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ULIPRISTAL ACETATE (ELLA®): A NEW EMERGENCY CONTRACEPTIVE

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In 2001, one-half of the 6.4 million pregnancies in the United States were unplanned.[1] Unplanned pregnancies result from unprotected intercourse, birth control failure, or sexual assault. Regardless of how the pregnancy occurs, the number of unplanned pregnancies may be reduced with an effective and accessible emergency contraceptive (EC).

The current gold standard for emergency contraception is levonorgestrel, taken as a one-time dose of 1.5 mg (Plan B One-Step®) or as two 0.75 mg doses taken 12 hours apart (Next Choice®).[2] However, levonorgestrel is only indicated within 72 hours following intercourse. Human sperm can survive for three to five days, suggesting that fertilization and implantation could occur after levonorgestrel administration resulting in EC failure.[3]

Ulipristal acetate (Ella®) is a new EC, FDA-approved on August 13, 2010 and available on December 1, 2010. It is the first selective progesterone receptor modulator (SPRM) approved by the FDA as an EC and is the only available EC indicated for up to 120 hours after unprotected intercourse. The objective of this article is to review the pharmacology and pharmacokinetics, clinical trial data, dosage and administration, adverse effects, safety, and cost of ulipristal acetate.

PHARMACOLOGY & PHARMACOKINETICS

Mechanism of Action

Ulipristal binds to the progesterone receptor, exerting both antagonistic and partial agonist properties. By occupying the progesterone receptor, ulipristal prevents progesterone from binding and subsequently affecting ovulation. The drug's primary role in preventing pregnancy is thought to be the inhibition or delay of ovulation. Ulipristal postpones follicular rupture by 5 to 9 days when administered at the time of the luteinizing hormone (LH) surge. Its other roles include inhibiting the maturation of the ovarian follicle when administered in the mid-follicular phase of the menstrual cycle and altering the endometrial thickness when administered during the early luteal phase (**Figure 1**).[4]

This mechanism of action differs from that of levonorgestrel. Ulipristal is effective even after the LH surge has begun, whereas levonorgestrel prevents pregnancy by interfering with the LH surge. Levonorgestrel, therefore, does not prevent ovulation once the LH surge has taken place.[6] Ulipristal may also present an advantage over levonorgestrel by delaying endometrial maturation and reducing endometrial thickness, resulting in prevention of the implantation of an already fertilized egg.[2]

Pharmacokinetics

Ulipristal has rapid pH-dependent absorption after oral administration, achieving peak plasma concentra-

INSIDE THIS ISSUE:

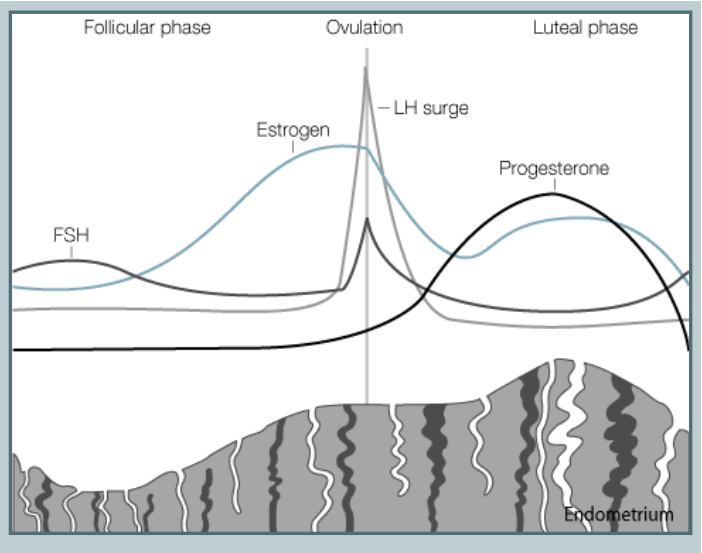

Figure 1 | Hormone surges during menstrual cycle.[5]

tions in 0.5 to 3 hours, depending on whether the tablet is taken with food.[2,4] High fat containing food delays the time to maximal absorption (t_{max}) from a median of 0.75 hours to 3 hours and lowers the maximal concentration (C_{max}) by 40-45%. These differences are not expected to cause clinically significant changes in its safety or efficacy.[4]

