

# The Medical Letter®

## On Drugs and Therapeutics

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For patients who cannot tolerate or are resistant to imatinib (*Gleevec*).

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At a lower dose than prn use

### IN BRIEF

#### **Meningococcal Prophylaxis**

The CDC recently reported that fluoroquinolone-resistant strains of *Neisseria meningitidis* have been detected for the first time in the US in an area around the border of North Dakota and Minnesota (CDC. MMWR, Feb 22, 2008). These isolates were all serogroup B, for which meningococcal vaccines ([Med Lett Drugs Ther 2005; 47:29](#)) do not offer protection. No fluoroquinolone-resistant strains of *N. meningitidis* have been reported to date by the Public Health Agency of Canada. Since many laboratories do not test *N. meningitidis* for antimicrobial susceptibility, it is possible that resistance is more prevalent than reports indicate.

A single oral dose of ciprofloxacin (*Cipro*, and others) 500 mg has been used for prophylaxis after close contact with infected patients. Oral rifampin (*Rifadin*, and others) 600 mg (10 mg/kg for children) q12h for 2 days, a single IM injection of ceftriaxone (*Rocephin*, and others) 250 mg (125 mg for children), or a single oral dose of azithromycin (*Zithromax*, and others) 500 mg (10 mg/kg for children) are reasonable alternatives.

#### **Simcor: A Niacin/Simvastatin Combination**

The FDA has approved the marketing of a second fixed-dose combination of extended-release niacin (*Niaspan*) with a generic statin. *Niaspan/simvastatin* (*Simcor* – Abbott; not approved in Canada) is approved for use in patients with hypercholesterolemia or mixed dyslipidemia (high LDL-cholesterol, low HDL-cholesterol and high serum triglycerides).

*Niaspan/lovastatin* (*Advicor*) was marketed previously for the same indications.<sup>1</sup>

**STATINS** — Statins are more effective than other drugs in lowering LDL-C, and they also lower triglycerides. Most statins increase HDL-C only modestly. Statins have dose-related differences in how much they lower LDL-C. A lovastatin dose of 20 mg usually lowers LDL-C by 25%-30%; a maximum dose of 80 mg lowers it by 35%-40%. A simvastatin dose of 20 mg lowers LDL-C by 35%-40%; a maximum dose of 80 mg lowers it by 45%-50%.<sup>2</sup>

**NIACIN** — In addition to the extended-release formulation, niacin is available in over-the-counter (OTC) immediate-release and sustained-release forms. Flushing has been a problem with immediate-release formulations and hepatotoxicity with high doses of the sustained-release drug; flushing has been less frequent and hepatotoxicity has seldom occurred with extended-release niacin.

**CLINICAL STUDIES** — FDA approval of *Simcor* was based on an unpublished study (SEACOAST) pre-

**Table 2. Niacin/Statin Combinations**

Drug	Tablet Strength	US Cost <sup>1</sup>	CAN Cost <sup>2</sup>
<b>Fixed-Dose Combinations</b>			
Niacin ER/ simvastatin – <i>Simcor</i> (Abbott)	500 mg/20 mg 750 mg/20 mg 1000 mg/20 mg	\$68.53 97.64 121.07	N.A. N.A. N.A.
Niacin ER/ lovastatin – <i>Advicor</i> (Oryx; Abbott in US)	500 mg/20 mg 750 mg/20 mg <sup>3</sup> 1000 mg/20 mg 1000 mg/40 mg	94.96 101.87 109.21 126.44	\$39.28 N.A. 44.04 59.88
<b>Individual Drugs</b>			
Niacin ER – <i>Niaspan</i> (Oryx; Abbott in US)	500 mg 750 mg 1000 mg	68.53 97.64 121.07	35.86 35.86 35.86
Simvastatin – generic	20 mg 40 mg	27.99 27.99	41.58 41.58
<i>Zocor</i> (Merck)	20 mg 40 mg	139.99 135.33	74.67 74.67

N.A. Not available in Canada

1. Cost of 30 tablets based on AWP listings in *Red Book Update* April 2008.

*Zocor* and generic simvastatin cost based on prices at drugstore.com accessed March 31, 2008.

