

NEW DRUG UPDATE

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Zetia[®] (ezetimibe)

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Introduction

Zetia[®] (ezetimibe [e-ZET-eh-mibe]) is a compound that inhibits the intestinal absorption of cholesterol and related phytosterols. It was approved by the FDA on October 25, 2002 as adjunctive therapy to diet for the reduction of total cholesterol, low density lipoprotein cholesterol (LDL) cholesterol, and apolipoprotein B (Apo B) in patients with primary heterozygous familial and non-familial hypercholesterolemia. It can be given as monotherapy or in combination with an HMG-CoA reductase inhibitor. Zetia[®] is also approved for use in combination with atorvastatin or simvastatin to reduce elevated total cholesterol and LDL cholesterol in patients with Homozygous Familial Hypercholesterolemia (HoFH), and as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Therapeutic Recommendation

Zetia[®] has been studied as monotherapy, as an addition to on-going HMG-CoA reductase inhibitor (HRI) therapy, and as a therapy to be initiated concurrently with an HRI. Two studies

comparing ezetimibe to placebo showed that ezetimibe significantly improved LDL cholesterol, total cholesterol, Apo B, triglycerides, and HDL cholesterol. Another study compared ezetimibe with placebo when added on to current HRI monotherapy in patients who had not reached a target LDL cholesterol level. Total cholesterol, LDL cholesterol, Apo B, triglycerides, and HDL cholesterol were all significantly improved in the ezetimibe + HRI group compared to the placebo + HRI group. Several studies compared initiation of an HRI alone with initiation of concurrent ezetimibe and an HRI. Specific agents studied include atorvastatin, lovastatin, pravastatin, and simvastatin. The combination significantly lowered total cholesterol, LDL cholesterol, ApoB, and triglycerides compared to an HRI alone. With the exception of pravastatin, the combination significantly increased HDL cholesterol compared to an HRI alone. Ezetimibe appears to improve the lipid profile when used as monotherapy, and to be more effective in combination with an HRI than an HRI alone. No outcome studies have been performed with ezetimibe. While ezetimibe appears to improve the lipid panel, it has not been shown to decrease mortality or reduce cardiac events such as myocardial infarction.

Inside This Issue:

- Benicar[®] (olmesartan)
- Zelnorm[®] (tegaserod maleate)
- Zetia[®] (ezetimibe)

Dosing and Administration

Ezetimibe is available as a 10 mg tablet to be given once daily. It may be given with or without food. For convenience, the daily dose may be taken at the same time as an HMG-CoA reductase inhibitor if patient is receiving combination therapy. No dosage adjustment is necessary in patients with mild hepatic insufficiency or renal insufficiency. Ezetimibe should be taken ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

Cost Comparison

Medication/Dose	Cost*			
	Drug Emporium	KMart	Kroger	Rite-Aid
Zetia® (ezetimibe)	76.92	77.97	85.59	87.99

* Prices shown indicate a one-month supply based on recommended dosing regimens.

Warnings/Precautions

- Use in combination with an HRI should be in accordance with the product labeling for the particular HRI.
- In studies initiating ezetimibe in combination with an HRI, the incidence of consecutive elevations in serum transaminases was 1.3% versus 0.4% when HRIs were administered alone. In studies evaluating monotherapy, the incidence was similar between ezetimibe (0.5%) and placebo (0.3%).

When ezetimibe is used in combination with an HRI, liver function tests should be done at initiation and in accordance with the recommendations of the HRI.

- In clinical trials, there was no excess of myopathy or rhabdomyolysis when compared to placebo or to an HRI used alone. Myopathy and rhabdomyolysis are known adverse reactions of other lipid-lowering drugs including HRIs.
- Ezetimibe is not recommended in patients with moderate or severe hepatic insufficiency due to the unknown effects of increased exposure to ezetimibe.

Contraindications

Hypersensitivity to ezetimibe or any inactive component of this medication.

