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EXFORGE®: A NEW COMBINATION TO TREAT HYPERTENSION

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The prevalence of hypertension continues to be unacceptably high in the United States and Europe, with about 1 billion individuals affected worldwide.[1,2] Despite the availability of a variety of antihypertensive medications, population-based surveys indicate that an estimated 40-80% of treated patients do not achieve their blood pressure (BP) goals[3] for reasons that include noncompliance and inadequate dosing.[4] Inadequately controlled hypertension has serious consequences, causing and promoting the progression of cardiovascular, renal and metabolic disease. However, effective interventions to lower BP can reduce the risk of cardiovascular events.[2]

Approximately two-thirds of all patients with hypertension require multi-drug regimens to achieve recommended BP targets.[2] European and US treatment guidelines recommend that therapy be initiated with a combination of individual agents or fixed-dose combinations in patients with a BP > 20/10 mm Hg above goal[2] or those at high risk for cardiovascular complications.[5] Use of combination therapy with ≥ 2 agents having complementary mechanisms of action such as an angiotensin-converting enzyme (ACE) inhibitor plus a calcium channel blocker (CCB), or a diuretic plus an ACE inhibitor or angiotensin II-receptor blocker (ARB), is more effective in lowering BP than either agent alone and leads to higher response rates versus monotherapy.[2,5,6,7] Dual therapy that blocks both calcium channels and angiotensin II type 1 (AT-1) receptors represent a new therapeutic option.

In June 2007, Novartis Pharmaceuticals received FDA approval for their new fixed combination product, Exforge®. The new product is a combination of previously approved amlodipine and valsartan. The combination of amlodipine + valsartan is approved for the treatment of hypertension in patients who do not respond to monotherapy of amlodipine or valsartan as single agents. This article will review the pharmacology and pharmacokinetics, clinical trials, safety profile, drug interactions, dosing and administration and cost for amlodipine + valsartan.

Pharmacology and Pharmacokinetics

Amlodipine + valsartan contain two antihypertensive medications that are effective in lowering blood pressure. Both amlodipine and valsartan lower blood pressure by reducing peripheral resistance. Their mechanisms of action, calcium influx blockade and reduction of angiotensin II vasoconstriction, are complementary mechanisms.[8]

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Amlodipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes. Serum calcium levels remain unchanged. The resultant decrease in intracellular calcium inhibits contractile processes of the myocardial smooth muscle cells, resulting in dilation of the coronary and systemic arteries. As with other calcium-channel blockers of the dihydropyridine class, amlodipine exerts its effects mainly on arteriolar vasculature.[9]

Valsartan antagonizes angiotensin II at the AT-1 receptor subtype. Valsartan has about a 20,000-fold greater affinity for the AT-1 subtype than the AT-2 subtype. By selectively blocking the AT-1 receptor in tissues such as vascular smooth muscle and the adrenal gland, valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Thus, by blocking the effects of angiotensin II, valsartan decreases systemic vascular resistance without a marked change in heart rate.[9] Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion. Circulating levels of both renin and angiotensin II rise 2- to 3-fold in response to blockade of the AT-1 receptor. The resulting increased plasma renin activity and angiotensin II circulating levels however, do not negate the effect of valsartan on blood pressure.[8]

Concomitant administration of amlodipine with valsartan has no effect on the bioavailability of either drug. The rate and extent of absorption of each drug administered in combination are the same as when each drug is administered as individual tablets. Amlodipine is slowly but almost completely absorbed after oral administration. Oral bioavailability ranges from 64—90%. Peak plasma concentrations are achieved between 6-12 hours post-dose, and maximum hypotensive effects are correspondingly delayed.[8,9] Food does not appear to influence these parameters significantly; however, grapefruit juice may increase bioavailability by inhibiting cytochrome P450 enzymes. Like other calcium-channel blockers, amlodipine is primarily metabolized by CYP3A4 isoenzymes. The drug is approximately 93% bound to plasma proteins, but drug interactions secondary to displacement from binding sites have not been documented.[10] Amlodipine is extensively metabolized to inactive compounds, and 10% of the parent compound and 60% of the inactive metabolites are excreted in the urine. The mean terminal half-life of amlodipine is 35 hours following single dose administration, which is significantly longer than the other dihydropyridines currently available.[10]