Ulipristal is more than 94% bound to plasma proteins, including high density lipoprotein, alpha-1-acid glycoprotein, and albumin. The drug is predominantly metabolized via CYP3A4 to an active monodemethylated metabolite and inactive di-demethylated metabolites. The half-lives of the parent compound and its active metabolite are 32 hours and 27 hours, respectively.[2,4]

Clinical Trials

Ulipristal's efficacy as an EC to prevent pregnancy has been assessed in three clinical trials (**Table 1**). Two of these studies compared ulipristal with levonorgestrel and the third was a placebo-controlled trial. Creinin et al conducted a double-blind non-inferiority trial to compare the efficacy and adverse effects of ulipristal acetate (50 mg unmicronized in one dose) and levonorgestrel (two 0.75 mg doses separated by 12 hours).[7] The 50 mg unmicronized formulation is thought to be bioequivalent to the currently marketed 30 mg micronized formulation.[8] This study took place at six study centers in the U.S. from September 1999 to June 2001 and analyzed data from 1549 subjects. The authors found that ulipristal was at least as effective as levonorgestrel in preventing pregnancies within 72 hours after intercourse.[7]

Glasier et al compared the safety and efficacy of a one-time dose of 30 mg micronized ulipristal acetate to a one-time dose of 1.5 mg levonorgestrel. This study included 35 family planning clinics in the UK, Ireland, and the U.S from April 2007 to April 2009 and analyzed data from 1696 patients for its primary outcome, pregnancy rates in women presenting within 72 hours of intercourse. For the comparison of ulipristal to levonorgestrel, the odds ratio (OR) for successful pregnancy was 0.68 (95% confidence interval [CI] 0.35 to 1.31). A secondary outcome, pregnancy rates in women presenting up to 120 hours after intercourse, was assessed in 203 women. Three pregnancies occurred in women presenting between 72 and 120 hours after intercourse and all occurred in the levonorgestrel group. For the comparison of ulipristal to levonorgestrel, the OR for successful pregnancy in both subgroups combined was 0.57 (95% CI 0.29 to 1.09).[9]

The study by Fine et al was a prospective, open-label trial intended to evaluate the safety and efficacy of ulipristal acetate (30 mg micronized). This study took place at 45 Planned Parenthood family planning clinics in the U.S. from November 2006 to May 2008 and analyzed data from 1241 subjects. The authors found that 2.1% of subjects became pregnant following ulipristal therapy. This rate is less than the expected pregnancy rate of 5.5% using the methodology of Trussell et al, which calculated the expected number of pregnancies by multiplying the number of treated women who had intercourse on each cycle day relative to the expected day of ovulation. The expected day of ovulation was defined as the usual cycle length minus 14 days.[10,11] Ulipristal was also considered to be well-tolerated, with the majority (89.1%) of adverse events being mild or moderate in intensity and resolving spontaneously.[10]

Brache et al conducted a study to determine the capacity of ulipristal, compared with placebo, to block follicular rupture when administered to a woman with a follicle of at least 18 millimeters. The study was conducted at two large reproductive health clinics in Latin America from May to December 2008 and analyzed data from 34 subjects. Although this study does not compare ulipristal to other methods of EC or directly measure its ability to prevent pregnancy, ulipristal's usefulness as an EC can be suggested by the extent to which it prevents ovulation. All women treated with placebo, but only 41.2% of women treated with ulipristal, had ruptured dominant follicles by day five.[6]

Exclusion criteria for all of these studies included pregnancy, breastfeeding, intrauterine device (IUD), hormonal contraception, and sterilization of the pa-

Table 1 | Summary of ulipristal acetate clinical trials.

