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Aripiprazole (ABilify®): A New Atypical Antipsychotic Drug

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Introduction

Abilify® (aripiprazole) is a quinolinone derivate, and the first of a new class of atypical antipsychotics. Its FDA approved indications include: acute, relapsing, and stable chronic schizophrenia. The drug was jointly developed by Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc. Aripiprazole was approved on Nov 15, 2002, and marketed around two weeks thereafter. It has demonstrated efficacy in clinical trials in patients with acute relapse or stable chronic schizophrenia, improving symptoms at least as effectively as haloperidol and to a similar extent as risperidone. Treatment with aripiprazole shows improvements in both positive and negative symptoms of schizophrenia. This article will focus on the pharmacology/pharmacokinetics, dosing, clinical trials, and safety profile of aripiprazole.

Pharmacology/Pharmacokinetics

Aripiprazole is a partial agonist at dopamine D_2 and serotonin 5-HT_{1A} receptors, and an antagonist at 5-HT_{2A} receptors. It is best described as a dopamine-serotonin system stabilizer. Aripiprazole's activity is due to the parent drug, and to a lesser extent, to its major metabolite, dehydro-aripiprazole. Dehydro-aripiprazole has affinity for D_2 receptors similar to the parent drug. It represents about 40% of the parent drug exposure in plasma. The mean elimination half-life is 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. At steady state, the pharmacokinetics are dose-proportional. There is some orthostatic hypotension observed with aripiprazole, which may be explained by its antagonist activity at adrenergic $alpha_1$ receptors.

Aripiprazole is well absorbed with peak plasma concentration occurring within 3-5 hours of administration. Absolute oral bioavailability of the tablet formulation is 87%. Aripiprazole can be given without regard to food. At steady state, following IV administration of the drug, the volume of distribution is 404 L or 4.9 L/kg. At therapeutic concentrations aripiprazole and its major metabolite are greater than 90% bound to serum proteins, mainly albumin. Pharmacokinetics of a single dose of aripiprazole 15 mg were not significantly altered by age or hepatic impairment (Child-Pugh class A to C).[9] The maximum plasma concentration (C_{max}) and area under the curve (AUC) of aripiprazole and its active metabolite are 30 to 40% higher in women than in men. The corresponding oral clearance of the drug is lower in women. These differences are explained by women's lower bodyweight compared to men. No dosage adjustment is necessary based on gender. Studies in human volunteers suggest that the pharmacokinetics of aripiprazole are dose proportional between dosages of 5 and 30 mg. In a study in which volunteers received titrated doses of aripiprazole 10 mg/day for 2 days, 20 mg/day for 2 days, and 30 mg/day for 10 days, C_{max} on day 14 was 452 mcg/L and T_{max} was 3 hours.[9] Half-life was 60 hours. Healthy human volunteers were given 0.15 mg to 30 mg/day of aripiprazole for 14 days, resulting in a dose-dependent D_2 receptor occupancy, indicating brain penetration of aripiprazole in humans.[10] When aripiprazole 30 mg/day was co-administered with therapeutic dosages of

lithium or valproic acid for 22 days, it produced no clinically significant changes in the pharmacokinetics of aripiprazole or the metabolite at steady state in healthy volunteers.[5] This was despite a 15-20% increase in aripiprazole C_{max} and AUC during lithium administration, and 25% decreases in these parameters with concurrent administration of valproic acid.

Aripiprazole is metabolized by three main pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on information gathered from in vitro studies, CYP3A4 and CYP2D6 are enzymes responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation.

Clinical Trials

Short-Term Trials

The efficacy of aripiprazole in patients with schizophrenia has been compared with that of haloperidol or risperidone in two randomized, 4-week, placebo-controlled trials and assessed in several dose-ranging studies. Additional trials include two randomized, double-blind long-term trials comparing aripiprazole with placebo or haloperidol, a trial in which patients were switched to aripiprazole monotherapy, a meta analysis of double blind, fixed-dose placebo-controlled trials, and an examination of the neurocognitive effects of the drug versus those of olanzapine. Primary endpoints were changes in scores for the Positive and Negative Symptom Scale (PANSS) as well as the Clinical Global Impressions Severity of Illness (CGI-S) and Global Improvement (CGI-I) scales. Other endpoints included changes in the Brief Psychiatric Rating Scale (BPRS), Montgomery-Asberg Depression Rating Scale (MADRS), mean CGI score, and responder rates (CGI-I score of 1 or 2 or a = 30% decrease in PANSS total score).

