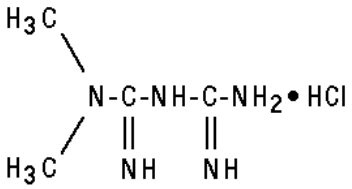
Rx only

GLUCOPHAGE® (metformin hydrochloride tablets)

GLUCOPHAGE® XR (metformin hydrochloride extended-release tablets)

DESCRIPTION

GLUCOPHAGE® (metformin hydrochloride tablets) and GLUCOPHAGE® XR (metformin hydrochloride extended-release tablets) are oral antihyperglycemic drugs used in the management of type 2 diabetes. Metformin hydrochloride (*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$ • HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE tablets contain 500 mg, 850 mg, or 1000 mg of metformin hydrochloride. Each tablet contains the inactive ingredients povidone and magnesium stearate. In addition, the coating for the 500-mg and 850-mg tablets contains hydroxypropyl methylcellulose (hypromellose) and the coating for the 1000-mg tablet contains hydroxypropyl methylcellulose and polyethylene glycol.

GLUCOPHAGE XR (metformin hydrochloride extended-release tablets) contains 500 mg of metformin hydrochloride as the active ingredient. Each tablet contains the inactive ingredients sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, and magnesium stearate.

System Components and Performance. GLUCOPHAGE XR (metformin hydrochloride extended-release tablets) comprises a dual hydrophilic polymer matrix system. Metformin hydrochloride is combined with a drug release controlling polymer to

phase of a second polymer. After administration, fluid from the gastrointestinal (GI) tract enters the tablet, causing the polymers to hydrate and swell. Drug is released slowly from the dosage form by a process of diffusion through the gel matrix that is essentially independent of pH. The hydrated polymer system is not rigid and is expected to be broken up by normal peristalsis in the GI tract. The biologically inert components of the tablet may occasionally remain intact during GI transit and will be eliminated in the feces as a soft, hydrated mass.

CLINICAL PHARMACOLOGY

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 (except in special circumstances, see **PRECAUTIONS**) 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 GLUCOPHAGE 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of GLUCOPHAGE 500 mg to 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 plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (T_{max}) 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.

Following a single oral dose of GLUCOPHAGE XR, C_{max} is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of GLUCOPHAGE, however, the extent of absorption (as measured by AUC) is similar to GLUCOPHAGE.

At steady state, the AUC and C_{max} are less than dose proportional for GLUCOPHAGE XR within the range of 500 mg to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 µg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from GLUCOPHAGE XR at a 2000 mg once-daily dose is similar to the same total daily dose administered as GLUCOPHAGE tablets 1000 mg twice daily.

plasma.

Within-subject variability in C_{max} and AUC of metformin from GLUCOPHAGE XR is comparable to that with GLUCOPHAGE.

Although the extent of metformin absorption (as measured by AUC) from the GLUCOPHAGE XR tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of GLUCOPHAGE XR.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of GLUCOPHAGE 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 GLUCOPHAGE, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 g/mL. During controlled clinical trials of GLUCOPHAGE, maximum metformin plasma levels did not exceed 5 g/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) nor 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.

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 (see **Table 1**), nor is there any accumulation of metformin in either group at usual clinical doses.

The pharmacokinetics of GLUCOPHAGE XR in patients with type 2 diabetes are comparable to those in healthy normal adults.

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 (see **Table 1;** also see **WARNINGS**).

Hepatic Insufficiency

No pharmacokinetic studies of metformin have been conducted in patients with hepatic

Geriatrics

Limited data from controlled pharmacokinetic studies of GLUCOPHAGE in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **Table 1**). GLUCOPHAGE and GLUCOPHAGE XR treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Table 1. Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of GLUCOPHAGE

Subject Groups: GLUCOPHAGE dose[a] (number of subjects)	**C_{max}[b]** (g/mL)	**T_{max}[c]** (hrs)	**Renal Clearance** (mL/min)
Healthy, nondiabetic adults:			
500 mg single dose (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (74)[d]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg three times daily for 19 doses[e] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses[e] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[f], healthy nondiabetic adults:			
850 mg single dose (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults:			
850 mg single dose			
Mild (CL_{cr}[g] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a]–All doses given fasting except the first 18 doses of the multiple dose studies

[b]–Peak plasma concentration

[c]–Time to peak plasma concentration

[d]–Combined results (average means) of five studies: mean age 32 years (range 23-59 years)

[e]–Kinetic study done following dose 19, given fasting

[f]–Elderly subjects, mean age 71 years (range 65-81 years)

[g]–CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics

No pharmacokinetic studies of metformin in pediatric patients have been conducted.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of GLUCOPHAGE was comparable in males and females.

Race

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of GLUCOPHAGE in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51),

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