Active liver disease or unexplained persistent elevation in serum transaminases when used in combination with an HRI.

Pregnancy and nursing when used in combination with an HRI.

Special Populations

Geriatric: Adjustment of dose is unnecessary

Pediatric: The absorption and metabolism of ezetimibe is similar in adolescents (10 -18 years) and adults. Pharmacokinetic data is not available in children < 10 years of age, and so ezetimibe is not recommended in this population.

Gender: In a multiple dose study of ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race: No pharmacokinetic differences between African-American and Caucasian patients.

Hepatic Insufficiency: No dosage adjustment is necessary in patients with mild hepatic insufficiency. However, ezetimibe is not recommended in patients with moderate to severe hepatic insufficiency.

Renal Insufficiency: No dosage adjustment is necessary.

Drug Interactions

Ezetimibe is not a cytochrome P450 inhibitor or



...A Primary Care Physician's Guide to Newly Released Medications...

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inducer. It is unlikely that drug interactions will occur with drugs metabolized by these enzymes.

Concomitant cholestyramine administration decreases the mean AUC of total ezetimibe approximately 55%. Dosing of ezetimibe should occur either ≥ 2 hours before or ≥ 4 hours after administration of any bile acid sequestrant.

Fibrates might increase cholesterol excretion into the bile, leading to cholelithiasis. Coadministration of ezetimibe with fibrates is not recommended until safety and efficacy are established.

The total ezetimibe level may be increased in patients receiving cyclosporine. Patients receiving both medications should be carefully monitored.

Adverse Effects

Ezetimibe is generally well tolerated. Overall incidence of adverse reactions, as well as discontinuation rate, is similar to placebo. Adverse events occurring in $\geq 2\%$ of patients and at an incidence greater than placebo include fatigue, abdominal pain, diarrhea, viral infection, pharyngitis, sinusitis, arthralgia, back pain and cough. Adverse effects are generally similar between ezetimibe in combination with an HRI and an HRI alone.

Pharmacology

Mechanism of Action: Ezetimibe has a mechanism of action that is different from any other lipid-lowering compound. It acts at the brush border of the small intestine to inhibit the absorption of dietary and biliary cholesterol, and thus decreases the delivery of cholesterol to the liver. Ezetimibe does not clinically effect plasma concentrations of the fat-soluble vitamins A, D, and E.

Absorption/Distribution: Following oral administration, ezetimibe is absorbed and conjugated to phenolic glucuronide, a pharmacologically active compound. After a single 10 mg dose in fasting adults, the C_{max} is 3.4 – 5.5 ng/mL and the T_{max} is 4 – 12 hours. The C_{max} of the glucuronide conjugate is 45 – 71 ng/ml and the T_{max} is 1 – 2 hours. The absolute bioavailability is unknown because ezetimibe is insoluble and so an intravenous formulation is unavailable. Administration with food, including high fat or non-fat meals, does not clinically affect the extent of absorption. The C_{max} value may be increased with high fat meals. Ezetimibe and the glucuronide conjugate are highly bound (>

90%) to plasma proteins.

Metabolism/Excretion: Ezetimibe is primarily metabolized in the small intestine and the liver by glucuronide conjugation. Oxidative metabolism occurs in a minimal amount. Ezetimibe and its glucuronide conjugate are detected in the plasma constituting 10 – 20% and 80 – 90% of total drug, respectively. The half-life for both compounds is about 22 hours. Enterohepatic recycling also occurs. Approximately 78% and 11% of active drug is eliminated in the feces and urine, respectively. Ezetimibe is the major component eliminated in feces while the glucuronide conjugate is the major component eliminated in the urine.

