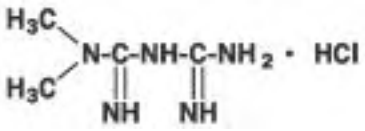
FORTAMET® (metformin hydrochloride) Extended-Release Tablets

DESCRIPTION

FORTAMET® (metformin hydrochloride) Extended-Release Tablets contain an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oral antihyperglycemics and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. The empirical formula of metformin hydrochloride is $C_4H_{11}N_5$•HCl and its molecular weight is 165.63. Its structural formula is:



Metformin hydrochloride is a white to off-white crystalline powder that is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.
FORTAMET® Extended-Release Tablets are designed for once-a-day oral administration and deliver 500 mg or 1000 mg of metformin hydrochloride. In addition to the active ingredient metformin hydrochloride, each tablet contains the following inactive ingredients: candellila wax, cellulose acetate, hypromellose, magnesium stearate, polyethylene glycols (PEG 400, PEG 8000), polysorbate 80, povidone, sodium lauryl sulfate, synthetic black iron oxides, titanium dioxide, and triacetin. FORTAMET® meets USP Dissolution Test 5.

SYSTEM COMPONENTS AND PERFORMANCE

FORTAMET®was developed as an extended-release formulation of metformin hydrochloride and designed for once-a-day oral administration using the patented single-composition osmotic technology (SCOT™). The tablet is similar in appearance to other film-coated oral administered tablets but it consists of an osmotically active core formulation that is surrounded by a semipermeable membrane. Two laser drilled exit ports exist in the membrane, one on either side of the tablet. The core formulation is composed primarily of drug with small concentrations of excipients. The semipermeable membrane is permeable to water but not to higher molecular weight components of biological fluids. Upon ingestion, water is taken up through the membrane, which in turn dissolves the drug and excipients in the core formulation. The dissolved drug and excipients exit through the laser drilled ports in the membrane. The rate of drug delivery is constant and dependent upon the maintenance of a constant osmotic gradient across the membrane. This situation exists so long as there is undissolved drug present in the core tablet. Following the dissolution of the core materials, the rate of drug delivery slowly decreases until the osmotic gradient across the membrane falls to zero at which time delivery ceases. The membrane coating remains intact during the transit of the dosage form through the gastrointestinal tract and is excreted in the feces.

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 plasma insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS AND DRUG METABOLISM

Absorption and Bioavailability

The appearance of metformin in plasma from a FORTAMET® Extended-Release Tablet is slower and more prolonged compared to immediate-release metformin.

In a multiple-dose crossover study, 23 patients with type 2 diabetes mellitus were administered either FORTAMET® 2000 mg once a day (after dinner) or immediate-release (IR) metformin hydrochloride 1000 mg twice a day (after breakfast and after dinner). After 4 weeks of treatment, steady-state pharmacokinetic parameters, area under the concentration-time curve (AUC), time to peak plasma concentration (T_{max}), and maximum concentration (C_{max}) were evaluated. Results are presented in **Table 1**.

Table 1 FORTAMET®vs. Immediate-Release Metformin Steady-State Pharmacokinetic Parameters at 4 Weeks

Pharmacokinetic Parameters (mean ±SD)	FORTAMET® 2000 mg (administered q.d.after dinner)	Immediate-Release Metformin 2000 mg (1000 mg b.i.d.)
AUC $_{0\text{-}24\ hr}$ (ng•hr/mL)	26,811 ± 7055	27,371 ± 5,781
T_{max} (hr)	6 (3-10)	3 (1-8)
C_{max} (ng/mL)	2849 ± 797	1820 ± 370

In four single-dose studies and one multiple-dose study, the bioavailability of FORTAMET® 2000 mg given once daily, in the evening, under fed conditions [as measured by the area under the plasma concentration versus time curve (AUC)] was similar to the same total daily dose administered as immediate-release metformin 1000 mg given twice daily. The geometric mean ratios (FORTAMET®/ immediate-release metformin) of $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}72hr}$, and $AUC_{0\text{-}inf.}$ for these five studies ranged from 0.96 to 1.08.

In a single-dose, four-period replicate crossover design study, comparing two 500 mg FORTAMET® tablets to one 1000 mg FORTAMET®tablet administered in the evening with food to 29 healthy male subjects, two 500 mg FORTAMET® tablets were found to be equivalet to one 1000 mg FORTAMET® tablet.

In a study carried out with FORTAMET®, there was a dose-associated increase in metformin exposure over 24 hours following oral administration of 1000, 1500, 2000, and 2500 mg.

In three studies with FORTAMET® using different treatment regimens (2000 mg after dinner; 1000 mg after breakfast and after dinner; and 2500 mg after dinner), the pharmacokinetics of metformin as measured by AUC appeared linear following multiple-dose administration.

The extent of metformin absorption (as measured by AUC) from FORTAMET® increased by approximately 60% when given with food. When FORTAMET® was administered with food, C_{max} was increased by approximately 30% and T_{max} was more prolonged compared with the fasting state (6.1 versus 4.0 hours).

Distribution

Distribution studies with FORTAMET® have not been conducted. However, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 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 immediate-release metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 µg/mL. During controlled clinical trials of immediate-release metformin, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism and Excretion

Metabolism studies with FORTAMET® have not been conducted. 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.

