



Featured in this issue:

Varenicline (Champix™)
Telbivudine (Sebivo®)

May 2007

Volume 26, Number 5

NEW DRUGS

Varenicline Tartrate (Champix™ - Pfizer)

- smoking-cessation aid

Pharmacology

- partial nicotine receptor agonist with high affinity for $\alpha 4\beta 2$ nicotinic acetylcholine receptors in the brain that are responsible for cravings and withdrawal associated with nicotine use and dependence
- modulates dopamine levels associated with nicotine addiction
- simultaneously prevents nicotine binding to receptors

Indications

- smoking-cessation treatment in adults in conjunction with smoking-cessation counseling

Pharmacokinetics

Absorption/bioavailability	Well absorbed; C_{max} occurs within 3-4 h; steady-state reached within 4 days
Effect of food on bioavailability	Unaffected by food
Elimination half-life	Approximately 24 h
Plasma protein binding	Low $\leq 20\%$
Metabolism	Undergoes minimal metabolism; 92% excreted unchanged in urine
Excretion	Major route of elimination is renal, primarily through glomerular filtration; also active tubular secretion via OCT2
Renal insufficiency	No dosage adjustment for mild to moderate renal impairment; reduce dose in severe renal impairment; avoid use in end stage renal disease; removed by hemodialysis
Hepatic insufficiency	No dosage adjustment required
Geriatrics	No dosage adjustment required for healthy elderly; in general, exercise caution, since elderly more likely to have decreased renal function
Pediatrics	Not recommended; safety and efficacy have not been established

Contraindications, Warnings and Precautions

- **general** – concomitant use of nicotine replacement therapy (NRT) may increase incidence of adverse reactions including nausea, headache, vomiting, dizziness, dyspepsia, fatigue; safety and efficacy of combination treatment have not been studied
- **smoking cessation** – smoking induces cytochrome P4501A2; therefore, smoking cessation with or without the use of a smoking-cessation aid may result in increased plasma levels of select CYP1A2 substrates (e.g., theophylline, warfarin, insulin)
- **dependence/discontinuation symptoms** – mild physical dependence may occur; no report of addiction or abuse
- at end of treatment period up to 3% of patients experienced discontinuation symptoms (e.g., increase in irritability, urge to smoke, depression, and/or insomnia); tapering dose may minimize withdrawal symptoms
- **driving/operating machinery** – may cause dizziness and somnolence; advise caution until individual effect known
- **pediatrics** – not recommended; safety and efficacy have not been evaluated
- **geriatrics** – substantially excreted by kidney; no dose adjustment required for healthy elderly; however, caution is advised in elderly population due to greater frequency of decreased renal function; monitoring recommended – may require reduced dose
- **psychiatric patients** – smoking cessation with or without pharmacotherapy has been associated with exacerbation of underlying psychiatric illness; use in this population is unknown; exercise caution
- **pregnancy** – potential for risk in humans is unknown; avoid use
- **lactation** – not known if excreted in human milk; unknown risk - therefore, nursing mother should either discontinue drug or discontinue nursing

Drug Interactions

- metabolism represents < 10% of clearance; *in vitro* studies have demonstrated that active renal secretion is mediated by human organic cation transporter, hOCT2
- based on pharmacokinetic characteristics and clinical experience to date, appears unlikely to produce or be subject to clinically meaningful drug interactions other than potential for interaction with cimetidine; **cimetidine** co-administration resulted in decreased varenicline renal clearance; no dose adjustment required in normal or mild-to-moderate renal impairment; avoid concomitant use in patients with severe renal impairment
- **other inhibitors of hOCT2 (e.g., trimethoprim, ranitidine, levofloxacin)** – no dosage adjustment required in normal, or mild-to-moderate renal impairment; avoid concomitant administration in patients with severe renal impairment
- interactions between varenicline and other cationic drugs eliminated via hOCT2 are unlikely (e.g., metformin)
- **warfarin** – no interaction; however, smoking-cessation itself may result in change to warfarin pharmacokinetics
- **other therapies for smoking cessation** – safety and efficacy of combination therapy have not been studied
- co-administration with **nicotine replacement therapy (NRT)** resulted in increased incidence of common adverse effects; based on mechanism of action, combination is unlikely to offer additional benefit

Adverse Effects

- smoking cessation with or without pharmacotherapy may be associated with a variety of symptoms including dysphoric or depressed mood, insomnia, irritability, frustration or anger,

- anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite or weight gain
- adverse events related to use of varenicline usually occurred within first few weeks of therapy; severity generally mild to moderate
 - **nausea** – most common adverse event; dose-related (following initial titration, incidence was 30% with dose of 1 mg BID and 16% with dose of 0.5 mg BID); mild to moderate in severity, usually transient, but may persist; 3% discontinued use due to nausea
 - consider dose reduction for patients with intolerable nausea
 - other – insomnia (18%), abnormal dreams (13%), constipation (8%), vomiting (5%), flatulence (6%), xerostomia (6%)
 - refer to Product Monograph for other adverse events