Patient Information

1. Ezetimibe can be taken at concomitantly with other medications with the exception of bile acid sequestrants. Bile acid sequestrants should be taken ≥ 2 hours before or ≥ 4 hours after administration of ezetimibe.
2. Ezetimibe can be taken without regard to meals.
3. When ezetimibe is used in combination with an HMG-CoA reductase inhibitor, monitoring of LFT's should be done in accordance with recommendations for that HMG-CoA reductase inhibitors.

References

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Benicar[®] (olmesartan)

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Introduction

Benicar (olmesartan medoxomil [ol-me-SAR-tan]) is a new angiotensin II receptor antagonist that was approved in April of 2002 for the treatment of hypertension. Benicar is co-marketed by Sankyo Pharma and Forest Pharmaceuticals and is supplied as a film coated tablet. Benicar is a pro-drug that is metabolized to the active form in the gastrointestinal tract. Olmesartan is selective to the AT1 subtype of angiotensin II receptors. It belongs to the class of drugs known as ARBs, or “angiotensin receptor blockers.”

Therapeutic Recommendation

Olmesartan is one of several ARBs on the market. This class of drugs is used to treat hypertension that can be associated with angiotensin II vasoconstriction. In a study consisting of 2693 patients, olmesartan showed a decrease in systolic and diastolic blood pressures. Compared to placebo, olmesartan 20 mg decreased systolic and diastolic blood pressures by 10 mmHg and 5 mmHg, respectively. The 40 mg tablet produced a reduction of 12 mmHg and 7 mmHg below the placebo.

In a head to head comparative trial involving 1090 patients treated with olmesartan, losartan, valsartan, or irbesartan, olmesartan was found to decrease mean 24-hour diastolic blood pressure by 8.5 mmHg, and mean 24-hour systolic blood pressure by 12.5 mmHg. In comparison, losartan, valsartan, and irbesartan showed decreases in diastolic of 6.2 mmHg, 5.6 mmHg, and 7.4 mmHg, respectively. Also, decreases in mean 24-hour systolic blood pressure of losartan, valsartan, and irbesartan were 9.0 mmHg, 8.1 mmHg, and 11.3 mmHg, respectively. These findings suggest olmesartan significantly decreases DBP above losartan and valsartan, with irbesartan being the closest comparison. Olmesartan and irbesartan have longer half-lives (12-18 hours and 11-15

hours, respectively) which may explain the greater 24-hour benefit. The author of this study suggests that a 2-4 mmHg difference, sustained over time, may be associated with reductions in risk of cardiovascular events; however, the clinical significance of such small BP changes remain controversial.

Olmesartan can be used alone or in combination with other anti-hypertensives, such as diuretics, for additive blood pressure reduction. Although olmesartan is only indicated for hypertension, it is well established that agents from this drug class are useful to treat congestive heart failure and diabetic nephropathy.

Dosing and Administration

Olmesartan is available as 5, 20, and 40 mg film coated tablets. Dosage of this medication must be individualized to the patient. However, the recommended starting dose of olmesartan is 20 mg once a day. After two weeks of therapy, the patient response should be assessed. If patient remains hypertensive, the dose may be increased to 40 mg once daily. Twice daily dosing does not show any advantages over once daily dosing. Extreme caution should be exercised when giving olmesartan to patients that are hypovolemic due to diuretics or other causes formulation components should not take tegaserod.

Cost Comparison

Medication/Dose	Cost*		
	CVS	Rite Aid	WalMart
Benicar [®] (olmesartan) 20 mg QD**	53.59	51.99	43.72
Avapro [®] (irbesartan) 150mg QD	62.59	67.99	53.54
Diovan [®] (valsartan) 80 mg QD	57.99	57.99	48.72
Cozaar [®] (losartan) 50 mg QD	60.59	49.99	47.46

* Prices shown indicate a one-month supply at usual doses.

