



# New Drug Update

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## Lunesta® (eszopiclone)

**Authors:** Richard Carney, Pharm.D.

Norman J. Montalto, D.O.  
Professor, Family Medicine  
West Virginia University-Charleston

### Introduction

Lunesta® (eszopiclone [es-zoe-PIK-lone]) is a hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone class. Eszopiclone is a nonbenzodiazepine schedule IV controlled substance under the Controlled Substance Act. The Federal Drug Administration (FDA) granted eszopiclone approval on December 15, 2004 for the treatment of insomnia and transient insomnia. In clinical trials, eszopiclone decreased sleep latency and improved sleep maintenance (duration of sleep).

### Therapeutic Recommendations

Insomnia is a condition that causes 2.5% of the American population to take hypnotic medications on a nightly basis. Up to 23% of these insomniacs will take hypnotic medications every night for four months or longer. Benzodiazepines and non-benzodiazepine medications such as zaleplon and zolpidem are not indicated for use longer than 2-4 weeks. Eszopiclone is the only medication that has been approved for long-term use in insomnia. Results from phase III trials demonstrate eszopiclone's efficacy over placebo after six months of treatment. Patients receiving eszopiclone had a higher median total sleep time (375 minutes) compared to 330 minutes in the placebo group ( $p < 0.0001$ ). The median sleep quality scores were higher in the eszopiclone group, 6.5 out of 10, compared to 5.5 out of 10 in the placebo group ( $p < 0.0001$ ). Overall,

an improvement of 20-40% in sleep quality, next-day functioning, daytime alertness, and sense of physical well-being was seen in the eszopiclone group. The improvement in the placebo group was 5-25%. All the patients were evaluated using the DSM-IV guidelines for components of insomnia.

Eszopiclone is the S isomer of the drug zopiclone, a medication that is readily available in Europe. While eszopiclone has not been compared in head to head trials with other hypnotics, zopiclone has been compared to zolpidem in a double-blinded study of 479 chronic primary insomniacs. Sixty-one point six percent of patients reported zopiclone moderately improved their insomnia compared to 67.9% of patients in the zolpidem group. Sleep onset latency improved in 77.5% of zopiclone patients compared to 85.8% of zolpidem patients. When the study concluded, the researchers stated that zolpidem was at least as effective as zopiclone. In this study zolpidem was better tolerated and demonstrated less rebound insomnia. Eszopiclone is the only hypnotic agent that has data supporting its efficacy and safety during a six-month trial and is approved for long-term use.

### Dosing and Administration

Eszopiclone is available as film-coated tablets that contain 1mg, 2 mg, or 3 mg of the active ingredient. The initial recommended dose to induce sleep in elderly patients is 1mg taken immediately prior to bedtime. In non-elderly patients the recommended starting dose is 2 mg at bedtime. The

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dose may be titrated upward if clinically necessary. If the patient needs help with sleep maintenance, the recommended dose is 2 mg at bedtime. While renal dosage adjustment is not necessary with eszopiclone, the dose should not exceed 2 mg in patients that have severe hepatic impairment. No dosage adjustment is necessary in mild to moderate hepatic impairment. Eszopiclone should not be taken with or immediately after eating a high-fat meal because the absorption will be decreased.

### Cost Comparison

Medication/Dose	Cost*		
	CVS	Kroger	Rite Aid
Lunesta® (eszopiclone) 2 mg	118.00	123.59	98.99
Sonata® (zaleplon) 10mg	101.99	91.55	85.27
Ambien® (zolpidem) 10 mg	92.59	115.07	81.99

\*Cost information based on 30 tablets at the cost to patient.

### Warnings/Precautions

Sleep disturbances occur for a variety of reasons. Before eszopiclone is prescribed for the treatment of any sleep disorders, a careful evaluation of the patient should be undertaken. If eszopiclone is taken for seven to ten days and the insomnia fails to be alleviated, this may be a sign of a more se-

vere condition. In the case of the insomnia worsening with the use of a hypnotic, the cause may be due to unrecognized psychiatric or physical disorders.

Eszopiclone is a schedule IV narcotic. Abruptly stopping eszopiclone may produce signs of withdrawal. Eszopiclone also has addictive properties. The lowest possible effective dose should always be used. Eszopiclone should not be used with alcohol of other medications that produce additive CNS-depressant effects. Examples of such medications are psychotropic medications, anticonvulsants, and antihistamines. Dosage reductions may be necessary if eszopiclone is administered with other CNS-depressant agents.

