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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. Since many laboratories do not test *N. meningitidis* for antimicrobial susceptibility, it is possible that such resistance is more widespread.

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) 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.¹

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%.²

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CLINICAL STUDIES — FDA approval of *Simcor* was based on an unpublished study (SEACOAST) presented at the November 2007 meeting of the American

Table 2. Niacin/Statin Combinations

Drug	Tablet Strength	Cost ¹
Fixed-Dose Combinations		
Niacin ER/ simvastatin – <i>Simcor</i> (Abbott)	500 mg/20 mg	\$68.53
	750 mg/20 mg	97.64
	1000 mg/20 mg	121.07
Niacin ER/ lovastatin – <i>Advicor</i> (Abbott)	500 mg/20 mg	94.96
	750 mg/20 mg	101.87
	1000 mg/20 mg 1000 mg/40 mg	109.21 126.44
Individual Drugs		
Niacin ER – <i>Niaspan</i> (Abbott)	500 mg	68.53
	750 mg	97.64
	1000 mg	121.07
Simvastatin – generic <i>Zocor</i> (Merck)	20 mg	27.99
	40 mg	27.99
	20 mg	139.99
	40 mg	135.33

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.

Heart Association³ 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*) 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.⁴

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 (*Tricor*, and others) or omega-3 fatty acids to achieve increases in HDL-C and decreases in triglycerides in addition to decreases in LDL-C.²

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*, 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), 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 in 2001.¹ 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.² 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, also for patients resistant to or intolerant of imatinib.³

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%.⁴ 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%.⁵

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.⁶ Responses to nilotinib have occurred among patients with a variety of imatinib-resistant BCR-ABL tyrosine kinase mutations,

Table 2. Tyrosine Kinase Inhibitors

Drug	Formulations	Dosage	FDA-approved Indications ¹	Cost ²
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
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
Nilotinib – <i>Tasigna</i> (Novartis)	200 mg caps	400 mg bid	Second-line treatment of Ph+ CML (chronic and accelerated phase)	6841.07

Ph+ CML: Philadelphia chromosome-positive chronic myelogenous leukemia

Ph+ ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia

1 For treatment of Ph+ CML and ALL. Imatinib is also approved for other indications.

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

but not in patients with the T315I mutation, which confers cross-resistance to imatinib, nilotinib and dasatinib.⁷

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,⁸ 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). 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.⁹ Nilotinib is also a substrate of the efflux transporter P-glycoprotein. Drugs that inhibit P-glycoprotein may increase nilotinib concentrations.¹⁰

CONCLUSION — Nilotinib (*Tasigna*) 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, in having a much longer duration of action.¹

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.² 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 hypertension³; 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 manufacturer recommends taking 2.5 mg at the same time each day, and increasing to 5 mg if necessary. For as-needed use, the recommended dose is 10 mg, increasing to 20 mg if necessary. The 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.

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*:

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Which Statin?

ER Amoxicillin for Strep Throat

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Issue 1283 Questions

(Correspond to questions #37-42 in
Comprehensive Exam #58, available July 2008)

Simcor: A Niacin/Simvastatin Combination

1. Mixed dyslipidemia is:
- low LDL-C, low HDL-C, high triglycerides
 - high LDL-C, low HDL-C, high triglycerides
 - low HDL-C, high LDL-C, normal triglycerides
 - none of the above

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2. The main advantage of extended-release niacin over immediate- and sustained-release formulations is:
- lower cost
 - convenience
 - less flushing and hepatotoxicity
 - greater efficacy

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3. Taking niacin in addition to a statin can:
- lower LDL-C
 - lower triglycerides
 - raise HDL
 - all of the above

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Nilotinib (*Tasigna*) for CML

4. Nilotinib (*Tasigna*) is approved for Ph+ CML patients who are refractory to:
- imatinib (*Gleevec*)
 - dasatinib (*Sprycel*)
 - tyrosine kinase inhibitors
 - none of the above

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

5. Tadalafil is less likely than sildenafil or vardenafil to:
- be effective
 - be safe
 - interact with alpha-blockers
 - none of the above

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6. PDE5 inhibitors are contraindicated in patients taking:
- beta blockers
 - warfarin
 - nitrates
 - none of the above

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