Study	Design	Comparator	Time Frame	Outcomes	Results
Creinin, et al.[7]	• N= 1549 (UPA=775; LNG=774) • Double-blind non-inferiority trial Inclusion: • 18 years of age or older • Regular MC of 24-42 (±5) days • ≥ 1 normal MC after delivery, abortion, or discontinuation of HC[b] Exclusion: • N/V within prior 2 weeks • Oral glucocorticoid use within prior 1 year • Current enrollment in another investigational trial	Levonorgestrel	72 hours	Pregnancy rate[a]	• UPA= 0.9% (95% CI 0.2-1.6%) • LNG= 1.7% (95% CI 0.8-2.6%) • Treatments were statistically non-inferior (p<0.001)

Glasier, et al.[9]	• N= 1696 (primary)
	  • 844 (UPA), 852 (LNG)
	• N= 203 (secondary)
	  • 97 (UPA), 106 (LNG)
	• Randomized, single-blinded, non-inferiority trial
	Inclusion:
	• 16 years of age or older in UK and 18 years or older in US
	• Regular MC of 24-35 days
		Levonorgestrel	• Primary: 72 hours
			• Secondary: 72 to 120 hours
				Pregnancy rate[a]	Primary:
					• UPA= 1.8%
					• LNG= 2.6%
					• OR= 0.68 (95%CI 0.35-1.31)
					Secondary:
					• UPA= 0%
					• LNG= 2.8%
					• OR= 0.57 (95% CI 0.29-1.09)

Fine, et al.[10]	• N= 1241 • Prospective, open-label trial Inclusion: • 18 years of age or older • Regular MC of 24-35 (±5) days • Barrier method of contraception until study completion	None	48-120 hours	Pregnancy rate[a]	• 2.1% (95% CI 1.4-3.1%)
Brache, et al.[6]	• N= 34 • 18 to 35 years of age • Double-blind, crossover, randomized, placebo-controlled trial Inclusion: • Regular MC in past 3 months	Placebo	Immediately before ovulation	Follicular rupture inhibition[b]	• UPA, 58.8% vs. Placebo, 0% (p<0.0001)

CI = confidence interval; **E_2** = estradiol; **HC** = hormonal contraceptive; **LH** = luteinizing hormone; **LNG** = levonorgestrel; **MC** = menstrual cycle; **N/V** = nausea or vomiting; **OR** = odds ratio; **UPA** = ulipristal acetate.

[a]Pregnancy rate is calculated by dividing the number of pregnancies in each treatment group by the number of women treated in that group, then multiplying by 100.

[b]Follicular rupture is defined as an abrupt disappearance or 50% size reduction of the leading follicle within 5 days of treatment. The follicle must have been 15-25 millimeters in the trans-vaginal ultrasound performed on the day before.

tient and/or her partner. Additional exclusion criteria specific to each study are listed in **Table 1**.

Adverse Effects

Ulipristal acetate is generally well-tolerated, with the majority of adverse reactions being mild to moderate, short-lived, and self-limiting. The most common adverse reactions are similar to those with levonorgestrel (**Table 2**). Women treated with either EC experienced a significant change in menstrual cycle length after treatment. The onset of menses was an average of 2.64 days later in the ulipristal treatment group and 2.10 days earlier in the levonorgestrel treatment group.[7]

Safety

Pregnancy

Ulipristal is labeled as pregnancy category X and is contraindicated in women with existing or suspected pregnancies. Pregnancy should be ruled out

before ulipristal is prescribed. Although no adequate well-controlled studies exist in pregnant women, a study of repeated ulipristal dosing in pregnant rats and rabbits resulted in fetal loss in all pregnant rats and half of the pregnant rabbits.[12] For ulipristal-treated women determined to be non-pregnant, ectopic pregnancies should be ruled out if the patient experiences abdominal pain after taking ulipristal.

Breastfeeding

Ulipristal should be avoided in nursing mothers. Although data are lacking regarding excretion of ulipristal acetate in human milk, the drug has been detected in the milk of lactating rats.[4]

Birth control

Ulipristal should not be used regularly as a form of birth control. Safety and efficacy of repeated use within the same menstrual cycle has not been determined. Barrier methods of birth control should be used after administration of ulipristal to prevent pregnancy as a result of subsequent acts of intercourse. Although data are lacking, EC may decrease the effectiveness of other hormonal contraceptives. In addition, patients should be reminded that ulipristal only works to prevent pregnancy and does not protect against sexually-transmitted infections (STIs).[4]