### Contraindications

Eszopiclone is contraindicated in patients with a hypersensitivity to the drug or any component of the formulation.

### Special Populations

**Pediatric:** Eszopiclone has not been studied in patients less than 18 years of age.

**Geriatric:** The starting dose of eszopiclone, regardless of the indication, should be 1 mg in the elderly. While the dose may be titrated upward, it should not exceed 2 mg.

**Gender:** Eszopiclone can be taken in both men and women. The pharmacokinetics is similar in both genders.

**Renal Impairment:** Less than ten percent of eszopiclone is excreted in the urine as parent drug. For this reason renal dosage adjustment is not required.

**Hepatic Impairment:** Eszopiclone will undergo hepatic elimination so patients with severe hepatic failure should not receive a dose greater than 2mg. Due to the hepatic impairment, the patients will be exposed to higher levels of eszopiclone. Patients with mild to moderate hepatic impairment require no dosage adjustment.

**Pregnancy:** Eszopiclone is a pregnancy category C medication without well-controlled studies performed in pregnant women. For this reason, eszopiclone should be used only if the benefit of giving the medication outweighs the potential harm to the fetus.

**Nursing Mothers:** It is not known whether eszopiclone is excreted in breast milk. Caution should be used when eszopiclone is administered in nursing



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EDITOR-IN-CHIEF - Kristy Lucas, Pharm.D.  
CO-EDITOR - Greg Rosencrance, M.D.  
MANAGING EDITOR - Tara White

Departments of Internal Medicine  
and Clinical Pharmacy  
3110 MacCorkle Ave., SE  
Charleston, WV 25304

(304) 347-1377 • Fax: (304) 347-1350

E-mail: [klucas@hsc.wvu.edu](mailto:klucas@hsc.wvu.edu)

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mothers because many medications are excreted in human milk.

## Drug Interactions

Eszopiclone is metabolized by CYP 450 2E1 and 3A4 isoforms. Because eszopiclone is metabolized by these isoforms, caution is advised when eszopiclone is given concurrently with other medications that are metabolized by the same isoforms. In clinical studies, eszopiclone levels were increased when ketoconazole was co administered. Eszopiclone, when administered with lorazepam or paroxetine, showed no evidence of pharmacodynamic or pharmacokinetic interactions. The study drug did not affect warfarin and digoxin levels. Exposure to CYP 450 3A4 inducers such as rifampicin caused a decrease of zopiclone by 80%. It is reasonable to expect the eszopiclone to be affected in a similar fashion. Ethanol produced an increased effect of eszopiclone when the two were administered together. Eszopiclone and olanzapine produced a pharmacodynamic interaction that showed a decrease in DSST scores.

## Adverse Effects

Eszopiclone acts to depress the central nervous system in patients. For this reason, patients taking eszopiclone should avoid situations that require motor coordination or alertness after taking the medication. It is also possible that patient performance may be impaired the day after taking the medication as well. Eszopiclone has a rapid onset of action so the medication should only be taken immediately prior to bedtime.

The adverse events reported have been separated into two groups: nonelderly and elderly. The most frequently reported adverse events in nonelderly patients who took eszopiclone 2 mg or 3 mg were headache (21% and 17%), unpleasant taste (17% and 34%), and somnolence (10% and 8%). In the elderly, the most frequent reported adverse event was headache (15% and 13%).

## Pharmacology

**Mechanism of Action:** The exact mechanism of action of eszopiclone is not known. The effect as a hypnotic is thought to be a result of an interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. The chemical structure of eszopiclone is unrelated to other drugs with known hypnotic properties.

**Absorption/ Distribution:** Eszopiclone is rapidly absorbed, with a time to peak concentration ( $t_{max}$ ) of approximately 1 hour. Eszopiclone is weakly bound to plasma protein (52-59%), which suggests that drug-drug interactions caused by protein binding should not be a factor. There should also be no selective uptake by red blood cells due to a blood to plasma ratio of less than one.