** Benicar 40 mg and 20 mg tablets are the same price.

Contraindications

Olmesartan is contraindicated in patients that have a hypersensitivity to this product. Pregnant patients should not receive olmesartan and if patients become pregnant while receiving olmesartan the medication should be discontinued immediately. It is important to note that fetal drug exposure during the first trimester alone did not appear to precipitate fetal defects. However, due to the high risk olme-

sartan should be discontinued as soon as pregnancy is determined.

Special Populations

Geriatrics: Olmesartan pharmacokinetic parameters were studied in patients greater than 65 years old. Maximum plasma levels were similar to young adult concentrations. Olmesartan showed modest accumulation after repeated dosing in the elderly patient. The AUC at steady state was 33% higher in patients greater than 65 years old after repeated doses. This corresponds to a 30 % reduction of renal clearance.

Pediatrics: Benicar has not been studied in patients less than 18 years of age.

Renal impairment: In patients with renal insufficiency serum concentrations of olmesartan were elevated compared to subjects with normal renal function. AUC was approximately tripled in patients with CrCl < 20 ml/min. Hemodialysis has not been studied with Olmesartan. No specific dosage adjustments are required.

Hepatic impairment: Blood concentrations were increased in patients with moderate hepatic impairment. However, no dosage adjustment is required.

Pregnancy: Category C in first trimester and category D in second and third trimesters. Patients should discontinue use of olmesartan when they become pregnant due to the potential for fetal injury or death.

Lactation: It is unknown whether olmesartan is excreted into human milk. Use of this drug is not recommended while breastfeeding.

Drug Interactions

No significant drug interactions were reported in studies with olmesartan medoxomil. Olmesartan is not metabolized by the cytochrome P450 system and has no identified effects on these enzymes. Also, bioavailability was not altered when co-administered with antacids. Olmesartan had no interaction with warfarin or digoxin.

Adverse Effects

Dizziness was the only adverse effect reported to occur more frequently than placebo in the initial drug approval trials. In the four drug comparison trial mentioned earlier, the most common report

with significance was headache. Increases in potassium levels have been reported with ARB's. Patients with altered levels of electrolytes should be monitored if receiving olmesartan.

Pharmacology:

Mechanism of Action: Olmesartan is a selective angiotensin II receptor blocker. Angiotensin II is a potent vasoconstrictor that increases blood pressure. Angiotensin II also stimulates the synthesis and release of aldosterone, increases cardiac stimulation, and increases renal reabsorption of sodium. Inhibiting Angiotensin II blocks these reactions and decreases blood pressure. ARBs block the receptor and do not inhibit the formation of products in the renin-angiotensin system. Unlike ACE inhibitors, ARBs do not alter bradykinin levels which may result in the absence of the chronic cough that is associated with ACE inhibitors.

Absorption/Distribution: Olmesartan is a prodrug that is metabolized in the GI tract and absorbed. The absolute bioavailability is 26%. Peak concentrations are seen in 1-2 hours following administration, and food does not affect the bioavailability. The terminal half-life of olmesartan is 13 hours with steady state reached in 3-5 days. Olmesartan is highly protein bound at 99%.

Metabolism/Excretion: After conversion of Olmesartan medoxomil to the active drug olmesartan, there is no appreciable amount of metabolism. The drug is excreted by the liver and the kidneys. Urine elimination consists of 35-50% of the absorbed dose. The remainder of drug is eliminated in the feces via the bile.

Patient Information

1. Patients that are pregnant or become pregnant should discontinue Benicar.
2. Benicar can be taken without regard to food.
3. Take medication at the same time every day.
4. Dizziness was the most reported side effect of olmesartan, however as your body adjusts to the medication, diarrhea, stomach upset, stuffy nose, or dry mouth may occur but should resolve over time. (If not contact your physician)
5. If dose is missed, take as soon as possible. If close to the next dose, skip previous dose and resume with the next scheduled dose.
6. Store at 20-25 degrees C (68-77 degrees F)
7. In the rare event of an allergic reaction to this drug, the drug should be discontinued and your

NEW DRUG UPDATE

prescriber should be contacted immediately. Allergic reaction symptoms include rash, itching, swelling, dizziness, and breathing trouble.

