

# NEW DRUG UPDATE

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## Crestor® (rosuvastatin)

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been determined. Unlike several other statins, rosuvastatin is not expected to exhibit drug interactions via the CYP-450 3A4 pathway. As with all statins, rosuvastatin should be monitored for increases in liver enzymes and for myopathy/rhabdomyolysis. The incidence of myopathy increases with doses above 40 mg per day, age greater than 65, renal insufficiency, and hypothyroidism. Rosuvastatin may show a potential benefit for patients who were not able to reach therapeutic goals with other statins. See table 1.

### Introduction

Crestor® (rosuvastatin calcium) is a synthetic lipid-lowering agent. Rosuvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, also referred to as a "statin". This class of drugs work by partially blocking the synthesis of cholesterol in the liver, which leads to, increased removal of cholesterol from the blood. The FDA approved Crestor® on August 12, 2003 to lower cholesterol.

### Therapeutic Recommendation

Rosuvastatin has been shown to reduce total cholesterol, LDL-C, and increase HDL-C more than atorvastatin, pravastatin, and simvastatin across all dosage ranges. Rosuvastatin decreased triglyceride levels more than simvastatin and pravastatin across all dosage ranges and increased HDL-C levels by a mean of 7.7% to 9.6% compared to 2.1% to 6.8% in the other groups. The patients' LDL-C goals were achieved by 82% to 89% with rosuvastatin 10 mg to 40 mg compared to 69% to 85% with atorvastatin 10 mg to 80 mg dosage ranges. The effect of rosuvastatin on cardiovascular morbidity and mortality has not

Table 1. Percentage LDL reduction with various statins at 6 weeks.

Dose	Atorva-	Prava-	Rosuva-	Simva-
10 mg	37	20	46	28
20 mg	43	24	52	35
40 mg	48	30	55	39
80 mg	51	NA	NA	46

\*Adapted from STELLAR trial (Ref. 2)  
NA = not assessed

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**Dosing and Administration**

Rosuvastatin is used as an adjunct agent to a cholesterol lowering diet. Rosuvastatin is available as tablets in 5 mg, 10 mg, 20 mg, and 40 mg strengths. It can be administered as a single dose, at any time of the day with or without food. The dosing of rosuvastatin depends on the patient. See table 2.

Condition	Dosing
Hypercholesterolemia (heterozygous familial and nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)	10 mg qd - (for those needing less aggressive LDL-C lowering start with 5 mg qd) - (for those with aggressive lipid targets and LDL-C > 190 mg/dL start with 20 mg qd) - (40 mg qd reserved for those who cannot reach target LDL-C on 20 mg)
Homozygous Familial	20 mg qd as adjunct to other lipid lowering treatments (max 40 mg qd)
Concomitant use of Cyclosporine	5 mg qd (limited to)
Concomitant use of Gemfibrozil	10 mg qd (limited to)
Renal Insufficiency	No adjustment for mild to moderate - CrCl < 30 ml/min/1.73 m <sup>2</sup> start with 5 mg qd (max dose 10 mg qd)

\*Prior to initiating therapy with rosuvastatin, secondary causes for hypercholesterolemia should be excluded and a lipid panel profile should be performed.

**Cost Comparison**

Medication/Dose	Cost <sup>^</sup>		
	CVS	KMart	Krogers
Crestor® 10 mg qd	92.59	84.97	92.79
Crestor® 20 mg qd	92.59	84.97	92.79
Crestor® 40 mg qd	92.59	84.97	92.79
Lipitor® 10 mg qd	84.59	69.29	85.59
Lipitor® 20 mg qd	122.99	101.19	123.19
Lipitor® 40 mg qd	122.99	104.99	123.19
Lipitor® 80 mg qd	131.99	112.97	123.19
Zocor® 10 mg qd	97.99	78.49	90.89
Zocor® 20 mg qd	148.99	129.09	153.29
Zocor® 40 mg qd	163.99	129.09	153.29
Zocor® 80 mg qd	163.99	129.09	153.29
Pravachol® 10 mg qd	106.99	98.79	95.97
Pravachol® 20 mg qd	102.99	100.29	94.19
Pravachol® 40 mg qd	140.99	119.69	141.49

<sup>^</sup>Pricing information represents a 30-day supply

**Warnings / Precautions**

Liver enzyme changes generally occur within the first 3 months of treatment, if at all. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. These abnormalities are usually transient and resolve with continued therapy. Should the ALT or AST levels remain > 3 times the upper limits of normal, then reduction of the dose or withdrawal of rosuvastatin is recommended.

Use with caution in people who consume substantial quantities of alcohol or who have a history of liver disease.

Caution in patients with predisposing factors to myopathy, such as renal impairment, hypothyroidism, and advanced age (> 65 years old).

Discontinue therapy if creatine kinase (CK) levels are markedly elevated or myopathy is diagnosed or suspected.

There is an increased risk of myopathy during treatment with rosuvastatin and other lipid lowering agents and cyclosporine. Concomitant therapy with gemfibrozil should generally be avoided and the risks should be considered with concomitant use of niacin or fibrates.

The risk of myopathy is increased when levels of rosuvastatin are increased in special circumstances (see special populations).

Rosuvastatin therapy should be withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).



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### Contraindications

- A known hypersensitivity
- Active liver disease
- Persistent elevations of serum transaminases
- Pregnant or nursing mothers

### Special Populations

**Race:** – no clinically relevant differences in pharmacokinetics among Caucasians, Hispanics, and Black or Afro-Caribbean groups. There is a 2-fold increase in the median exposure in Japanese subjects residing in Japan and in Chinese subjects residing in Singapore.

**Gender:** there were no differences in plasma concentrations between men and women.

**Geriatrics:** – there were no differences in plasma concentrations between non-elderly and elderly subjects (age  $\geq$  65 years).

**Pediatrics:** – 9 boys and 9 girls, age 10 to 17 years old with heterozygous FH were shown to have similar values as adults in both C<sub>max</sub> and AUC.

**Renal insufficiency:** – CrCl  $\geq$  30 ml/min/1.73m<sup>2</sup> had no influence on plasma concentrations with administration of 20 mg qd for 14 days. Plasma concentrations increased approximately 3-fold in patients with severe renal impairment (CrCl < 30 ml/min/1.73m<sup>2</sup>) compared with healthy subjects (CrCl > 80 ml/min/1.73 m<sup>2</sup>).

**Hemodialysis:** - Steady-state plasma concentrations of patients on chronic hemodialysis were approximately 50% greater compared with healthy subjects with normal renal function.

**Hepatic Insufficiency:** – Modest plasma increases with chronic alcoholic liver disease. Child-Pugh A disease exhibited elevations in C<sub>max</sub> of 60% and AUC of 5% compared to normal, healthy subjects. Child-Pugh B disease exhibited elevations of C<sub>max</sub> of 100% and AUC of 21%.

### Drug Interactions

- Cyclosporine – leads to clinically significant increase in plasma levels of rosuvastatin
- Warfarin – rosuvastatin leads to increased INR values
- Gemfibrozil – leads to clinically significant increases in the plasma levels of rosuvastatin

### Adverse Effects

The most frequent adverse reactions attributable to rosuvastatin were myalgia, constipation, asthenia, pain, and nausea. Rosuvastatin is generally well tolerated and ad-

verse effects are usually transient and mild.

Laboratory values that were reported elevated were creatinine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, bilirubin, and thyroid function abnormalities.

### Pharmacology

**Mechanism of Action:** Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Rosuvastatin is shown to have a high uptake and selectivity for the liver. First, it increases the number of LDL receptors on the cell surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles. Rosuvastatin reduces the total cholesterol, LDL-C, ApoB, and nonHDL-C in patients with homozygous and heterozygous familial hypercholesterolemia, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. It also reduces TG and produces increases in HDL-C. In patients with isolated hypertriglyceridemia, it reduces total-C, LDL-C, VLDL-C, ApoB, and TG.

**Absorption/Distribution:** Peak plasma levels were reached in 3 – 5 hours following oral dosing. The absolute bioavailability of rosuvastatin is ~20%. Administration with food decreased the rate of absorption by 20% but there was no effect on the extent of absorption. Plasma concentrations did not differ following evening or morning administration. Mean volume of distribution at steady-state is ~134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and is independent of plasma concentrations.

**Metabolism/Excretion:** Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose was recovered as a metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9. This metabolite has one-sixth to one-half the HMG-CoA reductase activity as rosuvastatin. Rosuvastatin and its metabolites are excreted primarily in the feces (90%). The elimination half-life is ~19 hours. After an intravenous dose, approximately 28% of the total body clearance was via the renal route, and 72% by the hepatic route.

### Laboratory tests

Liver function tests should be performed at baseline, at 12 weeks following both the initiation of therapy and any dosage elevations, and semiannually thereafter.

### Patient Information

1. Promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by

- malaise, fever or dark urine.
- Laboratory monitoring for effectiveness and safety will be necessary.
  - Rosuvastatin can be taken without regards to meals, preferably at the same time each day.

### References

- Crestor® (rosuvastatin calcium) product information: Astra-Zeneca Pharmaceuticals LP, Wilmington, DE: August 2003.
- Jones, PH, et al. Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR Trial). *Am J Cardiol* 2003;92:152-60.
- The Medical Letter. Vol. 45 (Issue 1167). October 13, 2003.

## Oxytrol® (oxybutynin chloride)

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### Introduction

Oxytrol® (oxybutynin chloride) transdermal system (OXY-TDS) offers an alternative dosage form indicated for treating overactive bladder. The FDA approved this product on February 26, 2003. Oxybutynin is the active ingredient and is dissolved in the thin layer of the patch adhesive. The patch delivers the medication at a slow but constant rate through the skin and bloodstream over a 3-4 day period.

### Therapeutic Recommendation

Anticholinergic agents are considered first line therapy for treating overactive bladder syndrome (OAB). The transdermal system is a recent addition to the current therapeutic alternatives. Studies evaluated the safety and efficacy of OXY-TDS in comparison to oral tolterodine (Detrol LA) and placebo. Both agents demonstrated superior efficacy at decreasing the number of urinary incontinence episodes per day in relation to placebo. Results showed comparable efficacy among the OXY-TDS and tolterodine treatment groups. Tolterodine use produced a greater reduction in daily urinary frequency, but the difference was not considered statistically significant. However, a lower incidence rate of adverse effects, particularly dry-mouth occurred in the OXY-TDS group. This reduction in anticholinergic effects is attributed to the avoidance of gastrointestinal and hepatic first-pass metabolism of oxybutynin to N-desethyloxybutynin. Application site reactions remain the most promi-

nent side effect associated with OXY-TDS. Generally, these reactions range from mild to moderate erythema and pruritis, and can be minimized by altering the site of application with each use. Compliance problems were not observed with either agent due to the simple regimens. The transdermal patch requires twice weekly application and tolterodine is dosed once daily. OXY-TDS has therapeutic effects comparable to long-acting tolterodine with an improved adverse effect profile. This agent may prove most beneficial with patients who have an increased sensitivity to, or cannot tolerate anticholinergic effects.

### Dosing and Administration

OXY-TDS is available as a 39 cm<sup>2</sup> patch containing 36 mg of drug. The patch should be applied twice a week (every 3-4 days) to dry, intact, skin on the abdomen, hip, or buttock area. Rotating application sites is necessary to avoid re-application to the same site within 7 days. After removal from package, the patch must be immediately applied to skin. Daily activities such as bathing, swimming, or showering do not affect the mechanism of this product. However, rubbing the patch should be avoided during this time. If the patch partially or completely falls off of the skin, it should be reapplied. If the patch is unable to adhere to the skin, then it should be discarded and replaced with a new patch.

### Cost Comparison

Medication/Dose	Cost*		
	CVS	Kroger	Rite Aid
Oxytrol® (OXY-TDS)	100.99	95.18	96.99
Ditropan® XL			
5 mg	114.99	109.59	124.99
10 mg	116.99	112.19	124.99
15 mg	131.99	123.89	136.99
Detrol® (tolterodine)			
1 mg	60.99	64.99	58.99
2 mg	61.99	66.49	60.99
Detrol® LA			
2 mg	113.99	105.29	95.99
4 mg	113.99	107.99	95.99

\* Cost is based on price for a 30-day supply at average doses.

### Contraindications/Precautions

- OXY-TDS should be avoided in patients at risk for, or those currently diagnosed with urinary retention, narrow angle glaucoma, and gastric retention.
- Patients with a hypersensitivity to oxybutynin or any component of the patch
- Patients with hepatic or renal impairment
- Alcohol may increase drowsiness.

- Use of this product increases the risk for developing a fever and heat stroke due to reduced sweating.
- Drowsiness and blurred vision may be associated with use of OXY-TDS.
- OXY-TDS has the ability to decrease gastrointestinal motility, so caution should be used in patients with ulcerative colitis, intestinal atony, and myasthenia gravis.
- Caution should also be used with patients diagnosed with gastroesophageal reflux disease and/or patients taking agents such as the bisphosphonates that may cause or exacerbate esophagitis.

### Special Populations

**Pediatrics:** OXY-TDS has not been studied in children less than 18 years of age.

**Geriatrics:** Studies show similar pharmacokinetics between elderly and the younger population. Geriatric patients may have increased sensitivity to the effects of the drug.

**Pregnancy:** OXY-TDS is a pregnancy category B product. There has been no evidence of impaired fertility or fetal harm due to oxybutynin chloride in rats, hamsters, or rabbits at doses exceeding the recommended human dose. However, there have not been any human studies. Avoid use in pregnancy unless the clinical benefit exceeds the possible risk.

**Lactation:** The use of OXY-TDS in nursing mothers has not been evaluated. Therefore, it is unknown if this product is excreted in human milk and should be used with caution.