## Metabolism/ Excretion

Eszopiclone is metabolized in the liver by oxidation and demethylation. There are two primary metabolites attributed to eszopiclone. One binds with a lower potency than eszopiclone to GABA receptors. The other metabolite does not bind to GABA receptors. The CYP 450 isoforms 3A4 and 2E1 are involved in the metabolism of eszopiclone *in vitro*. The terminal phase elimination half-life is approximately six hours. The racemic zopiclone is excreted in the urine primarily as metabolites. A similar result should be expected with eszopiclone.

## Patient Information

1. This medication is to help you sleep and get a full nights rest.
2. Take this medication when you are ready to go to sleep and can devote eight hours to sleep.
3. The effect of this medication may be reduced if you take it with or directly after high fat meals.
4. Take only the amount of medication that is recommended by your physician.
5. Common side effects occurring with this medication are headache, unpleasant taste, somnolence , and dizziness.
6. Do not take this medication with another sleep medication unless you are instructed to do so by your physician.
7. Do not crush or break the tablet.
8. If the medication does not start working for you after seven to ten days, contact your physician.

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## Campral® (acamprosate calcium)

**Authors:** Courtney L. Price, Pharm.D. Candidate  
School of Pharmacy  
West Virginia University

Kristy Lucas, Pharm.D.  
Clinical Associate Professor  
Schools of Pharmacy and Medicine  
West Virginia University - Charleston

### Introduction

Campral® [acamprosate calcium, (ah-CAM-prosate)] is a synthetic agent that is similar structurally to homotaurine, an amino acid found in the body, and gamma aminobutyric acid (GABA). It was approved by the Food and Drug Administration on July 9, 2004 and is indicated for alcoholic dependent patients seeking aid in becoming alcohol free. Through a mechanism that is not entirely understood, acamprosate decreases alcohol cravings to help prevent relapse, and is most effective when combined with psychotherapy and social support.

### Therapeutic Recommendation

**Acamprosate may not be effective in treating patients that are drinking at the start of treatment and in those who abuse other substances. Acamprosate does not treat withdrawal symptoms and should not be used acutely for that purpose. To prevent relapse, acamprosate is similar in efficacy to naltrexone. About 57% of patients remain abstinent at 12 weeks after initiation of treatment of either drug. In one controlled clinical trial comparing placebo to acamprosate, naltrexone, and a combination of both medications, nonrelapse rates were significantly higher than placebo in all active treatment groups. When acamprosate and naltrexone were combined, the relapse rates were significantly lower than placebo and acamprosate, but not naltrexone. Therefore, this particular trial found the combination of acamprosate and naltrexone was most effective in treating those with alcohol dependency. Seventy-five percent of patients receiving both acamprosate and naltrexone remain abstinent at 12 weeks after treatment begins. Another controlled trial evaluated the effectiveness of acamprosate with a voluntary addition of disulfiram. The group of acam-**

**prosate-treated patients that asked to receive disulfiram had the highest rates of abstinence while the acamprosate-treated patients that did not receive disulfiram achieved abstinence rates comparable to those patients who received disulfiram only. These findings suggest that acamprosate is similar in efficacy to disulfiram but the two drugs used together are even more efficacious. The suggested length of therapy is at least one year in a detoxified patient, regardless of relapse. In conclusion, acamprosate's role in therapy for alcohol-dependent patients is as an adjunct to current pharmacological and non-pharmacological therapy.**

### Dosing and Administration

Acamprosate is available as 333 mg enteric-coated tablets and the recommended dose is 666 mg orally three times a day. However, a lower dose may prove to be efficacious in some patients, and patients with a creatinine clearance between 30 and 50 mL/min should receive this dose. It has also been suggested that patients weighing ≤ 60 kg receive 666 mg in the morning, and 333 mg for the remaining two doses. Acamprosate can be given without regard to food, but patients may be more compliant if they take acamprosate with their daily meals.

### Cost Comparison

Medication/Dose	Cost*		
	CVS	Target	Rite Aid
Campral® (acamprosate calcium) 333 mg tablets 2 TID	138.99	129.49	140.00
RevVia® (naltrexone) 50mg tablets once daily	136.99	117.49	114.00
Antabuse® (disulfiram) 250 mg tablets once daily	49.69	39.99	46.00

\*Cost information based on one month supply.

### Precautions

Acamprosate does not alleviate withdrawal symptoms. Acamprosate should not be used in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) and should be reduced in patients with moderate renal impairment (creatinine clearance between 30 and 50 mL/min). Suicide attempts, successful suicides, and thoughts of suicide were infrequent adverse events in trials of acamprosate, but occurred more often than in placebo groups.