2. Cost of 30 tablets based on data from a national wholesaler (prices in Ontario, January 2008).

3. Strength not available in Canada.

sented at the November 2007 meeting of the American Heart Association<sup>3</sup> and summarized in the package insert. Among 641 patients with hyperlipidemia and mixed dyslipidemia, all doses of the combination after 24 weeks produced greater lowering of LDL-C, significantly greater increases in HDL-C and greater decreases in triglycerides than simvastatin 20 mg alone.

An earlier 3-year double-blind trial in 160 patients with coronary disease, low HDL-C and normal LDL-C found that simvastatin given with another slow-release niacin (*Slo-Niacin*; not approved in Canada) substantially lowered LDL-C and raised HDL-C, improved coronary stenosis and significantly decreased the occurrence of a first cardiovascular event, compared to placebo or antioxidants.<sup>4</sup>

**ADVERSE EFFECTS** — Flushing, dyspepsia, pruritus, headache and back pain have been the most common adverse effects of *Simcor*.

**DOSAGE AND COST** — As with any extended-release niacin formulation, *Simcor* should be taken at bedtime with a low-fat snack, starting with a low dose and increasing gradually (by 500 mg every 4 weeks). The maximum daily dose is 2000 mg/40 mg. The cost of *Simcor* is the same as the cost of the corresponding dose of *Niaspan*.

**DRUG INTERACTIONS** — Simvastatin interacts with many other drugs. In particular, it (and *Simcor*) should not be used with gemfibrozil (*Lopid*, and others).

**ALTERNATIVES** — In patients with mixed dyslipidemia, statins may be used in combination with niacin, fenofibrate (*Lipidil EZ*, and others; *Tricor*, and others in US) or omega-3 fatty acids to achieve increases in HDL-C and decreases in triglycerides in addition to decreases in LDL-C.<sup>2</sup>

**CONCLUSION** — Taking niacin in addition to a statin can substantially lower LDL-C and triglycerides, raise HDL-C, and possibly decrease the risk of cardiovascular events in patients with coronary artery disease. *Simcor* (not approved in Canada), a fixed-dose combination of simvastatin with extended-release niacin may be appropriate and convenient for some patients with mixed dyslipidemia, and may cost less than taking the 2 drugs separately. This combination is not recommended for initial treatment of hyperlipidemia. □

1. Three new drugs for hyperlipidemia. *Med Lett Drugs Ther* 2003; 45:17.
2. Drugs for lipids. *Treat Guidel Med Lett*, 2008; 6:9.
3. CM Ballantyne et al. The safety and efficacy of a combination of extended-release niacin and simvastatin in patients with dyslipidemia (SEACOAST): A dose-ranging study. *Circulation* 2007; 116:II-15, abstract 188.
4. BG Brown et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001; 345:1583.

## Nilotinib (*Tasigna*) for CML

Nilotinib (*Tasigna* – Novartis; not approved in Canada), a tyrosine kinase inhibitor, has been approved by the FDA for treatment of Philadelphia chromosome-positive (Ph+) chronic or accelerated phase chronic myelogenous leukemia (CML) in patients resistant to or intolerant of imatinib (*Gleevec*).

**STANDARD TREATMENT** — Imatinib, the first tyrosine kinase inhibitor for treatment of CML, was approved by the FDA and Health Canada in 2001.<sup>1</sup> It is now the standard first-line treatment for all phases of Ph+ CML. Primary treatment of chronic phase CML with imatinib results in a complete cytogenetic response rate of 87% and an overall survival rate of 89% at 5 years.<sup>2</sup> Patients who do not respond to imatinib may be treated with higher doses of imatinib, another tyrosine kinase inhibitor, or allogeneic stem-cell transplantation. Dasatinib (*Sprycel*), the second tyrosine kinase inhibitor for treatment of CML, was approved by the FDA in 2006 and Health Canada in 2007, also for patients resistant to or intolerant of imatinib.<sup>3</sup>

**CLINICAL STUDIES** — In an open-label study, 280 patients with CML in chronic phase who were intolerant of or refractory to imatinib received nilotinib 400

**Table 1. Pharmacology**

Mechanism of action	Selectively inhibits BCR-ABL tyrosine kinase; active <i>in vitro</i> against most cell lines resistant to imatinib
Route	Oral
Absorption	Tmax 3 hours
Plasma half-life	17 hours
Metabolism	CYP3A4, oxidation and hydroxylation
Excretion	Primarily in feces

mg twice daily. After 6 months, 48% of them had achieved a major cytogenetic response ( $\leq 35\%$  Ph+ cells), including 31% who achieved a complete cytogenetic remission; survival at 12 months was about 95%.<sup>4</sup> Another study in 119 patients with accelerated phase CML, treated with nilotinib 400 mg twice daily, found that 47% achieved a hematologic response and 29% had a major cytogenetic response; survival at 12 months was 79%.<sup>5</sup>

No data are available directly comparing nilotinib with dasatinib in patients intolerant of or resistant to imatinib. Available data suggest that cross-resistance between them is at least incomplete; patients who do not respond to one might respond to the other.<sup>6</sup> Responses to nilotinib have occurred among patients with a variety of

**Table 2. Tyrosine Kinase Inhibitors**

Drug	Formulations	Dosage	Approved Indications <sup>1</sup>	US Cost <sup>2</sup>	CAN Cost <sup>3</sup>
Imatinib – <i>Gleevec</i> (Novartis)	100, 400 mg tabs	400-600 mg once/d or 400 mg bid	First-line treatment of Ph+ CML (chronic phase); Second-line treatment of Ph+ CML (all phases) or Ph+ ALL	\$6841.46	\$6548.36
Dasatinib – <i>Sprycel</i> (Bristol-Myers Squibb)	20, 50, 70 mg tabs	70 mg bid or 100 mg once/d	Second-line treatment of Ph+ CML (all phases) or Ph+ ALL	5045.83	4528.03
Nilotinib – <i>Tasigna</i> (Novartis)	200 mg caps	400 mg bid	Second-line treatment of Ph+ CML (chronic and accelerated phase)	6841.07	N.A.

N.A. Not available in Canada

Ph+ CML: Philadelphia chromosome-positive chronic myelogenous leukemia

Ph+ ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia

1. By the FDA and Health Canada for treatment of Ph+ CML and ALL. Imatinib is also approved for first-line treatment of Ph+ ALL in Canada and for other indications in both the US and Canada.

2. Cost for 30 days' treatment at the highest recommended dosage, according to AWP listings in *Red Book* 2007 or April 2008 *Update*.

3. Cost for 30 days' treatment at the highest recommended dosage, according to data from a national wholesaler (prices in Ontario, January 2008).

imatinib-resistant BCR-ABL tyrosine kinase mutations, but not in patients with the T315I mutation, which confers cross-resistance to imatinib, nilotinib and dasatinib.<sup>7</sup>

**ADVERSE EFFECTS** — Most patients intolerant of imatinib seem to be able to tolerate nilotinib. Fluid retention, for example, which has been troublesome with imatinib, has occurred only rarely with nilotinib. Pleural effusion, which occurs in >10% of patients receiving dasatinib,<sup>8</sup> has occurred in about 1% of patients receiving nilotinib.

Nilotinib prolongs the QT interval, and sudden death has been reported. It should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Other drugs known to prolong the QT interval should be avoided in patients receiving nilotinib ([www.arizonacert.org](http://www.arizonacert.org)). Electrocardiograms should be obtained to monitor the QT interval at baseline, 7 days after initiation and periodically thereafter, as well as following dose adjustments.

The most frequently reported adverse effects of nilotinib have been thrombocytopenia, neutropenia, rash, pruritus, nausea, fatigue, headache and constipation. Electrolyte abnormalities and elevations in serum lipase, bilirubin and transaminases have been reported.

**DRUG INTERACTIONS** — Nilotinib is metabolized by CYP3A4. Concurrent use of strong CYP3A4 inhibitors or inducers should be avoided.<sup>9</sup> Nilotinib is also a substrate of the efflux transporter P-glycoprotein. Drugs that inhibit P-glycoprotein may increase nilotinib concentrations.<sup>10</sup>

**CONCLUSION** — Nilotinib (*Tasigna*; not approved in Canada) appears to be effective for treatment of CML in patients who are intolerant of or refractory to imatinib (*Gleevec*). How it compares to dasatinib (*Sprycel*) remains to be determined. □

1. *Gleevec* (STI-571) for chronic myeloid leukemia. *Med Lett Drugs Ther* 2001;43:49.
2. BJ Druker et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006; 355:2408.
3. *Dastinib* (*Sprycel*) for CML and Ph+ ALL. *Med Lett Drugs Ther* 2007; 49:6.
4. HM Kantarjian et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007; 110:3540.
5. P le Coutre et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated-phase chronic myelogenous leukemia. *Blood* 2008; 111:1834.
6. A Quintas-Cardama et al. Dasatinib (BMS-354825) is active in Philadelphia chromosome-positive chronic myelogenous leukemia after imatinib and nilotinib (AMN107) therapy failure. *Blood* 2007; 109:497.
7. HA Bradeen et al. Comparison of imatinib mesylate, dastinib (BMS-354825), and nilotinib (AMN107) in an N-ethyl-N-nitrosourea (ENU)-based mutagenesis screen: high efficacy of drug combinations. *Blood* 2006; 108:2332.
8. H Kantarjian et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: a randomized phase 2 trial. *Blood* 2007; 109:5143.
9. CYP3A and drug interactions. *Med Lett Drugs Ther* 2005; 47:54.
10. Drug interactions. *Med Lett Drugs Ther* 2003; 45:46.

## Tadalafil (*Cialis*) Once a Day for Erectile Dysfunction

The phosphodiesterase type 5 (PDE5) inhibitor tadalafil (*Cialis* – Lilly) is now being promoted for once-daily treatment of erectile dysfunction. Tadalafil differs from sildenafil (*Viagra*) and vardenafil (*Levitra*), the other PDE5 inhibitors marketed for erectile dysfunction in the US and Canada, in having a much longer duration of action.<sup>1</sup>

**EFFICACY** — The efficacy of taking tadalafil once daily has been demonstrated previously. In one published study, 5 mg once daily was as effective as 10 mg once daily, and both were more effective than placebo.<sup>2</sup> In 2 unpublished studies summarized in the

package insert, 2.5-mg doses once daily were as effective as 5-mg doses, and both were more effective than placebo.

**ADVERSE EFFECTS** — The most common adverse effects of PDE5 inhibitors have been headache, facial flushing, nasal congestion and dyspepsia. Back pain and leg pain can occur. Prolonged erection (priapism) has occurred rarely. Transient visual disturbances can also occur. Acute hearing loss, sometimes accompanied by tinnitus and dizziness, has been reported rarely with all PDE5 inhibitors; cause and effect have not been established.

**LONG-TERM SAFETY** — In addition to their use for erectile dysfunction, because of their beneficial effects on pulmonary vascular resistance, PDE5 inhibitors have been used to treat pulmonary arterial hypertension<sup>3</sup>; sildenafil has been taken 3 times a day for up to a year with no adverse effects.

**DRUG INTERACTIONS** — PDE5 inhibitors are contraindicated in patients taking nitrates. They should be used with caution in patients taking any antihypertensive drug; some alpha-blockers such as doxazosin (*Cardura*, and others) or tamsulosin (*Flomax*) are used to treat benign prostatic hyperplasia, which is common in the age group of men taking PDE5 inhibitors.

**DOSAGE AND COST** — For once-daily treatment of erectile dysfunction, the US manufacturer recommends taking 2.5 mg at the same time each day, and increasing to 5 mg if necessary. In Canada, the manufacturer recommends starting with 5 mg and decreasing to 2.5 mg if necessary. For as-needed use, the recommended dose in the US is 10 mg, increasing to 20 mg if necessary. In Canada, the recommended as-needed dose is 20 mg, with adjustment to 10 mg if necessary. The US cost of one box containing 30 2.5-mg tablets of *Cialis* at drugstore.com is \$124.97; the cost of 30 5-mg tablets is \$385.97. In Canada, the cost of one package containing 28 2.5-mg or 5-mg tablets is \$106.40 (Ontario prices from a national wholesaler, April 2008).

**CONCLUSION** — Taking tadalafil (*Cialis*) once daily in a lower dose may be as effective as taking higher doses as needed, and appears to be safe, at least for up to one year, based on long-term use of sildenafil to treat pulmonary arterial hypertension. □

1. Tadalafil (*Cialis*) for erectile dysfunction. *Med Lett Drugs Ther* 2003; 45:101.
2. H Porst et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol* 2006; 50:351.
3. Sildenafil (*Revatio*) for pulmonary arterial hypertension. *Med Lett Drugs Ther* 2005; 47:65.

### Coming Soon in *The Medical Letter*:

Diclofenac Topical Gel (*Voltaren*)

Which Statin?

ER Amoxicillin for Strep Throat

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