Two 4-week randomized, double-blind multicentre, placebo-controlled trials compared aripiprazole with either haloperidol or risperidone therapy in hospitalized patients with acute relapse of schizophrenia or schizo-affective disorder, who had previously responded to antipsychotic therapy.[2,14] Baseline PANSS score ranged from 92-100. After a 3-5 day washout period, patients received either placebo or active treatment. Both aripiprazole (15 mg or 30 mg/day; n=102 in both groups) and haloperidol (10 mg/day; n=104) significantly reduced scores for PANSS total and positive, CGI-I, CGI-S and BPRS (last observation carried forward analysis: p=0.002 vs. placebo).[2] Aripiprazole 15 mg/day ($p<0.006$) and haloperidol ($p<0.05$), but not aripiprazole 30 mg/day, also significantly improved PANSS negative score compared with placebo. In contrast, the response rate with either dosage of aripiprazole (35 and 28% respectively, $p<0.05$), but not haloperidol (26%) was greater than with placebo (17%). Likewise, PANSS total, positive and negative scores and those for CGI-I and CGI-S were significantly decreased with aripiprazole 20 or 30 mg/day (n=101; p=0.05 vs. placebo) and risperidone 3 mg twice daily (n=99; p=0.05 vs. placebo).[14] In addition, negative parameters improved at week 1 with aripiprazole, which was earlier than with risperidone.

Long-Term Trials

In a 26-week trial of 310 patients with stable, chronic schizophrenia, aripiprazole 15 mg/day increased the time to relapse (primary endpoint) 2-fold ($p<0.001$), produced fewer relapses (34 vs. 57%, $p<0.001$), and from week 6 of therapy improved PANSS total and positive scores greater than placebo (p=0.05).[1] Likewise, in a prospective, combined analysis of a US and European trial, more patients with acute relapse of chronic schizophrenia treated with aripiprazole 30 mg/day (n=853) than haloperidol 10 mg/day (n=430) responded to and continued with treatment at weeks 8, 26, and 52 (p=0.012). Response rate (defined as a 30% decrease in PANSS total score maintained for at least 28 days) at 52 weeks was 52% versus 44% (p=0.003) for aripiprazole and haloperidol respectively. Aripiprazole therapy was also superior to haloperidol on the PANSS negative subscale at weeks 26 and 52, and on the MADRS total score (assessing depressive symptoms) at weeks 8, 26 and 52 ($p<0.05$ for all). However, there were no differences between the two groups in the primary endpoints (response defined as a 20% decrease in PANSS total score at any time, and time to failure to maintain response) or in PANSS total score.[7]

Dose-Ranging or Switch Trials

In a double-blind, placebo-controlled trial by Daniel et al.,[6] 307 patients with acute relapse of

Table 1. Percentage of patients reporting adverse events in short-term placebo-controlled trials

Body System	Adverse Event	Aripiprazole (n=926)	Placebo (n=413)
Body as a whole	Headache	32%	25%
	Asthenia	7%	5%
	Fever	2%	1%
Digestive System	Nausea	14%	10%
	Vomiting	12%	7%
	Constipation	10%	8%
Nervous System	Anxiety	25%	24%
	Insomnia	24%	19%
	Lightheadedness	11%	7%
	Somnolence	11%	8%
	Akathisia	10%	7%
	Tremor	3%	2%
Respiratory System	Rhinitis	4%	3%
	Coughing	3%	2%
Skin and Appendages	Rash	6%	5%
Special Senses	Blurred vision	3%	1%

schizophrenia received either aripiprazole 2, 10 or 30 mg/day or haloperidol 10 mg/day for 4 weeks. Aripiprazole 30 mg/day significantly decreased scores for CGI-S, BPRS total, BPRS core, PANSS total and PANSS positive and negative subscales compared with placebo (p-value not given). Efficacy was apparent at week 1 and was sustained throughout the study. On the other hand, aripiprazole 2 or 10 mg/day showed significant reductions only in BPRS total and PANSS total score.[6]

In a separate pooled report of two 4-week double-blind, placebo-controlled studies of 410 patients with acutely relapsing schizophrenia, which included the trial by Daniel et al. and another by Petrie[15], aripiprazole 30 mg/day was more efficacious than either 2 or 10 mg/day, and showed an early onset of efficacy (apparent on all variables at week 1). In the study by Petrie[15], the aripiprazole dosage was titrated from 5 to 30 mg/day over 13 days and aripiprazole (2 to 30 mg/day) showed greater clinical efficacy than placebo, improving scores for BPRS (total and core), CGI-S and PANSS total.