### Contraindications

Acamprosate is contraindicated in severe renal impairment, which is defined as a creatinine clearance  $\leq 30$  mL/min, and in patients with a known hypersensitivity to acamprosate or any of its components.

### Drug Interactions

Acamprosate does not induce the cytochrome CYP1A2 and 3A4 systems and does not inhibit *in vivo* metabolism of cytochrome CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Acamprosate's pharmacokinetics are unaffected by concomitant use of alcohol, disulfiram and diazepam. Acamprosate does not affect the pharmacokinetics of ethanol, desipramine, diazepam, imipramine, naltrexone and nordiazepam. Concomitant use of acamprosate and naltrexone has been shown to cause a 25% increase in the AUC and a 33% increase in  $C_{max}$  of acamprosate, but no dose adjustment is recommended. Weight loss and weight gain were frequently reported in clinical trials when acamprosate was administered concomitantly with anxiolytics, hypnotics, sedatives or nonopioid analgesics.

### Common Adverse Effects

Diarrhea was the most commonly reported adverse event experienced in clinical trials. In addition, the following adverse effects seem to be related to treatment with acamprosate: abdominal pain, nausea, vomiting, pruritus, rash, dizziness, drowsiness and headache.

### Special Populations

**Renal Impairment:** A dose reduction (333 mg three times daily) is required in moderate renal impairment (creatinine clearance between 30 and 50 mL/min). Acamprosate is contraindicated in severe renal impairment (creatinine clearance  $\leq 30$  mL/min).

**Hepatic Impairment:** Acamprosate is not metabolized in the liver and no dose adjustment is necessary.

**Geriatrics:** Acamprosate has not been evaluated in the geriatric population (patients  $\geq 65$  years). Forty-one of 4,234 patients in one controlled trial were  $\geq 65$  years but  $< 75$  years. This population was too small to make recommendations about the use of acamprosate in the geriatric population.

The dose of acamprosate should be reduced with renal impairment, which is common among geriatric patients.

**Pediatrics:** Acamprosate has not been evaluated in the pediatric population (patients  $< 18$  years).

**Gender:** There are no significant differences in acamprosate pharmacokinetics among male and female patients.

**Pregnancy and Lactation:** Acamprosate is pregnancy category C. The decision to use acamprosate in pregnancy should be weighed against known development abnormalities associated with alcohol ingestion during pregnancy. It is unknown whether acamprosate is excreted in human milk.

### Pharmacology

**Mechanism of Action:** The mechanism by which acamprosate aids in maintaining alcohol abstinence is not entirely known. It has been suggested that acamprosate acts upon glutamate and GABA to restore a balance between excitatory and inhibitory neurotransmitters that is upset by chronic exposure to alcohol. Acamprosate does not cause disulfiram-like reactions upon alcohol ingestion.

**Absorption:** The absolute bioavailability of an oral dose is approximately 11%. Steady-state concentrations are achieved within 5 days and peak plasma levels occur within 3 to 8 hours after oral dose.

**Distribution:** The volume of distribution is approximately 1 L/kg and protein binding is insignificant.

**Metabolism/Excretion:** Acamprosate is excreted by the kidneys unchanged. The terminal half-life is between 20 and 33 hours.

### Patient Information

1. Acamprosate is a psychoactive medication. Patients should use caution while driving and operating heavy machinery until they know how acamprosate affects them.
2. Patients should notify their physician if they are pregnant, plan on becoming pregnant, or breastfeeding before starting or during therapy with acamprosate.
3. Acamprosate should always be taken as directed by a physician, even if relapse occurs. Patients should notify their physician in case of a relapse.

4. Patients should receive continued counseling and support as part of an alcohol treatment program while taking acamprosate.

### References

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## VESIcare® (solifenacin succinate)

**Authors:** **Wes Ellis, Pharm.D. Candidate**  
School of Pharmacy  
West Virginia University

**Kristy Lucas, Pharm.D.**  
Clinical Associate Professor  
Schools of Pharmacy and Medicine  
West Virginia University - Charleston

### Introduction

VESIcare® [solifenacin succinate (sol-i-FEN-a-sin)], a muscarinic receptor antagonist, was approved for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in November of 2004. Solifenacin has been shown to significantly decrease the number of voids, and increase the volume of each micturition in patients with OAB.

