

Aw. No.: 2000XXXXX

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Metswift XR 750 Leaflet

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2000XXXXX

METSWIFT XR 750

(Metformin Hydrochloride Prolonged Release Tablets 750mg)

Composition:

Each Prolonged Release Tablet Contains
Metformin hydrochloride Ph. Eur. 750mg equivalent to 585mg of metformin base

Presentation:

Box of 28 tablets (2 blisters of 14 tablets each), Box of 98 tablets (7 blisters of 14 tablets each) and Box of 100 tablets (10 blisters of 10 tablets each)

Presentation:

White to off white, capsule shaped, biconvex, tablets, debossed on one side with '750' and other side plain. The tablets are approximately 20.0mm in length and 9.6mm in breadth

Pharmacodynamics:

ORAL ANTI-DIABETICS

(A10BA02 – Gastrointestinal tract and metabolism)

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Mechanism of action

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Pharmacodynamic effects

The major non glycaemic effect of metformin is either weight stability or modest weight loss.

In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Pharmacokinetics:

Absorption

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} of 7 hours (T_{max} for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intra-subject variability of C_{max} and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

Following a single oral administration of 1500mg of Metformin Hydrochloride Prolonged Release 750mg, a mean peak plasma concentration of 1193ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Metformin Hydrochloride Prolonged Release 750mg was shown to be bioequivalent to Metformin Hydrochloride Prolonged Release 500mg at a 1500mg dose with respect to C_{max} and AUC.

Following a single oral administration in the fed state of one tablet of Metformin Hydrochloride Prolonged Release 1000mg, a mean peak plasma concentration of 1214ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin Hydrochloride Prolonged Release 1000mg was shown to be bioequivalent to Metformin Hydrochloride Prolonged Release 500mg at a 1000mg dose with respect to C_{max} and AUC.

When the 1000mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and T_{max} is slightly prolonged by about 1 hour).

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276L.

Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Characteristics in specific groups of patients

Renal Impairment

No reliable estimation of the systemic exposure to metformin could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations.

Indication:

- Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with IGT* and/or IFG*, and/or increased HbA1c who are:

- at high risk for developing overt type 2 diabetes mellitus and

- still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle changes for 3 to 6 months.

Treatment with METSWIFT XR must be based on a risk score incorporating appropriate measures of glycaemic control and including evidence of high cardiovascular risk.

Lifestyle modifications should be continued when metformin is initiated, unless the patient is unable to do so because of medical reasons.

* IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose

Treatment of type 2 diabetes mellitus in adults, when dietary management and exercise alone does not result in adequate glycaemic control. METSWIFT XR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

Recommended Dose:

Adults with normal renal function (GFR ≥ 90mL/min)

Reduction in the risk or delay of the onset of type 2 diabetes

- Metformin should only be considered where intensive lifestyle modifications for 3 to 6 months have not resulted in adequate glycaemic control.

- The therapy should be initiated with one tablet METSWIFT XR 500 once daily with the evening meal.

- After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended (OGTT and/or FPG and/or HbA1c values to be within the normal range). A slow increase of dose may improve gastro-intestinal tolerability.

- The maximum recommended dose of METSWIFT XR 1000 is 2 tablets (2000mg) once daily with the evening meal.

- It is recommended to regularly monitor (every 3-6 months) the glycaemic status (OGTT and/or FPG and/or HbA1c value) as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued.

- A decision to re-evaluate therapy is also required if the patient subsequently implements improvements to diet and/or exercise, or if changes to the medical condition will allow increased lifestyle interventions to be possible.

Monotherapy or combination with other oral antidiabetic agents

- METSWIFT XR 1000 should be taken once daily with the evening meal at a maximum recommended dose of 2 tablets per day.

- METSWIFT XR 1000 is intended as a maintenance therapy for patients treated with either 1000mg or 2000mg of metformin hydrochloride. On switch, the daily dose of METSWIFT XR should be equivalent to the daily dose of metformin hydrochloride.

