Metlong
Metformin Hydrochloride Extended-Release Tablets

DESCRIPTION

Metlong, brand of Metformin Hydrochloride Extended-release tablets, is chemically 1,1-dimethylbiguanide hydrochloride.

METLONG-500

Metlong-500 is a white to off-white, oblong, biconvex, uncoated tablet with imprints of "MTG" on one side and "500" on the other.

METLONG-DS

Metlong-DS is a white to off-white, oval, biconvex, uncoated tablet with imprints of "MTG" on one side and "DS" on the other.

COMPOSITION

METLONG-500
Each uncoated extended-release tablet contains:
Metformin Hydrochloride IP 500 mg

METLONG-DS
Each uncoated extended-release tablet contains:
Metformin Hydrochloride IP 1000 mg

PHARMACOLOGY

Metformin appears to act principally by reducing glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat. The mechanism by which metformin reduces hepatic glucose production is controversial, but the preponderance of data indicates an effect on reducing gluconeogenesis. Metformin also may decrease plasma glucose level by reducing the absorption of glucose from the intestine, but this action has not been shown to have clinical relevance.

Metformin has beneficial effects on serum lipid profiles in obese and lean patients with NIDDM, and in other patients with concomitant NIDDM, hypertension and/or hyperlipidaemia. In particular, reduced circulating levels of free fatty acids, triglycerides and low density lipoprotein (LDL) cholesterol, and increased high density lipoprotein (HDL) cholesterol levels have been reported. Potentially beneficial vascular properties, such as increased fibrinolytic activity and decreased
platelet density and aggregation, have also been observed in non-diabetic volunteers and patients with NIDDM.

PHARMACOKINETICS

In a single dose study in healthy human volunteers, Metlong extended-release tablets (500mg) resulted in the mean maximum concentration of 769 ng/ml at 3.625 hours. The AUC$_{0-\infty}$ was 5721.89 ng.h/ml. The reported absolute bioavailability of the tablets, given under fasting conditions is approximately 50-60%. The extent of absorption of the extended-release Metformin may increase when given with food. However, there is no effect of food on Cmax and Tmax reported. Metformin is negligibly bound to plasma proteins. It partitions into erythrocytes probably as a function of time. At usual dosage regimen, the steady state plasma concentration of Metformin is reached within 24–48 hours. It is excreted unchanged in the urine and does not undergo hepatic metabolism nor biliary excretion. Tubular secretion appears to be the major route of Metformin elimination.

SPECIAL POPULATIONS

Patients with type 2 diabetes and Gender
There are no reported differences in pharmacokinetics of Metformin between patients with type 2 diabetes and normal subjects when analyzed according to gender.

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
Reported data from controlled pharmacokinetic studies of Metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged and Cmax is increased, compared to healthy young subjects. From this data, it appears that the change in Metformin Hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatrics
No pharmacokinetic studies of Metformin Hydrochloride in pediatric patients have been conducted.

INDICATIONS
As a monotherapy, the drug is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type-2 diabetes.

It may be used concomitantly with a Sulfonylurea or Insulin to improve glycemic control.

CONTRAINDICATIONS
Renal or hepatic failure, alcoholism, NIDDM complicated by severe ketosis and acidosis, diabetic precoma and coma, patients undergoing surgery, after severe trauma or during infections, chronic obstructive pulmonary disease, coronary heart disease, cardiac failure, peripheral vascular disease, pregnancy, hypoglycemia and known hypersensitivity to Metformin.

WARNING
Lactic acidosis is a rare, but serious metabolic complication that can occur due to Metformin accumulation. The reported incidence of lactic acidosis during Metformin treatment is lower than 0.1 case per 1000 patient-years, and the mortality risk is even lower. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, the drug should be discontinued immediately and general supportive measures promptly instituted.

**PRECAUTIONS**
Adjust dose according to blood plasma glucose levels during the first few months.

**USAGE**
- **Pregnancy:** Contraindicated
- **Lactation:** Studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- **Pediatrics:** Safety and effectiveness in children have not been established.
- **Geriatrics:** As aging is associated with reduced renal function, care should be taken in dose selection and should be based on careful and regular monitoring of renal functions.

**ADVERSE EFFECTS**
- **Gastrointestinal disturbances:** Nausea, diarrhoea, gastric pain, constipation, vomiting, metallic taste in mouth.
- **Dermatological effects:** Rash, pruritus, urticaria, erythema and flushing
- **Miscellaneous:** Headache and dizziness

Impaired gastrointestinal absorption of vitamin B₁₂ and folic acid has been associated with long-term Metformin therapy. Measurement of serum vitamin B₁₂ level is advised on an annual basis as Metformin interfere with B₁₂ absorption from intrinsic factor complex.

**DRUG INTERACTIONS**
Drug interactions of Metformin is seen with phenprocoumon, hyperglycemic agents (e.g. thiazides, corticosteroids and others), alcohol, furosemide, nifedipine and cationic drugs (aminolide, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, cimetidine and vancomycin). The absorption of Metformin may be reduced by acarbose and guar gum.

**OVERDOSAGE AND TREATMENT**
Hemodialysis may be useful for removal of accumulating drug from patients in whom Metformin overdosage is suspected.

**DOSAGE AND ADMINISTRATION**
Dosage of Metlong - 500 mg and Metlong-DS (1000 mg) must be individualized on the basis of both effectiveness and tolerance in patients. The maximum recommended daily dose of 2000 mg should not be exceeded.

The drug 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 level should be used to determine the therapeutic response to the drug 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. Short-term administration of the drug may be sufficient during periods of transient loss of blood glucose control in patients usually well-controlled on diet alone.
The usual starting dose of Metlong is 500 mg once daily with the evening meal. Dosage increase should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved on 2000 mg once daily, trial of 1000 mg twice daily should be considered. The tablet should be swallowed whole and not to be chewed. The tablet should be taken after meals.

**KEEP THE MEDICINE OUT OF REACH OF CHILDREN**

**STORAGE INSTRUCTIONS**

Store at a temperature below 30°C, protect from light and moisture.

**REFERENCES**