Valsartan is rapidly absorbed, with peak plasma concentrations occurring 2—4 hours after administration. Absolute bioavailability for the capsule formulation is roughly 25% (range, 10—35%). Administration with food decreases the AUC by about 40%; therapeutic effect is maintained despite the reduction in bioavailability. AUC and C_{max} of valsartan increase linearly within the dosage range of 80—320 mg; however, the antihypertensive dose-response curve is nonlinear, with proportionally small decreases in blood pressure attained with increased dosage. Approximately 95% of valsartan is bound to serum proteins, primarily albumin. The primary metabolite of valsartan is valeryl-4-hydroxy valsartan, which is inactive and accounts for about 9% of the dose. The enzyme(s) responsible for the metabolism of valsartan is unknown. Duration of antihypertensive activity is approximately 24 hrs. Valsartan is excreted primarily in the feces, most likely via the biliary route. Only 13% of the dose is excreted unchanged in urine. The elimination half-life of valsartan averages 6 hrs.[8,9] A summary of the pharmacokinetics of amlodipine and valsartan is presented in **Table 1**.

Table 1. Pharmacokinetics of amlodipine and valsartan.[8,9]

	Amlodipine	Valsartan
Onset of action	30-50 min	2 weeks (maximal: 4 weeks)
Duration of action	24 hours	24 hours
Absorption (oral)	Well absorbed	Well absorbed
Distribution (V_d)	21 L/kg	17 L (adults)
Protein binding	93-98%	95%, mainly albumin
Metabolism	Hepatic (>90%) to inactive metabolite	Unknown pathway to inactive metabolite
Bioavailability	64-90%	25% (10-35%)
Half-life elimination	30-50 hours	6 hours
Time to peak (plasma)	6-12 hours	2-4 hours
Excretion	Urine (10% as parent, 60% as metabolite)	Feces (83%) and urine (13%) as unchanged drug

Clinical Trials

Two studies were conducted to compare the efficacy of various combinations of amlodipine and valsartan administered once daily with their individual components and placebo in patients with mild to moderate essential hypertension.[11] The studies were multinational, multi-center, 8-week, randomized, double-blind, placebo-controlled, parallel-group trials. The primary objective of both studies was to compare the BP-lowering effects of a once-daily regimen of various doses of amlodipine and valsartan with those of their individual components and placebo in patients with a mean sitting diastolic blood pressure [MSDBP] ≥ 95 and < 110 mm Hg. A secondary objective was to evaluate safety and tolerability. The primary efficacy variable in both studies was the change from baseline in MSDBP at study end in both the combination and monotherapy groups. Secondary efficacy variables in both studies included the change from baseline in mean sitting systolic blood pressure (MSSBP) and response rates (the proportion of patients achieving an MSDPB < 90 mm Hg or a ≥ 10 mm Hg reduction from baseline).

In Study 1[11], 1911 patients were randomized to receive 1 of 15 treatments: amlodipine 2.5 or 5 mg once daily, valsartan 40, 80, 160 or 320 mg once daily, the combination of amlodipine + valsartan 2.5/40, 5/40, 2.5/80, 5/80, 2.5/160, 5/160, 2.5/320 or 5/320 mg once daily or placebo. Global assessment of MSDBP reduction at study end indicated that both monotherapies contributed to the overall BP-lowering effects of combination treatment ($p<0.001$, both amlodipine and valsartan). The greatest effects were observed at the highest dose of combination therapy, amlodipine 5 mg + valsartan 320 mg. Combination treatments were associated with significantly greater reductions in MSDBP at the end of the study compared with their individual components and placebo ($p<0.05$) (**Table 2**). There was an increased reduction in MSDBP at each combination dose starting at the lowest strength combination of amlodipine 2.5 mg + valsartan 40 mg (MSDBP reduction of 10.8 mm Hg) to the highest strength combination of amlodipine 5 mg + valsartan 320 mg (MSDBP reduction of 15.9 mm Hg). Mostly all of the combination doses were significant vs. placebo, the same dose of valsartan monotherapy and the same dose of amlodipine monotherapy, with the highest reduction at the highest dose combination of amlodipine 5 mg + valsartan 320 mg which would justify a dose escalation from a combination of amlodipine 2.5 mg + valsartan 40 mg to amlodipine 5 mg + valsartan 320 mg. The MSDBP reduction of amlodipine 2.5 mg + valsartan 320 mg was not significant versus valsartan monotherapy although amlodipine 2.5 mg + valsartan 160 mg was significant versus valsartan monotherapy. However, amlodipine 2.5 mg is not available in combination with valsartan. The highest response rates were observed with amlodipine 5 mg + valsartan 320 mg (91.3%) and the lowest rates were observed with placebo (40.9%). The response rate for amlodipine 5 mg + valsartan 320 mg group was significantly greater than those for each monotherapy and placebo groups (all comparisons, $p<0.05$) (**Table 3**).