- In patients treated with metformin hydrochloride at a dose above 2000mg daily, switching to METSWIFT XR is not recommended.

- For patients new to metformin hydrochloride, the usual starting dose of METSWIFT XR is 500mg or 750mg once daily given with the evening meal.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increment in dose may improve gastrointestinal tolerability.

- If glycaemic control is not achieved on 2000mg Metformin Hydrochloride Prolonged Release once daily, patients may be switched to standard metformin hydrochloride immediate-release to a maximum dose of 3000mg daily.

- In the event of transfer from another oral antidiabetic agent, titration should begin with METSWIFT XR 500 before switching to METSWIFT XR 1000 as indicated above.

Combination with insulin

Metformin hydrochloride and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of METSWIFT XR is one tablet of 500mg or 750mg once daily with the evening meal, while insulin dosage is adjusted on the basis on blood glucose measurements. After titration, switch to METSWIFT XR 1000 should be considered.

Elderly

Due to potential for decreased renal function in elderly subjects, the metformin hydrochloride dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older and metformin initiation is therefore not recommended in these patients.

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g., every 3-6 months.

GFR (mL/m	Total maximum daily dose	Additional considerations
60-89	3000mg	Dose reduction may be considered in relation to declining renal function
45-59	2000mg	Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000mg	
<30	-	Metformin is contraindicated.

Paediatric patients

In the absence of available data, METSWIFT XR should not be used in children.

Route of Administration:



Contraindication:

- Hypersensitivity to metformin or to any of the excipients listed.
 - Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
 - Diabetic pre-coma.
 - Severely reduced kidney function (GFR <30mL/min).
 - Acute conditions with the potential to alter renal function such as:
 - Dehydration
 - Severe infection
 - Shock
 - Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as:
 - Decompensated heart failure
 - Respiratory failure
 - Recent myocardial infarction
 - Shock
- Hepatic insufficiency acute alcohol intoxication, alcoholism.

Warnings and Precautions:

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly there after [See Section Dosage and Administration]. Metformin is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function [See Section Contraindications].

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

Elderly

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.

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. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Surgery

Metformin must be discontinued at the time of surgery with general, spinal or epidural anaesthesia. 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.

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, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g., sulphonylureas or meglitinides)

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

Interactions with Other Medicaments:

Concomitant use not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics).

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the other drug and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy.

- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Pregnancy and Lactation:

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. No harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development seen in animals.

When the patient plans to become pregnant and during pregnancy, it is recommended that impaired glycaemic control or diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Breastfeeding

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breastfeeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effect on the child.

Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Side Effects:

In post marketing data, adverse event reporting in patients treated with prolonged release metformin was similar in nature and severity to that reported in patients treated with immediate release metformin.

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

The following undesirable effects may occur under treatment with METSWIFT XR:

Metabolism and nutrition disorders

Common:

Vitamin B12 decrease/deficiency

Very rare:

- Lactic acidosis (see section Special warnings and precautions for use).

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. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Very rare:

- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

Very rare:

- Skin reactions such as erythema, pruritus, urticaria.

Symptoms and Treatment of Overdose:

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

Effects on Ability to Drive and Use Machine:

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with otherantidiabetic agents (e.g., sulphonylureas, insulin, or meglitinides).

Storage Condition:

Store below 30°C. Protect from light and moisture.

Keep medicines out of reach of children.

Shelf Life:

36 months.

Manufacturer:

Ind-Swift Laboratories Limited

Off- NH-21, Village Jawaharpur,

Tehsil Derabassi, Distt. S.A.S Nagar

(Mohali) Punjab (India) Pin -140507

Product Registration Holder:

Synerri Sdn. Bhd.,

SD-29-2, Menara 1, KL Eco City,

Jalan Bangsar Kg Haji Abdullah Hukum,

59200 Bangsar Wilayah Persekutuan,

Kuala Lumpur Malaysia

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Paper should be Maplitho (60GSM)

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