Three-hundred and eleven patients with stable, chronic disease were randomized to aripiprazole 30 mg/day with abrupt discontinuation of the current antipsychotic or with 2-week tapering of the current medication, or aripiprazole 10 to 30 mg/day titrated over 2 weeks with simultaneous tapering of the current medication. Efficacy was maintained or improved after switching to aripiprazole monotherapy from current antipsychotics (haloperidol, thioridazine, risperidone, or olanzapine); whereas, PANSS total score decreased regardless of previous treatment.[3]

Meta Analysis

A meta analysis was performed on data from 1545 hospitalized patients with acute relapse enrolled in four 4– to 6-week randomized, multicenter, double-blind, fixed-dose, placebo-controlled trials (this included the 4-week comparisons between haloperidol and risperidone). Aripiprazole in dosages = 15 mg/day was superior to placebo at week 1 and throughout treatment.[8]

Neurocognitive function improved more with aripiprazole than with olanzapine in outpatients with stable schizophrenia. At 8 and 26

weeks, verbal learning increased to a greater extent in the group given aripiprazole 30 mg/day (n=76) than in olanzapine 15 mg/day recipients (n=93) ($p<0.04$). Both drugs improved working memory as compared with baseline at week 8 ($p<0.05$) and tended to do so at week 26. Neither drug had any effect on problem solving.[4]

Adverse Effects

Most Common Adverse Events

In the 4-week trial that compared aripiprazole versus haloperidol and placebo, headache, anxiety, insomnia, nausea, and dizziness were the most commonly reported adverse events at doses of 15 and 30 mg/day. Akathisia and somnolence were 3 times more frequent with haloperidol than with aripiprazole, whereas nausea and dizziness were experienced twice as often with aripiprazole.[2] The only adverse event to have an apparent dose-response relationship was somnolence and was most common at a 30 mg/day dose.

Extrapyramidal Symptoms

In the 4-week trials, the incidence of extrapyramidal symptoms (EPS) was similar in patients treated with aripiprazole 15-30 mg/day, risperidone 3 mg twice daily and placebo. However, it was higher in patients treated with haloperidol compared to aripiprazole and placebo treated patients.[2,14] The overall incidence of EPS was also lower in the aripiprazole group compared to haloperidol in the 52-week maintenance trial by Kujawa et al.[7] A meta analysis of 5 randomized 4 to 6-week double-blind trials found the overall incidence of EPS to be 21% and 44% for aripiprazole and haloperidol respectively compared to 19% for placebo.[13]

Prolactin Level, QT_c Prolongation

In short-term clinical trials, clinically significant increases in plasma prolactin levels occurred in a similar proportion of patients (~3%) who received aripiprazole versus placebo.[2,14] Conversely, according to a meta-analysis of five short term trials, aripiprazole significantly reduced prolactin levels by 50% versus placebo, although levels generally remained within normal limits.[1] The incidence of QT_c prolongation was similar in both aripiprazole and placebo groups.[2,13]

Dosing

The recommended starting and target dose of aripiprazole is 10-15 mg/day administered on a once a day schedule without regard to meals. Aripiprazole doses of 10 to 30 mg/day have been evaluated and shown to be effective. However, in clinical trials, doses higher than 10 to 15 mg/day were no more effective than 10 or 15 mg/day. A dosage increase should not be made before 2 weeks of therapy, as this is the time needed to reach steady state.

Cost

Aripiprazole is about twice the price of risperidone. A one month supply at a local retail pharmacy is $357 and $506 for the 10 or 15 mg and 20 mg tablets respectively. Bristol Myers Squibb has put in place a patient assistance program to aid patients who are unable to pay for the medication.