In Study 2[11], 1250 patients were randomized to receive 1 of 6 treatments: amlodipine 10 mg once daily, valsartan 160 or 320 mg once daily, the combination of amlodipine + valsartan 10/160 or 10/320 once daily or placebo. Similar to Study 1, global assessment of MSDBP reduction at study end indicated

Table 2. Least squares mean reduction in sitting diastolic blood pressure (DBP) at end of Study 1[11]

Valsartan dose (mg)	Amlodipine dose (mg)		
	0mg	2.5mg	5mg
0mg	7.0 (placebo)	9.3*	11.5*
40mg	10.1*	10.8*	14.6*†‡
80mg	9.7*	13.4*†‡	14.5*†‡
160mg	11.0*	13.3*†‡	14.2*†‡
320mg	13.4*	14.2*‡	15.9*†‡

*$p<0.05$ vs. placebo; †$p<0.05$ versus the same dose of valsartan monotherapy; ‡$p<0.05$ versus the same dose of amlodipine monotherapy.

Table 3. Proportions of responders (mean sitting diastolic blood pressure < 90 mm Hg or a ≥ 10 mm Hg reduction from baseline) at the end of Study 1 and 2[11]

Study 1	Response Rate, %
Amlodipine 5mg + valsartan 320mg	91.3*‡
Amlodipine 5mg + valsartan 160mg	81.1*†
Amlodipine 5mg + valsartan 80mg	84.9*†‡
Amlodipine 5mg + valsartan 40mg	83.7*†‡
Amlodipine 2.5mg + valsartan 320mg	79.7*‡
Amlodipine 2.5mg + valsartan 160mg	74.4*‡
Amlodipine 2.5mg + valsartan 80mg	77.5*†‡
Amlodipine 2.5mg + valsartan 40mg	57.0*
Amlodipine 5mg	71.9*
Amlodipine 2.5mg	60.3*
Valsartan 320mg	73.4*
Valsartan 160mg	67.7*
Valsartan 80mg	57.7*
Valsartan 40mg	59.1*
Placebo	40.9
Study 2	**Response Rate, %**
Amlodipine 10mg + valsartan 320mg	87.5*†
Amlodipine 10mg + valsartan 160mg	88.5*†
Amlodipine 10mg	86.9*
Valsartan 320mg	72.0*
Valsartan 160mg	74.9*
Placebo	49.3

*p<0.05 vs. placebo; †p<0.05 versus the same dose of valsartan monotherapy; ‡p<0.05 versus the same dose of amlodipine monotherapy

that both monotherapies contributed to the overall BP-lowering effects of combination treatment (p<0.001, both valsartan and amlodipine). Between-treatment comparisons of MSDBP indicated that both combination treatments were associated with significantly greater reductions in MSDBP compared with their individual components and placebo at study end (p<0.05) (**Table 4**). The highest response rates were observed with amlodipine 10 mg + valsartan 160 mg (88.5%) and the lowest with placebo (49.3%) (**Table 3**). The response rates with amlodipine 10 mg + valsartan 160 mg and amlodipine 10 mg + valsartan 320 mg were significantly greater than those with valsartan monotherapy (p<0.05) and with placebo (p<0.05); however, they did not differ significantly from the response rate with amlodipine monotherapy (**Table 3**).

In Study 2, the response rates for amlodipine 10 mg + valsartan 320 mg was actually lower (87.5%) than amlodipine 10 mg + valsartan 160 mg (88.5%) and

Table 4. Least squares mean reduction in sitting diastolic blood pressure (DBP) at end of Study 2[11]

Valsartan dose (mg)	Amlodipine dose (mg)	
	0mg	10mg
0mg	8.7 (placebo)	15.6*
160mg	13.3*	17.6*†‡
320mg	13.3*	18.6*†‡

*p<0.05 vs. placebo; †p<0.05 versus the same dose of valsartan monotherapy; ‡p<0.05 versus the same dose of amlodipine monotherapy

amlodipine 5 mg + valsartan 320 mg (91.3%, Study 1). However, the response rates were still significant vs. both placebo and the same dose of valsartan monotherapy in Study 2. The highest decrease in MSDBP was seen at the highest dose combination of amlodipine 10 mg + valsartan 320 mg (18.6 mm Hg). However, this was not significant versus the amlodipine 10 mg + valsartan 160 mg. Therefore, increasing the dose above the combination of amlodipine 5 mg + valsartan 320 mg is probably not a reasonable option.