Dosage and Administration

- **recommended dose** – advise patients to select a “target quit date”; begin therapy (Day 1) with varenicline one to two weeks prior to that date
- to optimize success of therapy titrate doses up to maximum of 1 mg twice daily, orally, as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Days 8 to end of treatment:	1 mg twice daily

- maximum daily dose is 2 mg
- treat for 12 weeks; if patient has successfully stopped smoking, consider an additional 12 weeks; no limit to total duration of use
- dose tapering at end of course of therapy may minimize discontinuation symptoms (see precautions)
- smoking-cessation therapies are more likely to succeed for patients motivated to stop and who receive additional counseling and/or support services
- **renal insufficiency** – no dose adjustment required in mild to moderate (≥ 30 and ≤ 80 mL/min); in severe renal impairment (≤ 30 mL/min) recommended dose is 0.5 mg once daily on days 1 to 3, then increase to 0.5 mg twice daily; based on lack of clinical experience, varenicline is not recommended for use in patients with end-stage renal disease
- no dosage adjustment required for healthy elderly or for patients with hepatic insufficiency
- not recommended for patients under 18 years of age

Availability and Cost

- supplied as oral tablets containing varenicline tartrate 0.5 mg (white) or 1 mg (light blue) strengths
- available as:
 - 2-week starter pack of 0.5 mg tablets (11) and 1 mg tablets (14) - \$42.13/pack
 - 2-week continuing pack of 1 mg tablets (28) - \$47.18/pack
 - 4-week bottle of 0.5 mg tablets (56) - \$94.36/56 tablets

Place in Therapy

Smoking is the leading cause of preventable death and has negative health impact on people of all ages, from unborn babies to seniors. According to the Canadian Tobacco Use Monitoring Survey, data collected between February and June 2006 indicated that just over 4.5 million people, 18% of the population aged 15 years and older, were current smokers. Nearly 41% of smokers (U.S. data)

try to quit smoking each year but relapse is common; only about 10% achieve and maintain abstinence. Varenicline, the first of a new class of drug, targets receptors in the brain responsible for mediating the reinforcing properties of nicotine, thus alleviating craving and withdrawal experienced during smoking cessation. Clinical trials have demonstrated higher quit rates compared to placebo and in some, also higher compared to bupropion.

Clinical Trials:

1. Gonzales D, et al, for the Varenicline Phase 3 Study Group. Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs. sustained-release bupropion and placebo for smoking cessation. A randomized controlled trial. *JAMA* 2006; 296: 47-55.
2. Jorenby DE, et al, for the Varenicline Phase 3 Study Group. Efficacy of Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation. A randomized controlled trial. *JAMA* 2006; 296: 56-63.

These were two identically designed studies, which evaluated the efficacy and safety of varenicline compared with placebo and bupropion SR in generally healthy adults. Both were randomized, multicentre, double-blind, parallel-group, placebo and active-treatment-controlled, phase 3 clinical trials with a 12-week treatment phase and blinded post-study drug follow-up to week 52. Each study was conducted at different sites. Participants were aged 18-75, smoked 10 or more cigarettes per day, had fewer than 3 months of smoking abstinence in the past year and were motivated to stop smoking. Participants were randomly assigned in a 1:1:1 ratio to receive brief counseling and varenicline titrated to 1 mg BID [$n = 352$ (1); $n = 344$ (2)], bupropion SR titrated to 150 mg BID, [$n = 329$ (1); $n = 342$ (2)] or placebo [$n = 344$ (1); $n = 341$ (2)] orally for 12 weeks, with 40 weeks of nondrug follow-up. The primary end point (for both studies) was exhaled carbon-monoxide-confirmed 4-week continuous abstinence for weeks 9 through 12. Secondary end points were continuous abstinence rates from week 9 through 24, and 9 through 52. Varenicline was safe and generally well tolerated. Results of both studies demonstrated that varenicline was significantly more efficacious than both placebo (at all time points) and bupropion (through to week 24). The following table details (some) results of each trial.