Summary

Aripiprazole, is the first of a new class of atypical antipsychotic drugs and has demonstrated efficacy in clinical trials in patients with acute relapse or stable chronic schizophrenia. It improves symptoms at least as effectively as haloperidol and to a similar extent as risperidone. In clinical trials, aripiprazole's incidence of EPS was similar to placebo and the atypical agent risperidone, and occurred less frequently than with haloperidol.

References

1. Carson WH, et al. Aripiprazole *vs* placebo in the treatment of chronic schizophrenia. International Journal of Neuropsychopharmacology 2002, Jun; 5 Suppl. 1; S187
2. Carson WH, Kane JM, et al. Efficacy and safety of aripiprazole and haloperidol *vs* placebo in patients with schizophrenia and schizoaffective disorder. Journal of Clinical Psychiatry 2002, Sep; 63(9): 763-71.
3. Casey D, Saha AR, Ali MW, et al. Switching to aripiprazole monotherapy. International Journal of Neuropsychopharmacology 2002 Jun; 5 Suppl. 1; S187
4. Cornblatt B, Kern RS, Carson WH, et al. Neurocognitive effects of aripiprazole vs olanzapine in stable psychosis. International Journal of Neuropsychopharmacology 2002 Jun; 5 Suppl. 1:S185
5. Citrome L, Josiassen R, Bark N, et al. Pharmacokinetics and safety of aripiprazole and concomitant mood stabilizers. International Journal of Neuropsychopharmacology 2002; 5 Suppl. 1 (Jun): S187
6. Daniel DG, Saha Ar, Ingenito G, et al. Aripiprazole, a novel antipsychotic: overview of a phase II study result.

International Journal of Neuropsychopharmacology 2000 Jul; 3 Suppl. 1: S157.
7. Kujawa M, Saha A, Ingenito G, et al. Aripiprazole for long-term maintenance treatment of schizophrenia. International Journal of Neuropsychopharmacology 2002 Jun; 5 Suppl. 1: S186-7
8. Lieberman J, Carson WH, Saha A, et al. Meta-analysis of the efficacy of aripiprazole in schizophrenia. International Journal of Neuropsychopharmacology 2002 Jun; 5 Suppl. 1:S186
9. Mallikaarjun S, Ali MW, Salazar DE, et al. The effects of age and gender on the pharmacokinetics of aripiprazole. Clin Pharmacol Ther 2002 Feb; 71(2):66
10. Mallikaarjun S, Salazar DE, Bramer SL. Pharmacokinetics, tolerability, and safety of aripiprazole following single and multiple oral dose administration. European Neuropsychopharmacology 2000 Sep;10 Suppl. 3: 306-7.
11. Product Information: Abilify®(aripiprazole). Bristol-Myers Squibb Company, Princeton, NJ (PI issued November 2002).
12. Shaun Jordan, Vuk Kprivica, Ruoyan Chen, Katsura Tottori, Tetsuro Kikuchi, C. Anthony Altar. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT_{1A} receptor. European Journal of Pharmacology 441 (2002) 137-140.
13. Stock E, Marder SR, Saha AR, et al. Safety and tolerability meta-analysis of aripiprazole in schizophrenia. International Journal of Neuropsychopharmacology 2002 Jun; 5 Suppl. 1:S186.
14. Yeung P, et al. Aripiprazole and risperidone versus placebo in schizophrenia [abstract]. Eur Psychiatry. 2002;17 (suppl 1): 102-3.
15. Petrie JL, et al. Aripiprazole, a new atypical antipsychotic: phase 2 clinical trial results [poster]. Xth European College of Neuropsychopharmacology Congress. September 13-17, 1997, Vienna, Austria.

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Olmesartan (Benicar™) A New Angiotensin II Receptor Antagonist

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Introduction

Approximately 50 million Americans have high blood pressure (>140/90 mmHg).[1] According to data from the National Health and Nutrition Examination Survey, Phase III, only 27% of these individuals control their blood pressure to <140/90 mmHg. Furthermore, only 41.5% of patients being treated for hypertension achieve controlled blood pressure.[2] Left untreated, hypertension can lead to death caused by cardiovascular events, cerebrovascular accidents, and renal failure.[3] Benicar™ (olmesartan medoxomil) was approved by the FDA in April of 2002 as a new treatment option for hypertension and is marketed by Sankyo Pharmaceuticals Inc.[4]

Olmesartan medoxomil is one of the newest entries in the growing angtiotensin II receptor blocker (ARB) class. Similarly to the angiotensin converting enzyme inhibitors (ACE-I), ARBs block the effects of the renin-angiotensin-aldosterone system. However, they do so through a different mechanism. Unlike ACE-I, ARBs block the effects of angtiotensin II generated by alternate pathways as well.[3] In addition, ARB's do not block the breakdown of bradykinin, a vasodilating substance.[3] This article will address the pharmacology, clinical trials, adverse effects, costs, and prescribing considerations of olmesartan medoximil.