Dosage & Administration

Ulipristal acetate is available by prescription only, under the brand name Ella®, as a single 30 mg tablet. Ella® is dispensed in a blister pack as a white or off-white tablet with "ella" imprinted on both sides. Patients should take this tablet as soon as possible within 120 hours following intercourse. Ella® may be taken with or without food and at any time during the menstrual cycle. If the patient vomits within 3 hours of ingestion, she may consider repeating the dose.[4]

Table 2 | Adverse events associated with ulipristal.[9]

Adverse Event	Ulipristal acetate (N= 1104)	Levonorgestrel (N= 1117)
Headache	19%	19%
Dysmenorrhea	13%	14%
Nausea	13%	11%
Fatigue	6%	4%
Dizziness	5%	5%
Abdominal pain	5%	7%
Upper abdominal pain	3%	7%
Back pain	3%	2%

Cost

An informal survey of five retail pharmacies in Florida, including chain and grocery store pharmacies, revealed the average retail price of Ella® to be $48.47 (range: $42.84 to $53.99). The average retail prices of alternative ECs are as follows: $49.61 for Plan B One-Step® (range: $44.95 to $51.99) and $33.75 for Next Choice® (range: $21.84 to $44.99).

Although the retail price for Ella® is comparable to the price for Plan B-One Step®, Ella® is available by prescription only. Therefore, patient preference will largely depend on the cost and availability of a timely clinician visit, prescription insurance, and cost associated with pregnancy testing.

Summary

Ulipristal acetate is the first SPRM approved as an EC and is the only EC indicated for use up to 120 hours after unprotected intercourse. Ulipristal is available by prescription only under the brand name, Ella®. Ella® is administered as a one-time 30 mg tablet that may be taken at any time during the menstrual cycle. The majority of adverse events are mild or moderate, self-limiting, and similar to those of levonorgestrel. Although the retail price is comparative to levonorgestrel, patient preference will largely depend on the cost and availability of a timely clinician visit, prescription insurance, and cost associated with pregnancy testing.

References

1. Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. Perspect Sex Reprod Health. 2006; 38: 90-96.
2. Gemzell-Danielsson K, Meng CX. Emergency contraception: potential role of ulipristal acetate. Int J Womens Health. 2010; 2:53-61.
3. Pregnancy FAQ: Early Pregnancy. American Pregnancy Association. 2011. http://www.americanpregnancy.org/gettingpregnant/pregnancyfaq.htm. Accessed April 1, 2011.
4. Ella (ulipristal) package insert. Morristown, NJ: Watson Pharma; 2010 Aug.
5. Getting Pregnant. Medicare Thailand. http://www.medicarethailand.com/getting_pregnant. Accessed April 1, 2011.
6. Brache V, et al. Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly

delays follicular rupture. Human Reprod. 2010; 25:2256-63.
7. Creinin MD, et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. Obstet Gynecol 2006;108:1089-97.
8. Ulmann A, Scherrer B, Mathe H, Gainer E, HRA Pharm. Meta-analysis demonstrating superiority of the selective progesterone receptor modulator ulipristal acetate versus levonorgestrel for emergency contraception. Abstract and Poster Presentation presented at the 8th Congress of the European Society of Gynecology, Rome, Italy. Sept 2009. http://static.vademecum.es/documentos/evidencia/EllaOne/Meta-analysis%20Ulmann%20ESG%202009.pdf. Accessed April 11, 2011.
9. Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. Lancet 2010;375:555-62.
10. Fine P, Mathe H, Ginde S, Cullins V, Morfesis J, Gainer E. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. Obstet Gynecol 2010; 115:257-263.
11. Trussell J, et al. New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 1998;57:363-9.
12. Harrison DJ, Mitroka JG. Defining reality: the potential role of pharmacists in assessing the impact of progesterone receptor modulators and misoprostol in reproductive health. Ann Pharmacother 2011;45:115-9.