Safety

Combination therapy of amlodipine + valsartan was generally well tolerated regardless of age, race or sex.[11] In the combined safety evaluation from both studies which included 1437 patients in the amlodipine + valsartan combination group and 337 patients in the placebo group, the most common adverse events (AEs), regardless of their relation to treatment, were peripheral edema (5.4%), headache (4.3%), nasopharyngitis (4.3%), upper respiratory tract infection (2.9%) and dizziness (2.1%). Adverse events associated with low BP, such as syncope, hypotension/orthostatic hypotension, postural dizziness and lightheadedness either did not occur or occurred at very low frequencies (≤ 0.3% of patients).

Amlodipine + valsartan is contraindicated in patients with known hypersensitivity to either of its components including dihydropyridine hypersensitivity. Amlodipine + valsartan should be used with caution in patients with coronary artery disease. Patients have rarely developed documented increased frequency, duration, and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. Caution is also warranted with impaired renal function as valsartan affects the renin-angiotensin-aldosterone system (RAS) and has caused increases in serum creatinine. Amlodipine + valsartan should also be used with caution in patients with hepatic disease. The clearance of both amlodipine and valsartan is prolonged in these patients. Amlodipine + valsartan has caused excessive hypotension in 0.4% of patients with uncomplicated hypertension during placebo-controlled trials. Angiotensin receptor blockers may cause symptomatic hypotension in patients with an activated renin-angiotensin system such as patients with hypovolemia and/or salt-depletion receiving high doses of diuretics. Intravascular volume depletion increases the risk of symptomatic hypotension. These conditions should be corrected prior to starting therapy, or therapy should be started under close medical supervision. Amlodipine + valsartan should be used with caution in patients whose renal function is critically dependent on the activity of the renin-angiotensin-aldosterone system (RAS) (e.g., patients with heart failure) and in patients undergoing surgery or dialysis. Amlodipine + valsartan should not be used during the second or third trimester of pregnancy (FDA pregnancy risk category D), unless the benefits outweigh the potential risks. Drugs which affect the renin-angiotensin system have been associated with fetal and neonatal injury when administered to pregnant women.

Drug Interactions

Amlodipine is a CYP3A4 substrate and its metabolism may theoretically be affected by CYP3A4 inducers (barbiturates, carbamezapine, phenytoin, etc) or inhibitors (amiodarone, antifungals, cimetidine, macrolides, etc). No pharmacokinetic drug interactions were observed when amlodipine was given with atorvastatin, cimetidine, digoxin, antacids, sildenafil, or warfarin.[9] One study demonstrated no significant affinity of valsartan for CYP2C9 or CYP2C19 isoenzymes.[12] No pharmacokinetic drug interactions were observed when valsartan was administered concomitantly with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The concomitant administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.[9] Valsartan tends to reverse potassium loss, but not the serum uric acid rise associated with hydrochlorothiazide monotherapy.[9]

Dosing and Administration

To minimize dose-independent hazards, it is usually appropriate to begin therapy with amlodipine + valsartan only after a patient has failed to achieve the desired antihypertensive effect with monotherapy. Although, initial combination therapy may be appropriate in patients with stage 2 hypertension. A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine CCB) alone or with valsartan (or another ARB) alone may be switched to combination therapy with amlodipine + valsartan. The dosage for a patient

should first be individualized by dose titration of both amlodipine and valsartan. The combination product is available as 5/160 mg, 5/320 mg, 10/160 mg, or 10/320 mg tablets of amlodipine/valsartan. The dosage of one or both drug components may be increased after 3—4 weeks depending on the clinical response. The maximum dosage per day is 10 mg amlodipine and 320 mg valsartan. Volume and/or sodium depletion should be corrected prior to administration.[8] Amlodipine + valsartan may be administered without regard to meals. Patients should be instructed to either not significantly alter grapefruit juice intake or to avoid grapefruit juice, if possible, while taking this drug.

Cost

Pricing data for Exforge® was obtained for a one month prescription from three community pharmacies located in Gainesville, FL. The average monthly cost (30 tablets) for all strengths was $84.45 (range $79.99-$95.68). This monthly cost is cheaper than the separate combinations of the two medications. An average one month prescription cost for amlodipine (30 tablets) for both strengths is $62.53 (generic; range $53.59-67.39) and $88.22 (as Norvasc®; range $80.99-95.68). An average one month prescription for valsartan (30 tablets) for all strengths is $75.28 (range $71.88-78.99).