Pharmacology

Olmesartan selectively blocks angiotensin II from binding to the AT_1 receptor.[5] By blocking the AT_1 receptor, it reduces vascular resistance and lowers blood pressure. Blocking the AT_1 receptors does inhibit the negative feedback of angiotensin II on renin secretion This results in an increase in renin activity and circulating angiotensin II levels. However, this does not overcome the effect of olmesartan on blood pressure.[6] Because its actions are independent of the pathways for angiotensin II synthesis, it provides a more specific and complete RAS blockade compared to ACE inhibitors.[5]

Table 1. Summary of olmesartan medoxomil's hypertension clinical studies

Authors	Study Design	N	Treatment Groups	Clinical Findings
Neutal et al. 2001[7]	R, DB, PC, PG, MC	2693	OLM 2.5mg, 5mg, 10mg, 20mg, 40mg, 80mg QD vs. PBO	Mean change from baseline in DBP and SBP was significantly greater in OLM treated group than PBO treated group.
Neutal et al. 2002[9]	R, DB, PC, PG, MC	334	OLM 5mg, 20mg, 80mg QD vs. OLM 2.5mg, 10mg, 40mg BID PBO	There is no significant advantage of twice-daily dosing versus once-daily dosing.
Oparil et al. 2001[10]	R, DB, PC, PG, MC	588	OLM 20mg QD vs. LOS 50mg QD, VAL 80mg QD, IRB 150mg QD	OLM showed a significant reduction only in DBP vs. the others, reduction in SBP was non-significant.
Chrysant et al. 2002[11]	R, DB, PC, PG, MC	440	OLM 20mg QD vs. AML 5mg QD vs. PBO	OLM showed efficacy similar to AML.
Ball et al. 2001[12]	R, DB, PG, MC	351	OLM 10mg + HCTZ 25mg vs. ATE 50mg + HCTZ 25mg	Response was similar in both groups.
Ball et al. 2001[12]	R, DB,PC, PG, MC	430	Starting dose: OLM 5mg + PBO QD vs. CAP 12.5mg BID	OLM was superior to CAP.

R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel-group, MC=multicenter, OLM=olmesartan, PBO=placebo, DBP=diastolic blood pressure SBP=systolic blood pressure, LOS=losartan, VAL=valsartan, IRB=irbesartan, HCTZ= hydrochlorothiazide, AML=amlodipine, ATE=atenolol, CAP=captopril

Pharmacokinetics

Olmesartan medoxomil is administered orally. In the gastrointestinal tract, olmesartan medoxomil is converted to active olmesartan. No further metabolism occurs. The absolute bioavailability of olmesartan is ~26%. It takes 1-2 hours to reach peak concentrations. Food does not affect the bioavailability of olmesartan. It is eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan reaches steady-state levels within 3-5 days. No accumulation in plasma occurs with once-daily dosing. Olmesartan is highly bound to plasma proteins (99%). The volume of distribution is about 17 liters. About 35-50% of the unchanged drug is eliminated in the urine, while the remainder is eliminated in the feces via the bile.[6,7]

The pharmacokinetics of olmesartan are not significantly different between the elderly and those younger than 65 years. In patients with renal insufficiency, serum concentrations of olmesartan were elevated compared to subjects with normal renal function. In patients undergoing hemodialysis the pharmacokinetics of olmesartan have not been studied. In patients with hepatic impairment, increases in AUC of 60% were observed.[6]

Clinical Trials

The efficacy and safety data for olmesartan were demonstrated in seven placebo-controlled studies involving patients with essential hypertension.[7] To summarize the efficacy data, patients treated with 20 mg/day of olmesartan had mean reductions of 12 mmHg in DBP and 15 mmHg in SBP after 6-12 weeks of treatment.[7] The antihypertensive response to olmesartan was seen within 2 weeks of initiating treatment with a maximum benefit seen at 4 weeks after initiation of therapy.[7] The drug is equally effective in older patients as it was in younger patients.