8. As always, inform your doctor of all medications you are taking—prescription and over the counter medications, including herbal and dietary supplement products.

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Zelnorm® (tegaserod maleate)

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Introduction

Zelnorm™ [tegaserod maleate, (te-GAS-a-rod)] is a serotonin 5-HT₄ receptor agonist that was FDA approved July 2002 for the treatment of irritable bowel syndrome (IBS) in women whose primary bowel symptom is constipation. When bound to the 5-HT₄ receptor, tegaserod stimulates gastrointestinal peristaltic reflex and intestinal secretions, as well as inhibiting visceral sensitivity through the actions of neurotransmitters.

Therapeutic Recommendation

Tegaserod is the only selective serotonin 5-HT₄ receptor agonist FDA approved in the treatment of irritable bowel syndrome. Until recently, patients suffering from IBS were limited in treatment options. In the past, patients were prescribed stool softeners, laxatives, antidiarrheal agents, and gastrointestinal propulsive medications for the symptomatic treatment of constipation, diarrhea, and abdominal cramping associated with IBS. Tegaserod may offer an advan-

tage in the treatment of IBS in women by preventing constipation and abdominal cramping by promoting gastrointestinal movement and secretions. Studies have shown that tegaserod is effective in women who have failed other types of therapy. Tegaserod is not recommended or approved for the symptomatic treatment of diarrhea associated with IBS. Currently, the use of tegaserod in male patients is not recommended due to the lack of sufficient study; however, recent studies have shown limited benefits in male patient.

Studies indicate that tegaserod demonstrates a significant improvement in constipation associated with IBS when compared to placebo. Tegaserod is not recommended for long-term use, nor should it be prescribed as such. Currently, tegaserod does offer some relief in women who have failed to respond to diet and exercise, laxatives, increased dietary fiber, and other forms of therapy.

Dosing and Administration

Tegaserod is available in 2mg (whitish to slightly yellowish, marbled, circular flat tablet engraved with “NVR” and “DL”) and 6mg (whitish to slightly yellowish, marbled, circular flat tablet engraved with “NVR” and “EH”) for oral intake. The recommended dosage of tegaserod is 6 mg taken orally twice daily one hour before meals for 4 to 6 weeks. Patients who respond to the initial 4-6 weeks of therapy can be considered for an additional 4-6 week course of 6mg twice daily, or slowly decrease the dose over the next course of therapy.

Cost Comparison

Medication/Dose	Cost*		
	CVS	Rite Aid	WalMart
Zelnorm® (Tegaserod)	129.43	136.84	125.98
Peri Colace® (Docusate/Casanthranol)	24.99	25.98	24.98
Metamucil® (Psyllium)**	11.99	11.99	9.49
Correctolr® (Bisacodyl)**	9.99	9.99	10.49
Cascara**	1.47	1.50	1.34
Metoclopramide**	25.03	24.72	24.26

* Prices shown indicate a one-month supply based on recommended dosing regimens.

** May need to use drug combinations to achieve the desired response.

Contraindications

Tegaserod is contraindicated in those patients who are known to have severe renal impairment, moderate or severe hepatic impairment and/or a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions. Patients who have a hypersensitivity to tegaserod or any of its other formulation components should not take tegaserod.

Special Populations

Reduced Renal Function: Dosage adjustments are not needed in patients with mild-to-moderate renal impairment (creatinine clearance between 20 – 90 ml/min/1.73m²). Tegaserod is contraindicated in patients with severe renal impairment and is not recommended (creatinine clearance \leq 15ml/min/1.73m²).

Reduced Hepatic Function: In patients with mild hepatic impairment, dosage adjustments are not required, although, caution is recommended in this patient population. Tegaserod is not recommended in patients with moderate-to-severe hepatic impairment since tegaserod has not been adequately studied in this patient population.