Summary

Exforge® (amlodipine + valsartan) is the newest addition to the anti-hypertensive drug market. It offers adequate BP lowering effects through a combination of two antihypertensive medications, amlodipine and valsartan, each with their own distinct but complementary mechanisms of action. The fixed-dose combination is more effective than monotherapy and may improve patient compliance by simplifying the drug regimen. Amlodipine + valsartan is not indicated for initial high blood pressure therapy. It is a viable option and should be considered for high blood pressure in patients who have not been controlled through the use of monotherapy with an angiotensin receptor blocker or calcium channel blocker and for patients who have experienced dose-limiting side effects on either valsartan or amlodipine monotherapy.

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MARAVIROC (SELZENTRY®): A NOVEL ANTIRETROVIRAL

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HIV/AIDS represents a significant health problem in the United States. By the end of 2003, approximately 2 million persons in the United States were living with HIV/AIDS, an estimated 24-27% of whom were unaware of their infection.[1] The CDC reports close to 85,000 deaths from AIDS from 2001-2005. Survival has increased for diagnoses made during 1997–1999 while year-to-year gains in survival were small during 2000–2004.[2] Treatment options for HIV/AIDS include four classes of antiretroviral therapy: protease inhibitors (PI), nucleoside/ nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and a fusion inhibitor. While these drugs have had a major factor on survival, not all patients have realized the benefits of these therapies due to drug intolerance and viral resistance.

Maraviroc (Selzentry®) is the first of a new pharmacological class of antiretroviral agents known as chemokine receptor 5 (CCR5) antagonists. It is a small molecule acting on a human cellular target to prevent infection; in other words, HIV-1 fusion and entry are inhibited. Developed by Pfizer Corporation, it was approved by the FDA on August 6, 2007. It is indicated in combination with other antiretroviral medications for patients who show evidence of viral replication and exhibit HIV-1 CCR5 tropism. This article will review the pharmacology, pharmacokinetics, dosing, cost, toxicity, and clinical trials of maraviroc.

Pharmacology

Maraviroc has a novel mechanism of action. It binds to CCR5 coreceptors on CD4 cells blocking entry of HIV into these cells. This first step of HIV-1 cell entry is the specific binding of viral gp120 to CD4, the primary receptor for HIV-1. This binding alone is not sufficient for HIV-1 entry. The binding of gp120 to CD4 causes a conformational change in gp120 that exposes the bridging sheet and forms a co-receptor binding site.[3] Once this has occurred, co-receptor binding triggers conformational changes in gp41, which drives the remaining steps in fusion and entry of the viral core.[4] The chemokine receptors most commonly utilized by HIV-1 *in vivo* are (CCR5) and/or CX chemokine receptor 4 (CXCR4).[5] The ability of gp120 to bind to either one or both receptors defines the tropism of the virus. HIV-1 strains are therefore categorized as R5 (CCR5-tropic), X4 (CXCR4-tropic) or R5X4 (strains using both CCR5 and CXCR4; also referred to as 'dual-tropic').[6] The ability of maraviroc to prevent infection by inhibiting viral entry provides another treatment mechanism in a oral dosage form compared to enfurvitide which requires an subcutaneous injection.

Maraviroc selectively inhibits CCR5-tropic HIV-1 replication *in vitro*. Maraviroc inhibited replication of 43 CCR5-tropic primary isolates in human peripheral blood lymphocytes containing primarily CD4+ T-cells, which represent the major cellular reservoir for HIV-1 replication *in vivo*. The unbound *in vitro* antiviral IC90 (inhibitory concentration of drug needed to suppress 90% of HIV replication) for maraviroc is estimated to be approximately 1.0 nM (0.5 ng/mL).[2]

Pharmacokinetics

Peak maraviroc plasma concentrations (C_{max}) are attained 0.5-4 h following single oral doses of 1-1200 mg in healthy volunteers. The pharmacokinetics of oral maraviroc are not dose proportional over the dose range.[2] The bioavailability of maraviroc is 23% after a single dose of 150 mg and is predicted to have a bioavailability of 33% after a single 300 mg dose.[7] Maraviroc is a substrate for the efflux transporter P-glycoprotein (Pgp). The effect of food resulted in a decreased C_{max} by 33% to 60%, and area under the curve (AUC) by 33% to 50% although there was no difference in the reduction of viral load at day 11 between groups who received maraviroc 150 mg orally twice daily in the fasted or fed state.[8] The terminal half-life ($t_{½}$) of maraviroc is between 14 and 18 h healthy subjects.[2]

Multiple dosing of maraviroc at 300 mg achieved steady state within 7 days and resulted in limited accumulation. The actual distribution in human tissue is unknown. Maraviroc is 76% bound to plasma proteins showing moderate affinity for albumin and alpha-1-glycoprotein. It is predominately confined to

plasma with little penetration into erythrocytes. It has a volume of distribution (Vd) of 194L or 2.8L/kg.[2]

The main route of metabolism of maraviroc is primarily by CYP 3A4 and it is not significantly metabolized by any polymorphic enzymes. Maraviroc is the major circulating component (42%) after a single 300 mg dose. Circulating metabolites include a secondary amine formed by N-dealkylation (22%) and other metabolites produced from mono-oxidation. Metabolites of maraviroc do not have pharmacologic activity. The pharmacokinetics of maraviroc have not been sufficiently studied in patients with hepatic impairment. Because maraviroc is metabolized by the liver, concentrations are likely to be increased in these patients.