Neutal et al.[9] studied the effect of once-daily versus twice-daily dosing of olmesartan. Treatment with olmesartan showed a significant reduction in DBP and SBP versus placebo. Both olmesartan dosing regimens reduced DBP and SBP significantly compared to placebo. The twice-daily dosing showed no clinical advantage over once-daily dosing.[8,9]

Olmesartan has also been studied against other leading ARB's. Oparil et al.[10] compared the recommended starting doses of olmesartan, losartan, valsartan, and irbesartan in patients with essential hypertension. This study showed that olmesartan had a significantly greater reduction in DBP over the other three ARB's. It also showed a numerically greater reduction in SBP compared to the others, however, this reduction was not found to be significant.

The antihypertensive effect of olmesartan was studied against other antihypertensive agents.

Table 2. Treatment-emergent adverse events reported in > 1% of hypertensive patients in double-blinded, placebo-controlled, monotherapy trials of olmesartan medoxomil[7]

Adverse Events	Olmesartan Medoxomil		Placebo	
	N	%	N	%
Headache	141	5.6	40	7.2
URT infection	83	3.3	27	4.9
Influenza-like symptoms	79	3.1	16	2.9
Dizziness	70	2.8	5	0.9
Bronchitis	51	2.0	10	1.8
Rhinitis	40	1.6	9	1.6
Increased CPK	40	1.6	6	1.1
Back pain	41	1.6	8	1.4
Pharyngitis	33	1.3	6	1.1
Hyperglycemia	32	1.3	15	2.7
Sinutsitis	29	1.1	11	2.0
Hypertriglyceridemia	29	1.1	6	1.1
Diarrhea	27	1.1	4	0.7
Peripheral edema	20	0.8	6	1.1
Patients experiencing ≥1 adverse event	1,071	42.2	237	42.7

N=number of patients; URT=upper respiratory tract; CPK=creatine phosphokinase

When comparing the efficacy of olmersartan to amlodipine besylate, both active treatments showed similar levels of blood pressure reduction. Ambulatory SBP/DBP was reduced by 2.5/1.6 mmHg in the placebo group, 12.9/7.4 mmHg in the amlodipine group, and 13.0/8.2 mmHg in the olmesartan group. The only difference in adverse events was a significantly higher incidence of nausea with amlodipine (2.7%) vs. olmesartan (0%) or placebo.[11]

Ball et al.[12] compared the efficacy of olmesartan plus HCTZ to atenolol plus HCTZ. Doubling of the dose was allowed at week 4 if needed. In both treatment groups, decreases of about 12 mmHg in sitting DBP and 14-55 mmHg in sitting SBP were achieved after 2 weeks of treatment. Differences between the treatments at weeks 2, 4 and 8 were not statistically significant, although at the early (weeks 2 and 4) visits, the mean decreases from those on atenolol were slightly higher than those on olmesartan.

Ball et al.[12] also studied olmesartan against captopril. Doubling of the dose was allowed at weeks 4 and 8 for up to 12 weeks if required. There were more patients titrated to higher doses in the captopril group than in the olmesartan group. By week 12, only 14% of captopril patients remained on the starting dose, compared with 42% of olmesartan patients. The mean change in SBP/DBP for the olmesartan group was -14.7/-9.9 versus -7.1/6.8 in the captopril group. Olmesartan was statistically significantly superior to captopril for reducing both systolic and diastolic blood pressure.

Dosing and Administration

Olmesartan medoxomil is available as 5, 20, and 40 mg tablets. The usual starting dose is 20 mg once daily when used as monotherapy, which may be increased to 40 mg/day if a further decrease in blood pressure is needed after 2 weeks of therapy. Doses higher than 40 mg/day do not have a greater effect in lowering blood pressure and there is no advantage to twice daily dosing. If blood pressure is not controlled by olmesartan alone, it may be administered with other antihypertensive agents. No initial dosage adjustments are needed for elderly patients, patients with mild to moderate hepatic impairment, or patients with mild to moderate renal impairment. Olmesartan may be administered without regard to food.[6]

