Metnurite® Tablets

Each Tablet Contains

- **Metformin – 500 mg SR**
- **Mecobalamin – 750 mcg**

PHARMACEUTICAL INFORMATION –

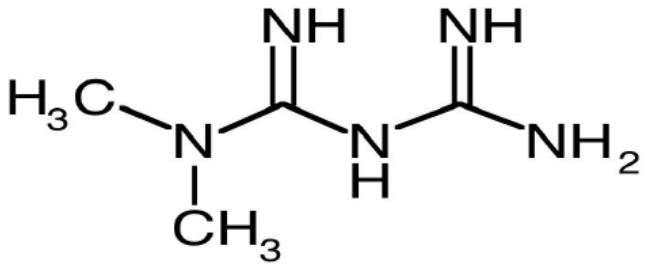
METFORMIN

Generic name: Metformin

Chemical name: N,N - dimethylimidodicarbonimidic diamide

Molecular mass: 129.164 g/mol

Structural formula:



Empirical formula – C4 H11 N5

Melting Point: 218-220°C.

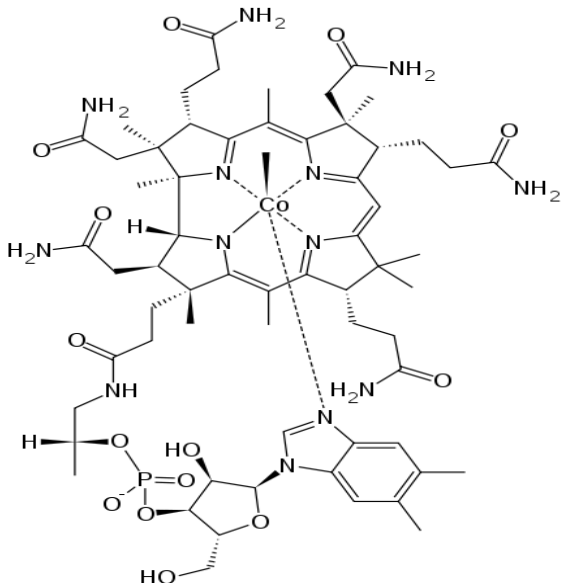
Storage and Stability: Store at room temperature (15°to 30°C)

MECOBALAMIN

Generic name: Methylcobalamin

Molecular mass: 1344.40 g/mol

Structural formula:



Empirical formula – C63H91CoN13O14P

PHARMACOKINETIC PROPERTIES –

Metformin

Absorption and Bioavailability

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak concentration (C,,,) and 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 + 358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas which are more than 90% protein bound, Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally c 1 pg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 ug/mL, even at maximum doses.

Metabolism and Elimination

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) or biliary excretion. Renal clearance (see Table 1) 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.

Mecobalamin

Evidence indicates Methylcobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B12. Experiments have demonstrated similar absorption of methylcobalamin following oral administration. The quantity of cobalamin detected following a small oral dose of methylcobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of methylcobalamin. Human urinary excretion of methylcobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention.

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION –

Metformin -

Metformin is antihyperglycemic, not hypoglycemic. It does not cause insulin release from the pancreas and generally does not cause hypoglycemia, even in large doses. Metformin has no significant effects on the secretion of cortisol, growth hormone, or somatostatin.

Metformin reduces plasma glucose levels primarily by

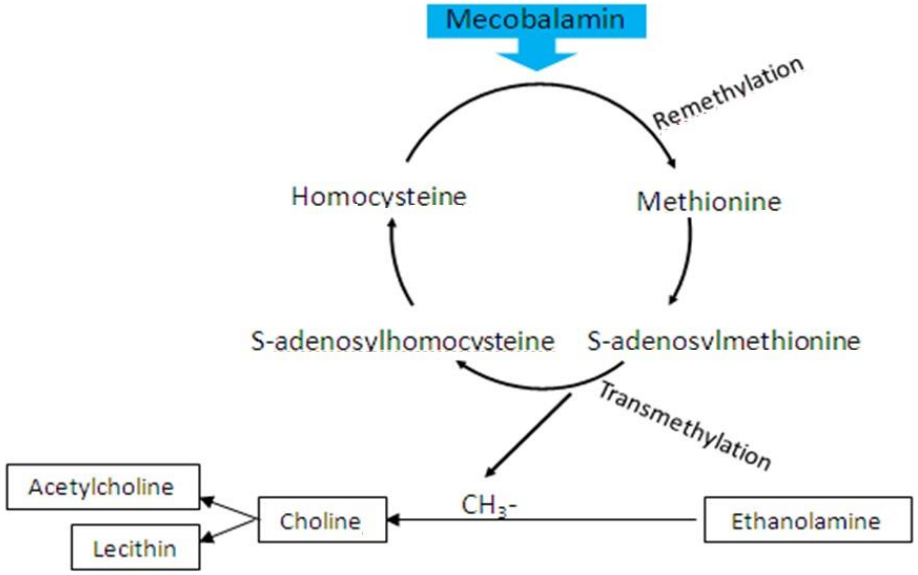
- Decreasing hepatic glucose production (Decreasing Gluconeogenesis and Glycogenolysis)
- Increasing insulin action in muscle and fat. (At a molecular level, these actions are mediated at least in part by activation of the cellular kinase - AMP kinase).