AZILSARTAN MEDOXOMIL: AN OVERVIEW OF SAFETY AND EFFICACY

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Hypertension ranks among the primary risk factors for cerebrovascular disease, ischemic heart disease and renal failure. Hypertension is a prevalent risk factor for the development of CVD throughout the industrialized world; and with a population that lives longer, and displays a tendency toward unhealthy lifestyle, obesity, physical inactivity and fast-food diets, the stage is set for hypertension-related adverse outcomes in the millions. Controlling hypertension is associated with an estimated reduction of stroke by about 40%, and of myocardial infarction by about 15%. [1] In the US, more than 65 million adults have hypertension, and in spite of the arsenal of drugs available, control remains suboptimal.[2] As per JNC-7 guidelines, blood pressure goals are defined as 140/90 mmHg for treatment of patients with CAD, and for patients with concomitant diabetes or renal disease as below 130/80 mmHg. In recent years, use of first line agents to treat hypertension, beta-blockers and diuretics, has declined due to concerns regarding tolerability and efficacy. Meanwhile, calcium channel blocker, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocking agent use has increased substantially.[3] The recommendations include angiotensin receptor blockers (ARBs) as add-ons to diuretics in the treatment of both stage 1 and 2 hypertension in patients with and without compelling indications.[4]

Azilsartan medoxomil, an ARB prodrug of azilsartan (AZL), is a new antihypertensive medication marketed by Takeda Pharmaceuticals as Edarbi®. It was approved by the FDA on February 25th 2011 for treatment of hypertension in adults.[5]

This article will review the pharmacology and pharmacokinetics of azilsartan medoxomil, define its position within the therapeutic group of ARBs by looking at comparisons with other ARBs, discuss pertinent clinical trials, and give an overview of dosing and cost considerations.

PHARMACOLOGY

ARBs block angiotensin II (AII), the major hormone responsible for regulating blood pressure and fluid balance, from interacting with the angiotensin type 1 (AT1) receptor, by either insurmountably or surmountably binding to the AT1 receptor. In vitro studies of ARBs' receptor binding have shown variable affinity for the AT1 receptor. The active azilsartan medoxomil metabolite, AZL, displays insurmountable inhibition and slow dissociation from the AT1 receptor, which adds to its long-lasting clinical effect. Even at low serum concentrations after 24 hours, and when renin and AII levels increase, AZL maintains its antagonistic activity because of its insurmountable antagonism and slow dissociation rate from the AT1 receptor.[6]

Most ARBs possess a biphenyl methyl moiety with an acidic group, a tetrazole or carboxylic acid, a structural feature that results in effective antagonism of the AT1 receptor; however, there are structural differences in the side chains between ARBs. These structural differences may account for possible variations in pharmacological effects of these agents.[6]

AZL and candesartan share a structural similarity

in the carboxyl side chain on the 7-position of the benzimidazole ring, a feature that is associated with a long -lasting clinical effect. Radiological binding studies on human AT1 receptors indicate a high affinity and a potent inhibitory effect of AZL on the AT1 receptors. This effect of AZL was greater than olmesartan, telmisartan, valsartan, irbesartan; in order of declining potency.[6]

Pharmacokinetics

Azilsartan medoxomil is hydrolyzed in the gastric tract to the active form, AZL, during absorption. The prodrug is not detectable in plasma. Oral bioavailability of azilsartan medoxomil is 60%, regardless of food intake. Plasma peak concentrations are reached within 1.5 to 3 hours. The volume of distribution of AZL is approximately 16 L, and protein binding is constant at > 99%, mainly to serum albumin. Azilsartan medoxomil is metabolized mainly by CYP 2C9; secondary paths of metabolism include O-dealkylation to a major metabolite, and decarboxylation to a minor metabolite, both being pharmacologically inactive. Approximately 55 % of the drug is excreted via the feces, 42 % via the kidneys, and 15 % unchanged in the urine. The elimination half life is 11 hours; and with once daily dosing no drug accumulation has been observed.[5]

Clinical Trials

The major search engines to find clinical studies conducted on AZL were PubMed and clinicaltrials.gov, a service of the National Institutes of Health. Of the 20+ clinical trials listed on clinicaltrials.gov, few study results had been published at the time this information was compiled. The results from only 2 clinical trials by White et al[7] and Bakris et al[8] have been published, and these studies will be discussed here.