Warnings

When pregnancy is detected, Benicar™ should be discontinued. It is classified as a pregnancy category C agent for the first trimester and D in the second and third trimesters. Drugs that directly act on the RAS can cause fetal and neonatal

Table 3. Cost comparison of Benicar™ 5, 20, 40 mg/day

Pharmacy	Price
Retail (chain)	$43.59
Independent	$48.43
Internet	$36.99
Mean Price	$43.00

morbidity and death when administered to pregnant women. It is not known whether olmesartan is excreted in human milk, but it is secreted in low concentrations in lactating rats.[6]

Therapy should be initiated at a low dose and under close medical supervision for patients with possible volume or salt depletion. These patients may develop symptomatic hypotension after the initiation of treatment.[6]

Adverse Events

In an integrated analysis of seven placebo-controlled studies, the incidence of adverse events (AE) was similar for olmesartan medoxomil and placebo. Table 2 shows the adverse events reported by >1% of patients in either treatment group. The only AE that was reported to occur at a frequency of >1% in olmesartan-treated patients compared to placebo was dizziness. No statistically significant relationship between olmesartan medoxomil and any severe AE was identified.[7,8]

Drug Interactions

There have been no clinically significant drug interactions shown with olmesartan medoxomil. Because olmesartan does not undergo metabolism by CYP450, there are no interactions reported with drugs that inhibit, induce or are metabolized by those enzymes. When olmesartan medoxomil was given with digoxin or warfarin in healthy volunteers no significant drug interactions were noted. Bioavailabity of olmesartan was not significantly altered by the co-administration of antacids.[6]

Cost

The retail cost for a 30-day supply is summarized in Table 3. There is no variation in price among the different strengths.

Summary

Olmesartan medoxomil is one of the newest ARB's to enter the market for the treatment of hypertension. It is as efficacious as other antihypertensive agents including amlodipine and atenolol, as well as other drugs in its class. Olmesartan is generally well tolerated and has not been associated with any serious complications. Dizziness was the most common adverse event noted. Because it is metabolized in the GI tract only, it has no significant drug interactions associated with its use. It should not be used in women who are pregnant or may become pregnant. Caution should be used in patients who are volume depleted.

References

1. The Sixth Report of the National Committee on detection, evaluation, and treatment of high blood pressure (JNC-VI). Arch Intern Med 1997;157:2413-2446.
2. Oparil S, et al. Hypertension control rates and hypertensive subtypes in the year 2000: An analysis comparing the clinics-based PATH and population-based NHANES III surveys (abstract). Am J Hypertens 2002;15:144A.
3. Hawkins DW, et al. Hypertension. In: Depiro JT, editor. Pharmacotherapy: A Pathophysiologic Approach. 4th ed. Stamford (CT): Appleton & Lange; 1999. p. 131-152.
4. FDA grants marketing approval for Benicar™ for treatment of hypertension. April 26, 2002. Available from: URL: http://www.benicar.com/b_in_the_news/fda.asp?ref=1110101010.
5. Smith D. Strategies to meet lower blood pressure goals with a new standard in angiotensin II receptor blockade. Am J of Hypertens. 2002;15:S108-S114.
6. Benicar™ Product Information. Sankyo Pharmaceuticals Inc., 2002.
7. Neutal JM. Clinical studies of CS-866, the newest angiotensin II receptor antagonist. Am J Cardiol 2001;87 (suppl):37C-43C.
8. Smith DH. Strategies to meet lower blood pressure goals with a new standard in angiotensin II receptor blockade. Am J Hypertens 2002;15 Supp 1:S108-S114.
9. Neutal JM, Elliott WJ, et al. Antihypertensive efficacy of olmesartan medoxomil, a new angiotensin II receptor antagonist, as assessed by ambulatory blood pressure measurements. J Clin Hypertens 2002;4: 325-330.
10. Oparil S, et al. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. J Clin Hypertens 2001;3:283-291.
11. Chrysant SG, Marbury T. The antihypertensive efficacy and safety of olmesartan medoxomil compared with amlodipine for mild-to-moderate hypertension. Am J Hypertens 2002;15: 57A.
12. Ball KJ, Williams PA, Stumpe KO. Relative Efficacy of an angiotensin II antagonist compared with other antihypertensive agents. Olmesartan medoxomil versus antihypertensives. J Hypertens 2001;19 (Suppl1):S49-S56.