Gender: Gender has no effect on the pharmacokinetics of tegaserod; however, tegaserod is not recommended in male patients due to the lack of studies in this population; however, recent studies have shown some benefits.

Geriatrics: There appears to be a slight increase in the AUC and C_{max} in the elderly population; however, dosage adjustments are not required.

Pediatrics: Tegaserod safety and efficacy have not been established in patients less than 18 years of age.

Pregnancy: Category B agent. Should only be used if benefit outweighs risks during pregnancy.

Lactation: It is unknown whether tegaserod is excreted in human milk. It is not recommended while breastfeeding.

Drug Interactions

Tegaserod exhibited no inhibition or induction of the cytochrome P450 isoenzymes, except for minor inhibition of CYP1A2 and CYP2D6 *in vitro*. No

clinically relevant drug-drug interactions have been observed *in vivo*.

Adverse Effects

The most common adverse drug reactions with tegaserod when compared to placebo were headache (15%/12%), abdominal pain (12%/11%), diarrhea (9%/4%), nausea (8%/7%), flatulence (6%/5%), back pain (5%/4%) and dizziness (4%/3%).

Pharmacology

Mechanism of Action: Tegaserod is a 5-HT₄ receptor partial agonist that binds selectively to the 5-HT₄ receptors in the gastrointestinal tract. Tegaserod has little to no affinity for 5-HT₃ or dopamine receptors found in the gastrointestinal tract; however, it does have moderate affinity for 5-HT₁ receptors. Clinical investigations have shown that serotonin is involved in regulating motility, visceral sensitivity and intestinal secretion. The binding of tegaserod to the 5-HT₄ receptors triggers the release of the neurotransmitter calcitonin gene-related peptide from sensory neurons, stimulating the gastrointestinal peristaltic reflex and intestinal secretions, as well as inhibiting visceral sensitivity.

Absorption/Distribution: When tegaserod is administered to fasting subjects, the absolute bioavailability is approximately 10%. Peak plasma concentrations of tegaserod are reached around 1 hour after oral dosing. Tegaserod exhibits dose proportional pharmacokinetics over the 2 mg to 12 mg range given twice daily for 5 days. After a course of tegaserod therapy, 6mg twice daily for 5 days, drug accumulation was not clinically relevant in the plasma. Tegaserod is approximately 98% bound to plasma proteins. Tegaserod is very lipophilic and therefore exhibits massive distribution into tissues following intravenous dosing. The estimated volume of distribution at steady-state for tegaserod is 368 ± 223 L.

Metabolism/Excretion: Tegaserod is metabolized mainly via two pathways resulting in inactive metabolites. Tegaserod is first subjected to pre-systemic acid catalyzed hydrolysis in the stomach followed by hepatic oxidation and conjugation resulting in the main metabolite, 5-methoxyindole-3-carboxylic acid glucuronide. The second metabolite is a consequence of tegaserod being directly

hepatically glucuronidated in to three isomeric N-glucuronides. The plasma clearance of tegaserod is 77 ± 15 L/h with an estimated terminal half-life of 11 ± 5 hours following intravenous dosing. Approximately two-thirds of orally administered tegaserod is excreted unchanged in the feces, with the remaining one-third excreted in the urine.

Patient Information

1. Do not take this medication if you are pregnant, planning to become pregnant, or are breast-feeding.
2. Take tegaserod twice a day on an empty stomach about one hour before eating.
3. If a dose is missed, just skip that dose. Do not take two tablets to make up for the missed dose. Resume your normal dosing schedule as prescribed by your doctor.
4. Contact your doctor if the condition does not improve or worsens.
5. Patients with moderate to severe kidney or liver impairment should not take tegaserod.
6. Currently the use of tegaserod is not recommended in male patients.
7. Tegaserod is not recommended for long-term use, nor should it be prescribed as such.

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