The only published major phase III trial assessing the efficacy of azilsartan enrolled 2,661 uncomplicated hypertensive patients with random assignment in a double-blind fashion to treatment with azilsartan medoxomil, another ARB (valsartan or olmesartan), or placebo over a period of 6 weeks. The primary efficacy outcome was 24-hour mean ambulatory systolic blood pressure. The patients were between 45 and 69 years old, with a mean age of 56; 54% of patients were men, and the baseline 24-hour mean systolic BP was 145 mmHg. Patients with clinic systolic blood pressure equal to or above 130 mmHg, and equal to or below 170 mmHg qualified for inclusion into the study. Exclusion criteria included known or suspected secondary hypertension, severe diastolic hypertension, or significant renal, hepatic, or psychiatric disorders. Patients with unstable cardiovascular disease and poorly controlled diabetes type 1 or 2, defined as HbA1c equal to or above 8%, were also excluded from the study.[7]

After a 3 to 4 week washout period of previous antihypertensive therapy the patients were randomized to one of the treatment arms or placebo, and all arms underwent a 2 week, single-blind placebo run-in period. After that, the patients on an ARB were force-titrated to the target doses, and treated for an additional 4 weeks. Ambulatory systolic blood pressure was assessed at baseline and at 6 weeks after randomization, and clinical blood pressure assessment was performed as seated blood pressure at 2, 4 and 6 weeks.[7]

This study showed that the 80 mg once daily dose of azilsartan medoxomil was superior to valsartan and olmesartan medoxomil at their clinical maximum doses in decreasing mean 24-hour ambulatory blood pressure in patients with stage 1 and stage 2 hypertension,[7] and the lower 40 mg dose was non-inferior to olmesartan in decreasing 24-hour mean systolic blood pressure.[8] **Table 1** summarizes the clinical trials reviewed in this paper.

Outcome measures

White et al[7] used 24-hour mean ambulatory systolic blood pressure as their primary efficacy endpoint, whereas effects on systolic blood pressure in clinic featured as secondary measures. The study

Table 1 | Review of azilsartan medoxomil clinical trials.

Reference	Study Design	N	Results
White et al [7]	R, DB, MC, PC	2661	AZL-M at its maximum dose has superior efficacy to both OLM-M and valsartan at their maximal, approved doses without increasing adverse events.
Bakris et al [8]	R, DB, MC, PC, PG	1260	Reduction in 24-hr mean SBP was greater with AZL-M 80mg than OLM-M 40mg. AZL-M 40mg was non-inferior to OLM-M 40mg. Side effect profiles of both ARBs were similar to placebo.

R = randomized; DB = double-blind; MC = multicenter; PC = placebo-controlled; PG = parallel group
AZL-M = azilsartan medoxomil; OLM-M = olmesartan medoxomil

Table 2 | Changes from baseline in systolic blood pressure.[7]

24-hr ambulatory SBP changes (mmHg)				
	AZL-M 40 mg (N = 237)	**AZL-M 80 mg (N = 229)**	**OLM-M 40 mg (N = 254)**	**Valsartan 320 mg (N = 234)**
Mean difference vs. placebo	-13.2 p<0.001	-14.3 p<0.001	-11.7 p<0.001	-10.0 p<0.001
AZL-M vs. OLM-M	-1.4 p=0.136	-2.5 p=0.009		
AZL-M vs. valsartan	-3.2 p=0.001	-4.3 p<0.001		
Clinical SBP changes (mmHg) at week 6				
	AZL-M 40 mg (N = 269)	**AZL-M 80 mg (N = 270)**	**OLM-M 40 mg (N = 283)**	**Valsartan 320 mg (N = 271)**
Mean difference vs. placebo	-14.6 p<0.001	-14.9 p<0.001	-11.4 p<0.001	-9.5 p<0.001
AZL-M vs. OLM-M	-3.2 p=0.018	-3.5 p=0.008		
AZL-M vs. valsartan	-5.1 p<0.001	-5.4 p<0.001		

SBP = systolic blood pressure, AZL-M = azilsartan medoxomil, OLM-M = olmesartan medoxomil

found a clinically significant difference vs placebo of the primary endpoint between azilsartan medoxomil 80 mg (-14.3 mmHg, p<0.001), olmesartan medoxomil 40 mg (-11.7 mmHg, p<0.001), and valsartan 320 mg (-10.0 mmHg, p<0.001). Mean blood pressure reduction from baseline in the placebo group was -0.3 mmHg. The mean difference in 24-hour blood pressure reduction of azilsartan medoxomil 80 mg compared to olmesartan medoxomil 40 mg was -2.5 mmHg (p=0.009), and compared to valsartan 320 mg was -4.3 mmHg (p<0.001).