Metformin reduces plasma glucose secondarily by (these action contributes little therapeutically)

- Reducing the absorption of glucose from the intestine
- By interfering with mitochondrial respiratory chain promoting peripheral utilization of glucose by enhancing anaerobic Glycolysis.

Mecobalamin -

- Treatment of Metformin induced decreased Vitamin B12 absorption. [25]
- Enhances synthesis proteins in nerve cells
  - promotes myelinization
  - axonal regeneration
- Helps in generation of enzyme methionine synthase - regeneration of methionine from homocysteine.
- Restores diminished neurotransmitter (Acetylcholine) levels.



INDICATION –

Newly Diagnosed Type 2 Diabetes Patients

CONTRAINDICATIONS –

- Hypersensitivity to any component of the drug
- Patients undergoing radiological investigations (introduction of dye)
- Patients with moderate to severe hepatic insufficiency.
- Conditions predisposing to tissue anoxia (eg, chronic cardiopulmonary dysfunction), because of an increased risk of lactic acidosis induced by Biguanide drugs in the presence of these diseases.

DOSAGE AND ADMINISTRATION –

1 tablet taken 12 hourly i.e. BD.

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of deterioration of their diabetic state. Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and

glycosylated hemoglobin (HbA1C) determinations, to determine the minimum effective dosage and to detect primary failure or secondary failure.

ADVERSE EFFECTS –

- GI adverse effects - The most common adverse effects of Metformin are gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, diarrhoea) and occur in up to 20% of patients. They tend to occur at the onset of therapy, and are often transient.
- Lactic acidosis - is less common with Metformin therapy than with Phenformin therapy.
- Dermatologic Reactions: very rare (<1/10,000 and isolated reports): The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for Metformin monotherapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.
- Special Senses: common (≥1/100): During initiation of Metformin therapy complaints of taste disturbance are common, i.e. metallic taste.
- Hepatic: very rare (<1/10,000 and isolated reports): Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented in isolated reports.

As Mecobalamin is a water soluble vitamin, it does not accumulate in the body causing toxicity.

According to a study published in Diabetes Care – 2012, the amount of Vitamin B12 recommended by the Institute of Medicine (IOM) (2.4 mcg/day) and the amount available in general multivitamins (6 mcg) may not be enough to correct this deficiency among those with Diabetes on Metformin.

This is because approximately 1% of orally ingested Vitamin B12 is absorbed throughout the gastrointestinal tract. A higher dose is required in such patients.

OVERDOSAGE

Available information concerning treatment of a massive overdosage of Metformin is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.
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 hydrochloride 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.

WARNINGS AND PRECAUTIONS

- Lactic acidosis is a rare, but serious, metabolic complication that occurs due to metformin accumulation during treatment with Metformin (see Endocrine and Metabolism, Lactic Acidosis section below).

- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Metformin, since alcohol intake potentiates the effect of metformin on lactate metabolism (see Endocrine and Metabolism, Lactic Acidosis section below).

DRUG INTERACTIONS –

The H2-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. Antibiotic Cefalexin increases Metformin concentrations.

Other drugs tend to produce hyperglycemia and may lead to a loss of blood sugar control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid, and beta-2-agonists. ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to patients receiving Metformin, the patient should be closely observed to maintain adequate glycemic control.

Special Populations

Pregnant Women:
Safety in pregnant women has not been established. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a

partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, the use of Metformin is not recommended during pregnancy.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Women:
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, but caution should be exercised in such patients, and 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.

Pediatrics:
Safety and effectiveness in pediatric patients have not been established.

Geriatrics:
Controlled clinical studies of Metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function. Because aging is associated with reduced renal function, Metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring or renal function. Generally, elderly patients should not be titrated to the maximum dose of Metformin.

SHELF-LIFE -

24 Months

PACKAGING INFORMATION -

Available in blister pack of 10 Tablets.