After a single radiolabeled dose, elimination of maraviroc is primarily via the fecal route (76%) and to a smaller degree renally (20%). Total body clearance is 10.5 mL/min/kg.[2] The safety and efficacy of maraviroc have not been specifically studied in patients with renal impairment; therefore maraviroc should be used with caution in this population. Maraviroc concentrations may be increased in patients with renal impairment, especially when CYP3A inhibitors are coadministered. Patients with a creatinine clearance of less than 50 mL/min who receive maraviroc and a CYP3A inhibitor may be at an increased risk of adverse effects related to increased maraviroc concentrations.

The safety and efficacy of maraviroc in patients < 16 or > 65 years of age have not been established. Therefore, maraviroc should be used cautiously in these patients. In addition, maraviroc has not been studied in pregnant women; thus, other alternatives must be explored.[2]

Drug Interactions

Maraviroc has been evaluated for its effect on other drugs. It had no clinically relevant effect on midazolam with an increase in the AUC of 18%. Maraviroc showed no effect on lamivudine, zidovudine, or oral contraceptives.

Drug concentrations of maraviroc will be affected by inducers or inhibitors of CYP 3A4/Pgp. Dosing recommendations have been issued surrounding pharmacokinetic interactions (**Table 1**). The CYP3A/Pgp inhibitors ketoconazole, lopinavir/ritonavir, ritonavir, saquinavir and atazanavir all increased the C_{max} and AUC of maraviroc. These drugs increased maraviroc exposure that ranged from an AUC increase of 2.6 fold (ritonavir 100 mg bid) to 8.3-9.7 fold with saquinavir/ritonavir. CYP3A inducers rifampin and efavirenz decreased C_{max} and AUC of maraviroc. Both drugs reduced maraviroc exposure by 45% or more. Doubling the maraviroc dose restored exposure (AUC) to approximately 100%. The combination of tipranavir/ritonavir, a CYP3A inhibitor and Pgp inducer respectively, did not affect the steady state pharmacokinetics of maraviroc

Clinical Trials

The clinical efficacy and safety of maraviroc is derived from analyses of 24-week data from two ongoing multi-center, double-blind studies, A4001027 and A4001028 in antiretroviral-treated adult subjects infected with CCR5-tropic HIV-1.[7,8] A total of 1049 subjects participated in both studies with the majority of subjects being male (89%), Caucasian (84%) and with mean age of 46 years. Eligible patients were required to have CCR5-trophic HIV-1 infection and an HIV-1 viral load of greater than 5000 copies despite at least 6 months of prior antiretroviral therapy with at least one agent from three of the four antiretroviral drug classes; ≥ 1 NRTI, ≥ 1 NNRTI, ≥ 2 PIs, and/or enfuvirtide, or documented resistance or intolerance to at least one member of each class. All subjects received an optimized background regimen (OBT) consisting of 3 to 6 antiretroviral agents (excluding low-dose ritonavir). OBT was selected on the basis of the subject's prior treatment history

Table 1. Maraviroc dosing schedule with interacting medications[9]

CYP3A4 inhibitor or inducer	Interacting medication	Adjusted maraviroc dose
Strong inhibitors (with or without an inducer)	Protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazadone, telithromycin	150 mg twice daily
Weak inhibitor or inducer, or neutral	Tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide	300 mg twice daily
Strong inducer (without a strong inhibitor)	Efavirenz, rifampin, carbamazepine, phenobarbital, phenytoin	600 mg twice daily
Inducer	St. John's wort	Concomitant use not recommended

NRTIs = nucleoside reverse transcriptase inhibitors

Table 2. Change in HIV-1 RNA from baseline to week 24 (combined studies A4001027 and A4001028)[2]