The reduction of clinical systolic blood pressure from baseline at week 6 vs placebo for azilsartan medoxomil 80 mg was -14.9 mmHg (p<0.001), for olmesartan medoxomil -11.4 mmHg (p<0.001), and for valsartan -9.5 mmHg (p<0.001). Placebo showed a reduction from baseline of -1.8 mmHg. The mean difference of azilsartan medoxomil 80 mg to olmesartan 40 mg was -3.5 mmHg (p=0.008), and to valsartan 320 mg was -5.4 mmHg (p<0.001). These results are summarized in **Table 2**.

Results by Age and Race

The ARB comparative trial which evaluated ambulatory systolic blood pressure reduction from baseline as a function of gender, age and body weight found no significant difference in 24-hour means systolic blood pressure reduction between men and women and between the age groups of ≥ 65 and < 65 years. The results were also similar in patients with normal body weight compared with obese patients. Caucasians had a 14.8 mmHg, and African Americans had a 7.4 mmHg reduction from baseline systolic blood pressure with azilsartan medoxomil dosed at 40mg daily, a marginally significant difference (p = 0.06).[7]

Limitations

Possible limitations include the short duration (6 weeks) of this trial, which may not allow for assessment of long-term efficacy or long-term risks and adverse effects. The main measurement was blood pressure, a surrogate outcome. Also, in order not to dilute the 24-hour antihypertensive effects, patients with "marked white-coat hypertension" were excluded from the trial, although the definition for such patients was not reported.

Adverse Effects

Known ARB side effects include hyperkalemia, orthostatic hypotension, dizziness, fatigue, diarrhea, dyspepsia, upper respiratory tract infections, and rarely - angioedema. The most common side effects observed in this phase 3 trial of azilsartan medoxomil included headache, dizziness and urinary tract infection (**Table**

Table 3 | Adverse events in phase III trials of azilsartan.[7]

Parameter	Placebo (n = 155)	AZL-M 40 mg (n = 280)	AZL-M 80 mg (n = 284)	Valsartan 320mg (n = 277)	Olmesartan 40mg (n = 290)
Adverse Event					
Headache	9.0 %	6.4 %	4.2 %	7.6 %	7.9 %
Dizziness	2.6 %	3.6 %	3.5 %	1.8 %	3.1 %
Urinary tract infection	3.2 %	3.2 %	2.1 %	1.1 %	2.2 %
Fatigue	0.6 %	1.1 %	2.5 %	1.4 %	4.5 %
Edema, peripheral	0.6 %	1.8 %	1.4 %	3.2 %	2.8 %
Diarrhea	1.3 %	1.1 %	4.2 %	1.4 %	1.7 %
Lab abnormalities of interest					
Creatinine >1.5x baseline	0.0 %	0.7 %	1.1 %	0.4 %	0.7 %
Increased liver enzymes *	3.3 %	2.9 %	5.5 %	6.1 %	4.9 %
Potassium > 6.0 mMol/L	0.0 %	0.0 %	0.0 %	0.0 %	0.0 %

* AST, ALT, and gamma glutamyl transpeptidase >3 times upper limit normal. AZL-M indicates azilsartan medoxomil.

3). There were no deaths reported and the few patients suffering adverse effects were distributed almost evenly among the trial arms.[7]

Laboratory abnormalities of interest

White et al reported similar changes from baseline across the 4 active treatment groups for serum creatinine, potassium and liver enzymes (Table 3); however, actual baseline numbers were not reported. No incidents of severe hyperkalemia ocurred.[7]

Drug Interactions

The drug interaction profile of AZL has not been addressed in published clinical trials. From the known properties of AZL, interactions with potassium supplementation and potassium sparing diuretics are possible. Concurrent use of drugs known to increase blood pressure, like NSAIDs because of their renal and peripheral vasoactive effects, methylphenidate, herbals with stimulant activity (e.g. ephedra and yohimbe), may decrease the blood pressure lowering effect of AZL.