### Therapeutic Recommendation

**Solifenacin has demonstrated efficacy over placebo in decreasing the number of micturitions in 24 hours. One study showed solifenacin 5mg and solifenacin 10mg significantly decreased the number of micturitions by 2.3 and 2.6, respectively, in 24 hours as compared to 1.2 with placebo. The average urinary frequency at baseline was 12.2 micturitions per 24 hours. In a second study solifenacin was shown to drastically increase the voided volume over placebo. Solifenacin 5 mg and 10 mg significantly increased voided volume by 32.9 mL and 39.2 mL, respectively, over placebo (7.4 mL). The number of inconti-**

**nent episodes per 24 hours was also reduced using solifenacin. Solifenacin 5 mg reduced incontinent episodes by 1.4 per 24 hours and solifenacin 10 mg reduced incontinent episodes by 1.5 per 24 hours as compared to a 0.8 reduction in 24 hours with placebo. At baseline the average number of incontinent episodes was 2.65 per 24 hours.**

**In a clinical study comparing solifenacin 5 and 10 mg to tolterodine (Detrol®) 2 mg twice daily and placebo, solifenacin 5 and 10 mg was equally effective in treating OAB with frequency, and diminished volume. The mean number of voids per 24 hours was significantly lower in tolterodine (-15%, P=0.0145) and solifenacin 5 mg (-17%, P<0.001) and 10 mg (-20%, P<0.001) as compared to placebo (-8.1%). Volume voided was significantly higher in tolterodine (24.4 mL) and solifenacin 5 mg (32.9 mL) and 10 mg (39.2, all P<0.001) compared to placebo (7.4 mL). In patients with incontinent episodes there was a statistically insignificant (P=0.1122) decrease in the number of episodes with tolterodine, but a statistically significant decrease in incontinent episodes using solifenacin 5 and 10 mg, P=0.008 and P=0.0038 respectively. Solifenacin 5 and 10 mg also significantly decreased urgency (-51.9% and -54.7%, respectively) compared to tolterodine (-37.9%) and placebo (-32.7%). Urgency is the key symptom in treating OAB with solifenacin over other antimuscarinic agents.**

### Dosing and Administration

Solifenacin is available in 5 and 10 mg tablets. The recommended daily dosing of solifenacin is 5 mg daily. If the initial dose of 5 mg is not clinically effective and there is not evidence of adverse effects, then the dose may be increased to 10 mg daily. Solifenacin should be taken with fluids and swallowed whole, and can be taken with or without food.

### Contraindications

Solifenacin is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, urgency, and hypersensitivity to solifenacin or any other component of the compound.

### Precautions

Bladder outflow obstruction: Solifenacin should

be administered cautiously to patients with bladder outflow obstruction because of increased urinary retention.

**Gastrointestinal obstructive disorders and decreased GI motility:** Solifenacin can exhibit anticholinergic effects and should be administered with caution to patients that have decreased gastric function. This could lead to the enhancement of GI obstruction that can present as severe constipation, nausea, vomiting, and/or dyspepsia.

**QT Prolongation:** QT prolongation does occur with solifenacin dosing. Solifenacin 10 mg increased the QT interval by 2 msec, and solifenacin 30 mg (three times the recommended therapeutic dose) increased the QT interval by 8 msec. Patients receiving solifenacin 10 mg should be counseled on not taking more than the recommended dose, and patients with an elevated QT interval should be closely monitored for adverse effects.

## Cost Comparison

Medication/Dose	Cost		
	CVS	Kroger	RiteAid
VESIcare® (solifenacin) 5 mg QD	132.99	122.99	116.99
VESIcare® (solifenacin) 10 mg QD	132.99	122.99	116.99
Detrol® (tolterodine) 2 mg BID	138.99	139.79	124.99
Detrol LA® 4 mg QD (tolterodine extended release)	111.99	121.39	115.99
Ditropan® (oxybutynin) 5 mg BID	88.99	82.09	105.99
Ditropan XL® 5 mg QD (oxybutynin extended release)	117.99	121.99	140.99

Price represents 30 days of therapy at cost to the patient

## Special populations

**Renal impairment:** Solifenacin should be used cautiously in patients with renal impairment (CrCl > 30 mL/min). Patients with severe renal impairment (CrCl < 30 mL/min) should not receive doses greater than 5 mg.