Treatment group	Number of patients	Change from baseline to week 24 in HIV-1 RNA (log_{10} copies/ml)			Treatment difference (maraviroc minus placebo)	
		Raw median	Raw mean (se)	Adjusted mean (se)	Estimate (se)	97.5% CI
Maraviroc 300 mg daily	414	-2.27	-1.87 (0.069)	-1.88 (0.069)	-0.89 (0.118)	-1.15, -0.62
Maraviroc 300 mg bid	426	-2.42	-1.96 (0.069)	-1.96 (0.068)	-0.973 (0.118)	-1.24, -0.71
Placebo	209	0.00	-0.99 (0.097)	-0.99 (0.097)	NC	NC

Missing values have been imputed as the baseline value for subjects who discontinued blinded therapy
CI = confidence interval; NC = not calculated; se = standard error

and baseline genotypic and phenotypic viral resistance. In addition to OBT, subjects were then randomized in a 2:2:1 ratio to maraviroc 300 mg once daily, maraviroc 300 mg twice daily, or placebo. Doses were adjusted based on background therapy as described in **Table 1**.

The primary endpoint for these studies was change from baseline in log_{10} HIV-1 RNA level at Week 24. The secondary endpoints compared each of the two maraviroc dosing regimens (300 mg daily and 300 mg bid) to the placebo regimen at week 24 in eight categories. The secondary endpoints consisted of: 1) % of subjects with an HIV-1 RNA < 400 copies/mL; 2) % of subjects with an HIV-1 RNA < 50 copies/mL; 3) % of subjects who achieved at least a 0.5 log_{10} reduction in HIV-1 RNA from baseline or < 400 copies/mL; 4) % of subjects who achieved at least a 1.0 log_{10} reduction in HIV-1 RNA from baseline or <4 00 copies/mL; 5) differences in the magnitude of change in CD4 cell count from baseline; 6) differences in the magnitude of change in CD8 cell count; 7) time-averaged difference (TAD) in log_{10} HIV-1 RNA; 8) assess HIV-1 genotype and phenotype at baseline and at the time of failure. The primary endpoint results are summarized in **Table 2**.

Mean change from baseline to week 24 in HIV-1 RNA for subjects taking maraviroc daily + OBT, maraviroc bid + OBT, and placebo (OBT) were -1.87 log_{10} copies/mL, -1.96 log_{10} copies/mL, and -0.987 log_{10} copies/mL, respectively. Both dosing regimens demonstrated superiority compared to placebo. After 24 weeks the proportion of subjects who had < 400 copies/mL taking maraviroc daily + OBT, maraviroc bid + OBT, and placebo (OBT) were 69.2% for both dosing regimens and 27.8% for placebo.

The evaluation of the secondary endpoint that looked at CD4 cell count at baseline and week 24 showed a greater increase for both maraviroc dosing regimens compared to placebo. The adjusted mean increase of CD4 cells was 108.6 cells/μL and 106.3 cells/μL for maraviroc daily and bid, compared with 57.4 cells/μL for placebo. These results are summarized in **Table 3**.

Toxicity and Safety

Warnings and Precautions

Maraviroc has a black box warning for potential hepatotoxicity, which has been reported with its use. Symptoms of a systemic allergic reaction such as pruritic rash, eosinophilia or elevations in IgE may

Table 3. Change in CD4 cell count from baseline to week 24 (combined studies A4001027 and A4001028)[2]

Treatment group	Number of patients	Change from baseline to week 24 in CD4 cell count (cells/μL)			Treatment difference (maraviroc minus placebo)	
		Raw median	Raw mean (se)	Adjusted mean (se)	Estimate (se)	97.5% CI
Maraviroc 300 mg daily	407	86	109 (6.0)	108.6 (5.3)	51.2 (9.2)	33.3, 69.2
Maraviroc 300 mg bid	418	88	106 (4.9)	106.3 (5.3)	49.0 (9.1)	31.1, 66.9
Placebo	206	31	56 (6.7)	57.4 (7.5)	NC	NC

Missing values have been imputed as the baseline value for subjects who discontinued blinded therapy
CI = confidence interval; NC = not calculated; se = standard error

occur prior to the development of hepatotoxicity. Patients with signs or symptoms of hepatitis or allergic reaction following use of maraviroc should be evaluated immediately.[2] Use caution when administering maraviroc to patients with liver dysfunction or who are coinfected with viral hepatitis B or C.

Use maraviroc cautiously in patients with increased risk for cardiovascular events. In Phase 3 clinical trials, 11 patients (1.3%) who received maraviroc experienced a cardiovascular event including myocardial infarction and/or ischemia while no events were reported in the placebo group. The relative contribution of the drug to the events is not known. Although symptomatic postural hypotension occurred at similar rates between treatment and placebo groups in phase III clinical trials, earlier clinical trials showed higher rates as compared to placebo at higher than recommended doses.[2] Therefore, use caution when maraviroc is administered to patients with a history of postural hypotension or medications that are known to lower blood pressure.

