The H_2-receptor antagonist cimetidine causes an increase in the plasma concentration of metformin, by reducing clearance of metformin by the kidneys; both metformin and cimetidine are cleared from the body by tubular secretion, and both, particularly the cationic (positively charged) form of cimetidine, may compete for the same transport mechanism. A small double-blind, randomized study found the antibiotic cefalexin to also increase metformin concentrations by a similar mechanism; theoretically, other cationic medications may produce the same effect.

Storage Condition
Store in a cool (below 25°C) and dry place. Protect from light.

Commercial Pack
Metsa 500mg tablet: 10 x 10's tablet in alu-pvc blister pack.
Metsa 850mg tablet: 5 x 10's tablet in alu-pvc blister pack.
Metsa XR 500mg tablet: 5 x 10's tablet in alu-pvc blister pack.
Metsa XR 1000mg tablet: 3 x 10's tablet in alu-pvc blister pack.

Manufactured by:
synovia
Synovia Pharma PLC., Station Road, Tongi, Gazipur.
A Subsidiary of BEXIMCO PHARMACEUTICALS LTD.

518037/2

Direction Slip artwork legend

Product Name	:	Mesta
Code number	:	518037/2
Dimension	:	L 14 x W 8.9 inches
Min. size of text	:	8 pt
Used Colors	:	Black C ■ Red ■