Results	Trial 1	Trial 2	Statistical significance
Continuous abstinence rate weeks 9 – 12			$p < .001$ for all values
Varenicline	44.0%	43.9%	
Bupropion SR	29.5%	29.8%	
Placebo	17.7%	17.6%	
For weeks 9 through 24			p values
Varenicline	29.5%	29.7%	
Bupropion SR	20.7%	20.2%	.007 (1); .003 (2)
Placebo	10.5%	13.2%	< .001 (1); < .001 (2)
For weeks 9 through 52			p values
Varenicline	21.9%	23%	
Bupropion SR	16.1% 8.4%	14.6%	.057 (1); .004 (2)
Placebo		10.3%	< .001 (1); < .001 (2)
Treatment discontinuation rates for adverse events			
Varenicline	8.6%	10.5%	
Bupropion SR	15.2%	12.6%	
Placebo	9.0%	7.3%	
Common side effects – nausea			
Varenicline	28.1%	29.4%	
Bupropion SR	12.5%	7.4%	
Placebo	8.4%	9.7%	

Results	Trial 1	Trial 2	Statistical significance
Insomnia			
Varenicline	14.0%	14.3%	
Bupropion SR	21.9%	21.2%	
Placebo	12.8%	12.4%	
Abnormal dreams			
Varenicline	10.3%	13.1%	
Bupropion SR	5.5%	5.9%	
Placebo	5.5%	3.5%	

It was also noted that varenicline reduced cravings and smoking satisfaction, which suggests that this novel agent may represent a new direction for the development of smoking cessation therapies. Limitations of these studies were the exclusion of smokers with major concomitant illness and previous use of bupropion, both of which limit applicability to many smokers likely to seek treatment. It should be noted that all participants received smoking cessation counseling, which has been previously shown to positively influence quit rates.

- Tonstad S, et al. for the Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation. A randomized controlled trial. *JAMA* 2006; 296: 64-71.

This trial, reported in the same issue of *JAMA* as the two studies summarized above, was a 52-week, multicentre, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of an additional 12 weeks of treatment with varenicline in smokers who achieved complete abstinence following an initial 12-week open-label varenicline treatment. Participants who had successfully achieved complete abstinence following 12 weeks of open-label treatment with varenicline 1 mg twice daily were randomly assigned to receive either varenicline ($n = 603$) or placebo ($n = 603$) for 12 additional weeks. A 28-week non-treatment period followed for a total of 52 weeks in the study. All participants received smoking cessation counseling in accordance with the U.S. Public Health Service guidelines. The primary efficacy endpoint was the carbon monoxide confirmed (CO-confirmed) continuous abstinence rate from weeks 13 through 24. A secondary endpoint was the continuous abstinence rate from week 13 through 52. The Minnesota Nicotine Withdrawal Scale (MNWS) was self-administered after the end of treatment with varenicline to assess the experience of craving and withdrawal. In this study, smokers who successfully abstained for an initial 12 weeks of varenicline treatment experienced a significantly reduced rate of relapse when taking an additional 12 weeks of varenicline 1 mg twice daily (continuous abstinence rate for varenicline vs. placebo for weeks 13 to 24: 70.5% vs. 49.6%; odds ratio, 2.48; 95% CI, 1.95 – 3.16; $p < 0.001$). There was a smaller but still significant difference 6 months later (weeks 13 to 52: 43.6% vs. 36.9%; odds ratio, 1.34; 95% CI, 1.06 – 1.69; $p = 0.02$). The median time to first lapse (post-randomization to double-blind treatment) was significantly longer for those receiving varenicline than placebo (198 days [95% CI, 159-260] vs. 87 days [95% CI, 58-143], respectively; log-rank $p < 0.001$). At weeks 13 and 25, using the MNWS, withdrawal symptoms tended on average to be low. Varenicline was well tolerated. The incidence of adverse events (mostly mild to moderate) during the double-blind treatment phase was similar for varenicline and placebo. The authors concluded that extended use of varenicline helps recent ex-smokers maintain their abstinence and prevent relapse. As well, the authors noted that at the end of this trial, as in all existing literature on smoking cessation with 1-year of follow-up, more than 50% of participants in each group returned to smoking; study of longer medication treatment periods may be of value.

- Oncken C, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med* 2006; 166: 1571-77.

This was a multicentre, double-blind, placebo-controlled randomized study of healthy smokers designed to evaluate the efficacy, safety, and tolerability of 4 dose regimens of varenicline for 12 weeks, with a 40 week non-treatment follow-up period. Eligible subjects were randomly assigned to 1 of 5 groups: 0.5 mg once daily for 12 weeks ($n = 129$); 0.5 mg twice daily titrated (0.5 mg once daily x 7 days then 0.5 mg twice daily x 11 weeks; $n = 130$); 1 mg twice daily for 12 weeks ($n = 129$); 1 mg twice daily titrated (0.5 mg x 3 days, then 0.5 mg twice daily x 4 days, then 1 mg twice daily for 11 weeks, $n = 130$) or placebo ($n = 129$). The primary efficacy measures were carbon-monoxide-confirmed 4-week continuous quit rate for weeks 4 to 7, weeks 9 through 12, and continuous abstinence rates for weeks 9 through 52. In all dose groups, varenicline quit rates were significantly higher than placebo. Varenicline was found to significantly reduce the urge to smoke and reduced the reinforcing effects of smoking compared to placebo. The most common side effect was nausea, which appeared to be dose-related. