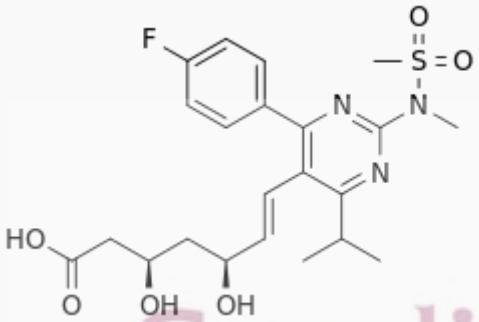
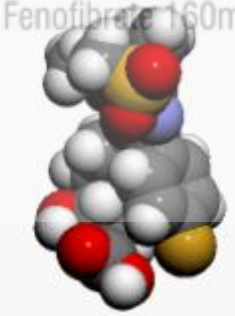
# Rosuvastatin

**Rosuvastatin**





**Systematic (IUPAC) name**

5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid

**Clinical data**

| | |
|---|---|
| **Trade names** | Crestor |
| **AHFS/Drugs.com** | monograph |
| **MedlinePlus** | a603033 |
| **Pregnancy category** | AU: D<br>US: X (Contraindicated) |

| | |
|---|---|
| **Legal status** | AU: Prescription Only (S4)<br>UK: Prescription-only (POM)<br>US: ℞-only |
| **Routes of administration** | oral |
| **Pharmacokinetic data** | |
| **Bioavailability** | 20%[1] |
| **Protein binding** | 88%[1] |
| **Metabolism** | Liver (CYP2C9(major) andCYP2C19-mediated; only minimally (~10%) metabolised)[1] |
| **Biological half-life** | 19 hours[1] |
| **Excretion** | Faeces (90%)[1] |
| **Identifiers** | |
| **CAS Registry Number** | 287714-41-4 ✓ |
| **ATC code** | C10AA07 |
| **PubChem** | CID: 446157 |
| **IUPHAR/BPS** | 2954 |
| **DrugBank** | DB01098 ✓ |
| **UNII** | 413KH5ZJ73 ✓ |
| **KEGG** | D01915 ✗ |
| **ChEBI** | CHEBI:38545 ✗ |
| **ChEMBL** | CHEMBL1496 ✗ |
| **PDB ligand ID** | FBI (PDBe, RCSB PDB) |
| **Chemical data** | |
| **Formula** | $C_{22}H_{28}FN_3O_6S$ |
| **Molecular mass** | 481.539 |
| **SMILES**[show] | |
| **InChI**[show] | |
| ✗ **(what is this?)** **(verify)** | |

Rosuvastatin (marketed by AstraZenecaas Crestor) 10 mg tablets

**Rosuvastatin**, marketed as **Crestor**, is a member of the drug class of statins, used in combination with exercise, diet, and weight-loss to treat high cholesterol and related conditions, and to prevent cardiovascular disease. It was developed by Shionogi. Crestor is the fourth-highest selling drug in the United States, accounting for approx. $5.2 billion in sales in 2013.[2]



**Contents**

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## Medical uses[edit]

The primary use of rosuvastatin is for the treatment of dyslipidemia.[3] It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels.[3]

## Side effects and contraindications[edit]

Side effects are uncommon. The following side effects should be reported to the prescribing doctor if they persist or get worse:[4]

- constipation
- heartburn
- dizziness
- insomnia

- depression
- joint pain
- cough
- memory loss or forgetfulness
- confusion

The following rare side effects are more serious. Like all statins, rosuvastatin can possibly cause myopathy, rhabdomyolysis. Stop taking rosuvastatin and contact the prescribing doctor if any of these occur:[4][5]

- muscle pain, tenderness, or weakness
- lack of energy
- fever
- chest pain
- jaundice: yellowing of the skin or eyes
- dark colored, or foamy urine
- pain in the upper right part of the abdomen
- nausea
- extreme tiredness
- weakness
- unusual bleeding or bruising
- loss of appetite
- flu-like symptoms
- sore throat, chills, or other signs of infection

If any signs of an allergic reaction develop, contact an emergency medical service immediately:[5]

- rash
- hives
- itching
- difficulty breathing or swallowing
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- numbness or tingling in fingers or toes

Rosuvastatin has multiple contraindications, conditions that warrant withholding treatment with rosuvastatin, including hypersensitivity to rosuvastatin or any component of the formulation, active liver disease, elevation of serum transaminases, pregnancy, or breast-feeding.[6] Rosuvastatin must not be taken while pregnant as it can cause serious harm to the unborn baby.[5] In the case of breastfeeding, it is unknown whether rosuvastatin is passed through breastmilk, but due to the potential of disrupting the infant's lipid metabolism, patients should not breast feed while on rosuvastatin.[5][7]

## Drug interactions[edit]

The following drugs can have negative interactions with rosuvastatin and should be discussed with the prescribing doctor:[4]

- Anticoagulants ('blood thinners') can affect the removal of rosuvastatin, examples include: warfarin (Coumadin); cimetidine (Tagamet); cyclosporine (Neoral, Sandimmune); ketoconazole (Nizoral)
- Additional medications for high cholesterol such as clofibrate (Atromid-S), fenofibrate (Tricor), gemfibrozil (Lopid), and niacin (Niaspan, Niacor);
- Specific HIV protease inhibitors including atazanavir (Reyataz), taken with ritonavir (Norvir) and lopinavir and ritonavir (Kaletra); and spironolactone (Aldactone).

- Alcohol intake should be reduced while on rosuvastatin in order to decrease risk of developing liver damage.[5]
- Aluminum and magnesium hydroxide antacids such as Mylanta and Maalox, should not be taken within two hours of taking rosuvastatin[5]
- Coadministration of Rosuvastatin with Eluxadoline may increase the risk of Rhabdomyolysis and myopathy caused by the former. [8]

## Structure[edit]

Rosuvastatin has structural similarities with most other synthetic statins, e.g., atorvastatin, cerivastatin and pitavastatin, but unlike other statins rosuvastatin contains sulfur.

Crestor is actually rosuvastatin calcium,[9] in which calcium replaces the hydrogen in the carboxylic acid group on the right of the two structure diagrams.

## Mechanism of action[edit]

*Further information: Statin*

Rosuvastatin is a competitive inhibitor of the enzyme HMG-CoA reductase, having a mechanism of action similar to that of other statins.[10] Its approximate elimination half life is 19 h and its time to peak plasma concentration is reached in 3–5 h following oral administration.[11]

Putative beneficial effects of rosuvastatin therapy on chronic heart failure may be negated by increases in collagen turnover markers as well as a reduction in plasma coenzyme Q10 levels in patients with chronic heart failure.[12]

## Pharmacokinetics[edit]

Absolute bioavailability of rosuvastatin is about 20% and $C_{max}$ is reached in 3 to 5 h; administration with food did not affect the AUC. It is 88% protein bound, mainly to albumin.[13]

Rosuvastatin is metabolized mainly by CYP2C9 and not extensively metabolized; approximately 10% is recovered as metabolite. It is excreted in feces (90%) primarily and theelimination half-life is approximately 19 h.[13]

## Indications and regulation[edit]

Rosuvastatin is approved for the treatment of high LDL cholesterol (dyslipidemia), total cholesterol (hypercholesterolemia), and/or triglycerides (hypertriglyceridemia).[14] In February 2010, rosuvastatin was approved by the FDA for the primary prevention of cardiovascular events.[15]

As of 2004, rosuvastatin had been approved in 154 countries and launched in 56. Approval in the United States by the FDA came on August 12, 2003.[16]

The results of the JUPITER trial (2008) suggested rosuvastatin may decrease the relative risk of heart attack and stroke in patients without hyperlipidemia, but with elevated levels of highly sensitive C-reactive protein. This could strongly impact medical practice by placing many patients on statin prophylaxis who otherwise would have been untreated.[17][18] As a result of this clinical trial, the FDA approved rosuvastatin for the primary prevention of cardiovascular events.[15]

The AURORA trial randomized 2776 patients undergoing hemodialysis due to kidney damage to receive either rosuvastatin or placebo. The randomized, double-blind study (2005 to 2009) found no difference in the two groups in the primary end-point, a combination of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke. The study found no difference in all-cause mortality among this population at a mean follow-up of 3.8 years.[19]

### Effects on cholesterol levels[edit]

The effects of rosuvastatin on LDL cholesterol are dose-related. Rosuvastatin 10 to 40 mg was more efficacious in improving the lipid profile of patients with hypercholesterolemia than milligram-equivalent doses of atorvastatin and milligram-equivalent or higher doses of simvastatin and pravastatin. [20]

Meta-analysis showed that rosuvastatin treatment (5 or 10 mg) is able to modestly increase levels of HDL cholesterol as well, as with other statins.[21] A study in Japanese diabetics showed the low dose (2.5 mg) can also improve HDL levels.[22] A 2014 Cochrane review determined there was good evidence for rosuvastatin lowering non-HDL levels linearly with dose.[23] HDL increases by 7% with no dose effect noted.

### FDA advisory for East Asian patients[edit]

According to the FDA, the risk of myopathy during rosuvastatin therapy may be increased in Asian Americans:

Because Asians appear to process the drug differently, half the standard dose can have the same cholesterol-lowering benefit in those patients, though a full dose could increase the risk of side-effects, a study by the drug's manufacturer, AstraZeneca, indicated.[24]

Therefore, physicians should start Asian-American or East Asian patients at the lowest dose level.[25]



## Marketing and competition[edit]

### Patent protection[edit]

The main patent protecting rosuvastatin (RE37,314 - due to expire in 2016) was challenged as being an improper reissue of an earlier patent. This challenge was rejected in 2010, confirming protection until 2016.[26][27][28][29]

### Marketing[edit]

The drug was billed as a "super-statin" during its clinical development; the claim was that it offers high potency and improved cholesterol reduction compared to rivals in the class. The main competitors to rosuvastatin are atorvastatin (Lipitor) and simvastatin (Zocor). However, people can also combine ezetimibe with either rosuvastatin or atorvastatin and other agents on their own, for somewhat similar augmented response rates. So far, some published information for comparing rosuvastatin, atorvastatin, and ezetimibe/simvastatin results is available, but many of the relevant studies are still in progress.[10]

First launched in 2003, sales of rosuvastatin were $129 million and $908 million in 2003 and 2004, respectively, with a total patient treatment population of over 4 million by the end of 2004.[*citation needed*] Typical per patient costs to the UK NHS are £18.03-26.02/month (compared to £0.85-1.37/month for simvastatin).

### Debate and criticisms[edit]

In October 2003, several months after its introduction in Europe, Richard Horton, the editor of the medical journal *The Lancet*, criticized the way Crestor had been introduced. "AstraZeneca's tactics in marketing its cholesterol-lowering drug, rosuvastatin, raise disturbing questions about how drugs enter clinical practice and what measures exist to protect patients from inadequately investigated medicines," according to his editorial. *The Lancet's* editorial position is that the data for Crestor's superiority rely too much on extrapolation from the lipid profile data (surrogate end-points) and too little on hard clinical end-points, which are available for other statins that had been on the market longer. The manufacturer responded by stating that few drugs had been tested so successfully on so many patients. In correspondence published in *The Lancet*, AstraZeneca's CEO Sir Tom McKillop called the editorial "flawed and incorrect" and slammed the journal for making "such an outrageous critique of a serious, well-studied medicine."[30]

In 2004, the consumer interest organization Public Citizen filed a Citizen's Petition with the FDA, asking that Crestor be withdrawn from the US market. On March 11, 2005, the FDA issued a

letter to Sidney M. Wolfe, M.D. of Public Citizen both denying the petition and providing an extensive detailed analysis of findings that demonstrated no basis for concerns about rosuvastatin compared with the other statins approved for marketing in the United States.[31]

### Myopathy[edit]

As with all statins, there is a concern of rhabdomyolysis, a severe undesired side effect. The FDA has indicated that "it does not appear that the risk [of rhabdomyolysis] is greater with Crestor than with other marketed statins", but has mandated that a warning about this side-effect, as well as a kidney toxicity warning, be added to the product label.[9]

### Diabetes mellitus[edit]

Statins increase the risk of diabetes,[32] consistent with FDA's review of the JUPITER trial, which reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-treated patients compared to placebo-treated patients.[33]

## Notes[edit]



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17. **Jump up^** *Ridker PM, Danielson E, et al. (November 2008). "Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein". N. Engl. J. Med. **359** (21): 2195–207. doi:10.1056/NEJMoa0807646. PMID 18997196.*
18. **Jump up^** *Brendan M. Everett, MD, MPH; Robert J. Glynn, ScD; Jean G. MacFadyen, BA; Paul M Ridker, MD, MPH (2010). "Rosuvastatin in the Prevention of Stroke Among Men and Women With Elevated Levels of C-Reactive Protein" (PDF). Circulation **121** (1): 143–150. doi:10.1161/CIRCULATIONAHA.109.874834. PMID 20026779.*
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30. **Jump up^** *Horton, Richard (October 25, 2003). "The statin wars: why AstraZeneca must retreat". Lancet **362** (9393): 1341. doi:10.1016/S0140-6736(03)14669-7. PMID 14585629. McKillop T (November 1, 2003). "The statin wars". Lancet **362** (9394): 1498. doi:10.1016/S0140-6736(03)14698-3. PMID 14602449.*
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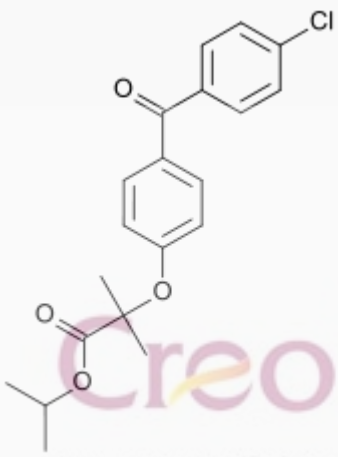
# Fenofibrate

**Fenofibrate**






**Systematic (IUPAC) name**

an-2-yl 2-{4-[(4-chlorophenyl)carbonyl]phenoxy}-2-methylpropanoate

| **Clinical data** | |
|---|---|
| Trade names | Fenoglide, Lipofen |
| AHFS/Drugs.com | monograph |
| MedlinePlus | a601052 |
| Pregnancy category | US: C (Risk not ruled out) |
| Legal status | Legend |
| Routes of administration | Oral |
| **Pharmacokinetic data** | |
| Protein binding | 99% |
| Metabolism | glucuronidation |

| | |
|---|---|
| **Biological half-life** | 20 hours |
| **Excretion** | urine (60%), feces (25%) |
| | **Identifiers** |
| **CAS Registry Number** | 49562-28-9 ✓ |
| **ATC code** | C10AB05 |
| **PubChem** | CID: 3339 |
| **IUPHAR/BPS** | 7186 |
| **DrugBank** | DB01039 ✓ |
| **UNII** | U202363UOS ✓ |
| **KEGG** | D00565 ✓ |
| **ChEBI** | CHEBI:5001 ✓ |
| **ChEMBL** | CHEMBL672 ✓ |
| | **Chemical data** |
| **Formula** | $C_{20}H_{21}ClO_4$ |
| **Molecular mass** | 360.831 g/mol |
| **SMILES**[show] | |
| **InChI**[show] | |
| ✓ **(what is this?)** **(verify)** | |



**Fenofibrate** (INN), marketed as **Tricor** and under several other brand names, is a drug of the fibrate class. It is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Like other fibrates, it reduces both low-density lipoprotein(LDL) and very low density lipoprotein (VLDL) levels, as well as increasing high-density lipoprotein (HDL) levels and reducingtriglyceride levels.[1] It is used alone or along with statins in the treatment of hypercholesterolemia and hypertriglyceridemia.

Fenofibrate has been used since 1975, is one of the most commonly prescribed fibrates, and has a well known efficacy and tolerability profile.[1]

**Contents**

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## Medical uses[edit]

Fenofibrate is mainly used for primary hypercholesterolemia or mixed dyslipidemia. Fenofibrate appears to decrease the risk ofcardiovascular disease and possibly diabetic retinopathy in those with diabetes mellitus,[2][3] and firstly indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy in Australia.[4] It also appears to be helpful in decreasing amputations of the lower legs in this same group of people.[5] Fenofibrate also has an unlabeled use as an added therapy of high blood uric acid levels in people who have gout.[6]

It is used in addition to diet to reduce elevated low-density lipoprotein cholesterol (LDL), total cholesterol, triglycerides (TG), and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL) in adults with primary hypercholesterolemia or mixed dyslipidemia.[7]

- Severe hypertriglyceridemia type IV or V

It is used in addition to diet for treatment of adults with severe hypertriglyceridemia. Improving glycemic control in diabetics showing fasting chylomicronemia will usually decrease the need for pharmacologic intervention.[7]

Statins remain first line for treatment of blood cholesterol. AHA Guidelines from 2013 did not find evidence for routine use of additional medications.[8]

## Contraindications[edit]

Fenofibrate is contraindicated in:[7]

- Patients with severe renal impairment, including those receiving dialysis (2.7-fold increase in exposure, and increased accumulation during chronic dosing in patients with estimated glomerular filtration rate (eGFR)<30mL/min)
- Patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function test (LFT) abnormalities
- Patients with preexisting gallbladder disease
- Nursing mothers
- Patients with known hypersensitivity to fenofibrate or fenofibric acid

# Adverse effects[edit]

The most common adverse events (>3% of patients with coadministered statins) are[9]

- Headache
- Back pain
- Nasopharyngitis
- Nausea
- Myalgia
- Joint pain or arthralgia
- Diarrhea
- Upper respiratory tract infection

### Precautions[edit]

Musculoskeletal

- Myopathy and rhabdomyolysis; increased risk when coadminstered with a statin, particularly in the elderly and patients with diabetes, renal failure, hypothyroidism[9]

Hepatotoxicity

- Can increase serum transaminases; liver tests should be monitored periodically[9]

Nephrotoxicity

- Can increase serum creatinine levels; renal function should be monitored periodically in patients with renal insufficiency[9]

Biliary

- Can increase cholesterol excretion into the bile, leading to risk of cholelithiasis; if suspected gallbladder studies are indicated. See "Interaction" section under Bile Acid Sequestrant[9]

Coagulation/Bleeding

- Exercise caution in concomitant treatment with oral coumarin anticoagulants (e.g. Warfarin). Adjust the dosage of coumarin to maintain the prothrombin time/INR at desired level to prevent bleeding complications[9]

# Overdose[edit]

"*There is no specific treatment for overdose with fenofibric acid delayed-release capsules. General supportive care Is indicated, including monitoring of vital signs and observation of clinical status*". Additionally, hemodialysis should not be considered as an overdose treatment option because fenofibrate heavily binds to plasma proteins and does not dialyze well.[9]

# Interactions[edit]

The following drug interactions with fenofibrate is considered major and may need therapy modifications:

- Bile acid sequestrants (e.g. cholestyramine, colestipol, etc.): If taken together, bile acid resins may bind to fenofibrate, resulting in a decrease in fenofibrate absorption. In order to maximize absorption, patients need to separate administration by at least 1 hour before or 4–6 hours after taking the bile acid sequestrant.[9][10]

- Immunosuppressants (e.g. cyclosporine or tacrolimus): There is an increased risk of renal dysfunction with concomitant use of immunosuppressants and fenofibrate. Please approach with caution when coadministering additional medications that decrease renal function.[11]
- Vitamin K antagonists (e.g. warfarin): As previously mentioned, fenofibrate interacts with coumarin anticoagulants to increase the risk of bleeding. Dosage adjustment of Vitamin K antagonist may be necessary.[9]
- Statins: Combination of statins and fenofibrate may increase the risk of rhabdomyolysis or myopathy.[12]

# Mechanism of action[edit]

*"In summary, enhanced catabolism of triglyceride-rich particles and reduced secretion of VLDL underlie the hypotriglyceridemic effect of fibrates, whereas their effect on HDL metabolism is associated with changes in HDL apolipoprotein expression."*[13]

Fenofibrate is a fibric acid derivative, a prodrug comprising fenofibric acid linked to an isopropyl ester. It lowers lipid levels by activating Peroxisome proliferator-activated receptor alpha (PPARα). PPARα activates lipoprotein lipase and reduces apoprotein CIII, which increases lipolysis and elimination of triglyceride-rich particles from plasma.[13]

PPARα also increases apoproteins AI and AII, reduces very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) containing apoprotein B, and increases high-density lipoprotein (HDL) containing apoprotein AI and AII.

# Formulations[edit]

Fenofibrate is available in several formulations and is sold under several brand names, including Tricor by AbbVie, Lipofen by Kowa Pharmaceuticals America Inc, Lofibra byTeva, Lipanthyl, Lipidil, and Supralip by Abbott Laboratories, Fenocor-67 by Ordain Health Care, Fibractiv 105/35 by Cogentrix Pharma( India), Fenogal by SMB Laboratories, Antara by Oscient Pharmaceuticals, Tricheck by Zydus (CND), Atorva TG by Zydus Medica, Golip by GolgiUSA and Stanlip by Ranbaxy (India). Different formulations may differ in terms of pharmacokinetic properties, particularly bioavailability; some must be taken with meals, whereas others may be taken without regard to food.[14]

The active form of fenofibrate, fenofibric acid, is also available in the United States, sold as Trilipix. Fenofibric acid may be taken without regard to the timing of meals.[9][15]

When fenofibrate and a statin are given as combination therapy, it is recommended that fenofibrate be given in the morning and the statin at night, so that the peak dosages do not overlap.[16]

## Controversy[edit]

In the United States, Tricor was reformulated in 2005. This reformulation is controversial, as it is seen as an attempt to stifle competition from generic equivalents of the drug,[17]and is the subject of antitrust litigation by generic drug manufacturer Teva.[17] Also available in the United States, Lofibra is available in 54 and 160 mg tablets, as well as 67, 134, and 200;mg micronized capsules.[18] Generic equivalents of Lofibra capsules are currently available in all three strengths in the United States. In Europe, it is available in either coated tablet or capsule; the strength range includes 67, 145, 160 and 200 mg. The differences among strengths are a result of altered bioavailability (the fraction absorbed by the body) due to particle size. For example, 200 mg can be replaced by 160 mg micronized fenofibrate. The 145 mg strength is a new strength that appeared in 2005-2006 which also replaces 200 or 160 mg as the fenofibrate is nanonised (i.e. the particle size is below 400 nm).

# History[edit]

Fenofibrate was first synthesized in 1974 as a derivative of clofibrate, and was launched on the French market shortly thereafter. It was initially known as *procetofen*, and was later

renamed *fenofibrate* to comply with World Health Organization International Nonproprietary Name guidelines.[19]

Fenofibrate was developed by Groupe Fournier SA of France, which was acquired in 2005 by Solvay Pharmaceuticals, a business unit of the Belgian corporation Solvay S.A.. In 2009, Solvay was in turn acquired by Abbott Laboratories (now AbbVie).

## Research[edit]

In adult rat studies using pentylenetetrazol and lithium-pilocarpine models, Fenofibrate exhibits anticonvulsant properties comparable to the ketogenic diet potentially via agonism of PPAR-a. These findings may be useful for future ketogenic diet study protocols.[20]

## Notes[edit]


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10. **Jump up^** Product Information: TriCor(TM), fenofibrate. Abbott Laboratories, North Chicago, IL, 1998.
11. **Jump up^** Product Information: Sandimmune(R) oral capsules, oral solution, intravenous injection, cyclosporine oral capsules, oral solution, intravenous injection. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2010.
12. **Jump up^** Product Information: TRICOR(R) oral tablets, fenofibrate oral tablets. Abbott Laboratories, North Chicago, IL, 2007.
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