### Drug Interactions

Co-administration with other anticholinergic agents may potentially increase the frequency and/or severity of adverse effects including dry mouth, constipation, somnolence, and decreased sweating. Studies have not been conducted to evaluate patients concomitantly receiving cytochrome P450 inhibitors such as antimycotic agents or macrolide antibiotics.

### Adverse Effects

The most common adverse effects such as pruritis, erythema, and rash, were primarily associated with the application site. During clinical trials, pruritis occurred in approximately 15% of the patient population. Although a common effect, dry mouth was reported at a similar incidence compared to placebo (9.6 vs 8.3% in one study, and 4.1 vs 1.7% in another). Other, less common effects included diarrhea, headache, constipation, and blurred vision.

### Pharmacology

**Mechanism of Action:** OXY-TDS acts competitively to inhibit acetylcholine, resulting in smooth muscle bladder relaxation. Studies have also proven that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction. Oxybutynin thus decreases urgency and frequency of both incontinence episodes and voluntary urination.

**Absorption/Distribution:** An average daily dose of 3.9 mg of oxybutynin is absorbed from the 39 cm<sup>2</sup> system. Bioequivalent absorption has been achieved when the patch is applied to the abdomen, buttocks, or hip. Generally, two applications are required to reach steady state. Average steady state concentrations were 3.1 ng/ml for oxybutynin and 3.8 ng/ml for N-desethyloxybutynin.

**Metabolism/Excretion:** OXY-TDS is metabolized in the liver by cytochrome P450 isoenzymes and converted into two major metabolites. The metabolites include N-desethyloxybutynin, which is pharmacologically active, and phenylcyclohexylglycolic acid, the inactive compound. This product bypasses first-pass metabolism resulting in a decreased amount of the active metabolite. Studies conclude this reduction of metabolite formation creates the potential for reduced anticholinergic side effects and allows for a convenient twice-weekly dosing regimen. Oxybutynin is excreted unchanged in the urine.

### Patient Information

1. A new patch should be applied 2 times a week (every 3 to 4 days) to a clear, dry, and fold-free area of the skin including the abdomen, hips, and buttocks. It is important to change the patch on the same 2 days each week. Refer to the provided calendar checklist as a reminder.
2. Do not apply the patch to areas that have been treated with oils, lotions or powders that could prevent the patch from sticking to the skin.
3. Wear only one patch at a time and do not remove it until it is time for a new one. Remember to rotate application sites (avoid same site for at least one week) to decrease irritation. Patch should be worn under clothing.
4. Refer to your doctor and/or package instructions for proper application and removal techniques. After removal, the site may be washed gently with warm water and mild soap to remove any adhesive that remains on the skin.
5. Properly discard used patch in order to avoid reuse or accidental use by another person.
6. Most common side effects include application site reactions, dry mouth, constipation, diarrhea, and abnormal vision.
7. Alcohol use may increase drowsiness associated

- with product use.
8. Be aware of the potential risk for developing a fever and heat stroke due to reduced sweating associated with use of this product when used in warm or hot environments.
  9. Exercise and drive cautiously due to the potential for developing blurred vision and/or drowsiness.

### References

1. Oxytrol® Oxybutynin Transdermal System. Product Information. Watson Pharma Inc. Corona, CA. February 2003.
2. Dmochowski RR, Sand PK, et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology* 2003;62:237-242.
3. Dmochowski RR, Zinner NR, et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol.* 2002;168:580-6.
4. Sanders SW, Stanworth S, et al. Pharmacokinetics and metabolism of transdermal oxybutynin: in vitro and in vivo performance of a novel delivery system. *Pharm Res* 2003;20:103-09.
5. The Medical Letter. Vol. 45 (Issue 1156) May 12, 2003.

## Subutex® (buprenorphine) and Suboxone® (buprenorphine / naloxone combination)

Letter to Editor:

The recent review of buprenorphine (Subutex®) and buprenorphine /naloxone (Suboxone®) was timely and informative. However, critical information about the strict requirements for prescribing these medications was not included in the article.

While office based access for the treatment of opiate dependence is possible utilizing these medications, there are important rules governing their use. Only physicians who are certified in addiction medicine (from the American Society of Addiction Medicine) or hold subspecialty certification in Addiction Psychiatry from the American Board of Medicine Specialties may prescribe these medications. Alternatively, a physician may take an eight (8) hour course on the use of these medications to obtain authorization. Osteopathic physicians may qualify by obtaining certification in Addiction Medicine from the American Osteopathic Association.

Physicians who are qualified by any of the above pathways must then register with the Substance Abuse and Mental Health Services (SAMHSA) within the Department of Health and Human Services, prior to prescribing either of these medications. They must also limit the number of such patients to thirty (30) or less in their individual or group practices. Additional information about the guidelines is available at a useful website: [www.suboxone.com](http://www.suboxone.com).

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