**Hepatic impairment:** Doses greater than 5 mg are not recommended in patients with moderate hepatic impairment. For patients with severe hepatic impairment solifenacin should not be given.

**Pediatric patients:** Safety and efficacy data has not been collected in this patient population.

**Geriatric patients:** There are no special concerns when dosing solifenacin in this age group. Dosage adjustments for renal or hepatic insufficiencies are not based on age.

**Pregnancy and lactation:** Solifenacin is pregnancy category C. There are no adequate or well-controlled studies of solifenacin in this patient population. If solifenacin should be administered to pregnant patients the potential benefits must significantly outweigh the potential risks. It is not known if solifenacin is excreted in breast milk; therefore, a decision of continuing treatment or breast-feeding must be made.

## Drug interactions

Solifenacin is a substrate of the CYP 3A4 isoenzyme; therefore, potent CYP 3A4 inhibitors will allow the solifenacin concentration to increase. Doses of 10 mg are not recommended while treating with CYP 3A4 inhibitors. Accumulation of solifenacin above the therapeutic concentration can result in QT wave prolongation. Therefore, doses of 5 mg are given with CYP 3A4 inhibitors. There are no other significant drug interactions between solifenacin and other medications that have been identified. Solifenacin can be safely used with warfarin, digoxin, and oral contraceptives.

## Adverse effects

The most common adverse effects reported were anticholinergic effects. Dry mouth was the most common adverse effect reported in 10.9% of patients receiving 5 mg and 27.6% receiving 10 mg compared to 4.2% receiving placebo. Constipation (5 mg = 5.4%, 10 mg = 13.4%, placebo = 2.9%), blurred vision (5 mg = 3.8%, 10 mg = 4.8%, placebo = 1.8%), and UTIs (5 mg = 2.8%, 10 mg = 4.8%, placebo = 2.8%) were also common adverse effects. Some of the less common adverse effects were nausea (5 mg = 1.7%, 10 mg = 3.3%, placebo = 2.0%), dyspepsia (5 mg = 1.4%, 10 mg = 3.9%, placebo = 1.0%), dizziness (5 mg = 1.9%, 10 mg = 1.8%, placebo = 1.8%), fatigue (5 mg = 1.0%, 10 mg = 2.1%, placebo = 1.1%), lower limb edema (5 mg = 0.3%, 10 mg = 1.1%, placebo = 0.7%), and upper abdominal pain (5 mg = 1.9%, 10 mg = 1.2%, placebo = 1.0%).

## Pharmacology

**Mechanism of action:** Muscarinic receptors play a major role in cholinergic mediated functions, including bladder smooth muscle contraction (muscarinic-3 receptors (M3) in particular). Solifenacin is a selective M3 antagonist that results in decreased bladder constriction, increased residual urine volume, and decreased detrusor

muscle pressure.

**Absorption/Distribution:** After oral administration of solifenacin peak plasma levels are reached within 3 to 8 hours. The absolute bioavailability is 90%, and food has no effect on solifenacin. Solifenacin is 98% protein bound to  $\alpha_1$ -acid glycoprotein. Solifenacin has a mean steady-state volume of distribution of 600L, and is highly distributed to non-CNS tissues.

**Metabolism/Excretion:** Solifenacin is extensively metabolized by the liver, and has one active metabolite and three inactive metabolites. The active metabolite is thought to have such little activity that it has no clinical effect. The primary metabolic pathway is through CYP 3A4 oxidation and hydroxylation. Approximately 70% is excreted in the urine, and roughly 23% is excreted in the feces. The elimination half-life of solifenacin is 45-68 hours.

### Patient information

1. Solifenacin maybe taken with or without food.
2. The most common side effects of this medication are dry mouth, and constipation.
3. Inform your physician or healthcare provider if you have urinary retention, gastric retention, un-

controlled narrow-angle glaucoma, urgency, or hypersensitivity to solifenacin.

4. Inform your physician or healthcare provider of any medication that is currently being used. This includes other prescription medications, any over-the-counter (OTC) medications, and herbal or nutritional supplements.
5. Excessive alcohol use should be avoided due to increased risk of liver damage.

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West Virginia University  
Robert C. Byrd Health Sciences Center  
Charleston Division

Departments of Internal Medicine  
and Clinical Pharmacy  
3110 MacCorkle Ave., SE  
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