In healthy nondiabetic adults (N=18) receiving 2500 mg q.d. FORTAMET®, the percent of the metformin dose excreted in urine over 24 hours was 40.9% and the renal clearance was 542 ± 310 mL/min. After repeated administration of FORTAMET®, there is little or no accumulation of metformin in plasma, with most of the drug being eliminated via renal excretion over a 24-hour dosing interval. The $t_{1/2}$ was 5.4 hours for FORTAMET®.

Renal clearance of metformin (**Table 2**) 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

Geriatrics

Limited data from controlled pharmacokinetic studies of immediate-release metformin 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 (**Table 2**). FORTAMET® 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, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Pediatrics

No pharmacokinetic data from studies of pediatric patients are currently available (see **PRECAUTIONS**).

Gender

Five studies indicated that with FORTAMET® treatment, the pharmacokinetic results for males and females were comparable.

Table 2
Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Immediate-Release Metformin

Subject Groups: Immediate-Release Metformin dose[a] (number of subjects)	C_{max}[b] (µg/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

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 (Table 2; also see WARNINGS).

Hepatic Insufficiency

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

Race

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of immediate-release metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Clinical Studies

In a double-blind, randomized, active-controlled, multicenter U.S. clinical study, which compared FORTAMET® q.d. to immediate-release metformin b.i.d., 680 patients with type 2 diabetes who had been taking metformin-containing medication at study entry were randomly assigned in equal numbers to double-blind treatment with either FORTAMET® or immediate-release metformin.

Doses were adjusted during the first six weeks of treatment with study medication based on patients' FPG levels and were then held constant over a period of 20 weeks. The primary efficacy endpoint was the change in HbA_{1c} from baseline to endpoint. The primary objective was to demonstrate the clinical non-inferiority of FORTAMET® compared to immediate-release metformin on the primary endpoint.

FORTAMET® and metformin patients had mean HbA_{1c} changes from baseline to endpoint equal to +0.40 and +0.14, respectively (**Table 3**).The least-square (LS) mean treatment difference was 0.25 (95% CI = 0.14, 0.37) demonstrating that FORTAMET® was clinically similar to metformin according to the pre-defined criterion to establish efficacy.

Table 3
FORTAMET®vs. Immediate-Release Metformin Switch Study:
Summary of Mean Changes in HbA_{1c}, Fasting Plasma Glucose, Body Weight, Body Mass Index, and Plasma Insulin

	FORTAMET®	Immediate-Release Metformin	Treatment difference for change from baseline (FORTAMET® minus Immediate-Release Metformin) LS mean (2 sided 95% CI[a])
HbA_{1c} (%)			
N	327	332	0.25
Baseline (mean ± SD)	7.04 ± 0.88	7.07 ± 0.76	(0.14,0.37)[b]
Change from baseline (mean ± SD)	0.40 ± 0.75	0.14 ± 0.75	
Fasting Plasma Glucose (mg/dL)			
N	329	333	6.43
Baseline (mean ± SD)	146.8 ± 32.1	145.6 ± 29.5	(0.57, 12.29)
Change from baseline (mean ± SD)	10.0 ± 40.8	4.2 ± 35.9	
Plasma Insulin (µu/mL)			
N	304	316	0.02
Baseline (mean ± SD)	17.9 ± 15.1	17.3 ± 10.5	(-1.47, 1.50)
Change from baseline (mean ± SD)	-3.6 ± 13.8	-3.2 ± 8.6	
Body Weight (kg)			
N	313	320	0.30
Baseline (mean ± SD)	94.1 ± 17.8	93.3 ± 17.4	(-0.22, 0.81)
Change from baseline (mean ± SD)	0.3 ± 2.9	0.0 ± 3.7	
Body Mass Index (kg/m^2)			
N	313	320	0.08
Baseline (mean ± SD)	31.1 ± 4.7	31.4 ± 4.5	(-0.11, 0.26)
Change from baseline (mean ± SD)	0.1 ± 1.1	0.0 ± 1.3	

a CI= Confidence Interval
b FORTAMET® was clinically similar to immediate-release metformin based on the pre-defined criterion to establish efficacy. While demonstrating clinical similarity, the response to FORTAMET® compared to immediate-release metformin was also shown to be statistically smaller as seen by the 95% CI for the treatment difference which did not include zero.
Footnote: Patients were taking metformin-containing medications at baseline that were prescribed by their personal physician.

The mean changes for FPG (**Table 3**) and plasma insulin (**Table 3**) were small for both FORTAMET® and immediate-release metformin, and were not clinically meaningful. Seventy-six (22%) and 49 (14%) of the FORTAMET® and immediate-release patients, respectively, discontinued prematurely from the trial. Eighteen (5%) patients on FORTAMET® withdrew because of a stated lack of efficacy, as compared with 8 patients (2%) on immediate-release metformin (p=0.047).

Results from this study also indicated that neither FORTAMET® nor immediate-release metformin were associated with weight gain or increases in body mass index.

A 24-week, double blind, placebo-controlled study of immediate-release metformin plus insulin, versus insulin plus placebo, was conducted in patients with type 2 diabetes who failed to achieve adequate glycemic control on insulin alone (**Table 4**).

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