Adverse Events

Safety data was based on 840 HIV-infected subjects who received at least one dose of maraviroc during two phase III trials. Data was evaluated for safety in a 24-week interim analysis. A total of 426 participants received bid dosing and greater than 75% of participants received a dose of 150 mg because of concurrent OBT.[2]

The most common treatment-related adverse events reported during the phase III studies were diarrhea (21.8%), nausea (17.6%), headache (13.7%), and fatigue (11.8%). The most common adverse events reported with maraviroc twice daily therapy with frequency higher than placebo were cough, pyrexia, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain and dizziness. In participants receiving once daily therapy, diarrhea, edema, influenza, esophageal candidiasis, sleep disorders, rhinitis, and urinary abnormalities were reported at rates higher than placebo. Treatment-emergent adverse events, regardless of causality, from A4001027 and A4001028 are summarized in **Table 4**. Serious and medically significant adverse events such as myocardial infarction, myocardial ischemia, cirrhosis of liver, cholestatic jaundice syndrome, liver failure, immune reconstitution syndrome are uncommon and rare.

Table 4. Adverse events (AE) reported in phase III studies A4001027 and A4001028[2]

	Maraviroc daily N (%)	Maraviroc bid N (%)	Placebo N (%)
Total patients with AEs (≥ 2%)	366 (88.4)	383 (89.9)	175 (83.7)
Specific adverse events (≥ 5%)			
Constipation	19 (4.6)	23 (5.4)	6 (2.9)
Diarrhea	94 (22.7)	89 (20.9)	45 (21.5)
Nausea	75 (18.1)	73 (17.1)	39 (18.7)
Vomiting	38 (9.2)	31 (7.3)	20 (9.6)
Fatigue	45 (10.9)	54 (12.7)	31 (14.8)
Injection site reaction	28 (6.8)	31 (7.3)	18 (8.6)
Pyrexia	30 (7.2)	51 (12.0)	17 (8.1)
Upper respiratory tract infection	38 (9.2)	44 (10.3)	11 (5.3)
Arthralgia	18 (4.3)	22 (5.2)	6 (2.9)
Back pain	22 (5.3)	21 (4.9)	6 (2.9)
Dizziness	39 (9.4)	34 (8.0)	14 (6.7)
Headache	61 (14.7)	54 (12.7)	32 (15.3)
Insomnia	23 (5.6)	29 (6.8)	9 (4.3)
Cough	35 (8.5)	48 (11.3)	10 (4.8)
Rash	27 (6.5)	34 (8.0)	8 (3.8)

*Does not include adverse events experienced by patients who switched to open label bid treatment

Dosage and Administration

Maraviroc is supplied as blue, biconvex, oval film-coated tablet that is available in 150 mg and 300 mg strengths. The recommended dose of maraviroc differs based on concomitant medications due to drug interactions (**Table 1**). Maraviroc can be taken with or without food.[2] Maraviroc must be given in combination with other antiretroviral medications and duration of treatment is indefinite or as long as treatment is safe and effective.

In patients with hepatic impairment, maraviroc should be used with caution. The safety and efficacy of maraviroc have not been specifically studied in patients with renal impairment; therefore, maraviroc should be used with caution in this population.[2]

Cost

Maraviroc retail cost from three community pharmacies located in Gainesville, FL is identical for 150 mg and 300 mg tablets. The average cost for 60 tablets of 150 mg or 300 mg is $1070 with a range between $1069 and $1080.

Summary

Maraviroc provides a novel drug for the treatment of HIV/AIDS. By blocking the binding of the viral envelope to CCR5 receptor, maraviroc prevents viral entry into the T-lymphocytes by a method distinct from all other HIV medications. When treating CCR5 tropic, HIV-1 patients, maraviroc with OBT shows greater efficacy than OBT therapy alone in short term studies. For those patients who have failed or have become resistant to current therapies, maraviroc provides a potential alternative. Maraviroc treatment doses are affected by concomitant medications that impact the CYP3A4 isoenzymes which will require dosing modifications. The adverse event profile of maraviroc includes common side effects such as diarrhea, nausea, headache, and fatigue. Maraviroc has a black box warning for heptatotoxicity that may be accompanied by allergic features. Serious and medically significant adverse events such as myocardial infarction, myocardial ischemia, cirrhosis of liver, cholestatic jaundice syndrome, liver failure, immune reconstitution syndrome are uncommon and rare.

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