Dosing & Administration

Dosing recommendations are 80 mg once daily for most patients. A reduced dose recommendation of 40 mg should be administered to patients taking concomitant full doses of diuretics.[5] AZL can be administered with or without food.[5]

AZL should not be used during pregnancy or while breast feeding. No other contraindications currently exist.[9] Dose adjustment is not required for patients

Table 4 | ARB cost comparison per 30-day supply.

Drug name	Dose	Mean price (USD)	Price range (USD)
azilsartan (Edarbi®)	40 mg / 80 mg	91.58	72.77 – 101.99
olmesartan (Benicar®)	20 mg	93.50	85.88 – 98.95
	40 mg	130.59	114.84 – 140.99
valsartan (Diovan®)	160 mg	105.80	93.46 – 115.99
	320 mg	132.82	114.54 – 147.99
losartan (Cozaar®)	50 mg	91.00	85.54 – 97.00
	100 mg	127.84	110.54 – 130.00
losartan (*generic*)	50 mg	63.69	49.54 – 77.95
	100 mg	84.79	68.84 – 103.95

Information from 3 community pharmacies; telephone inquiries March/April 2011

with mild to severe renal impairment or end stage renal disease. No dose adjustment is necessary in patients with mild to moderate hepatic dysfunction. AZL has not been studied in patients with severe hepatic dysfunction.[5]

No dose adjustments are needed for the elderly; however, the package insert notes that although there is no difference in efficacy versus younger patients, the possibility of patients > 75 years old being more sensitive to azilsartan medoxomil cannot be ruled out. The drug has not been studied in pediatric populations.[5]

Cost

The mean retail price based on three community pharmacies for 30 tablets of both Edarbi® 40mg and 80mg is $ 91.58. The price range is between $ 72.77 and $ 101.99. A cost comparison with other ARBs, especially the newly turned generic losartan, is summarized in **Table 4**.

Summary

Azilsartan medoxomil (Edarbi®) is a new ARB prodrug approved by the FDA for treatment of hypertension in adults. At maximum approved dosing, azilsartan medoxomil is more efficacious and equally safe as other ARBs in reducing blood pressure in patients with uncomplicated stage 1 or 2 hypertension.

The dose of azilsartan medoxomil is 80 mg once daily in adults and 40 mg once daily for patients on concomitant full-dose diuretics. Further research is needed to evaluate how azilsartan compares to candesartan and antihypertensive drugs of different classes.

References

1. Kaplan N, Mendis S, Poulter N, Whitworth J. 2003 World Health Organization(WHO)/ International Society of Hypertension (ISH) Statement on Management of Hypertension. J Hypertension 2003;21 (11):1983-92.
2. Matchar D, McCrory C, et al. Systematic Review: Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers for Treating Essential Hypertension. Ann Intern Med 2008;148:16-29.
3. Song JC, Singh P, Fung WF. Focus on Azilsartan: A next-generation angiotensin II receptor blocker for the treatment of hypertension. Formulary [Internet]. 2010 Dec 10 [cited 2011 March 6];45:342–349. Available from: http://formularyjournal.modernmedicine.com/formulary/Modern+Medicine+Now/Focus-on-Azilsartan-A-next-generation-angiotensin-/ArticleStandard/Article/detail/700419
4. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure - Complete Report (JNC-7). Hypertension 2003;42:1206-52.
5. Takeda Pharmaceuticals America, Inc. Edarbi® (azilsartan medoxomil) package insert. Deerfield, IL;2011 February.
6. Ojima M, Igata H, Tanaka M, et al. In vitro antagonistic properties of a new Angiotensin type 1 receptor blocker, azilsartan, in receptor binding and function studies. J Pharmacol Exp Ther. 2011;336 (3):801-8.
7. White WB, Weber MA, Sica D, Bakris GL, Perez A, Cao C, Kupfer S. Effects of the Angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension 2011;57(3):413-20.
8. Bakris G, Sica D, Weber M, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. J Clin Hypertens 2011;13 (2):81-8.

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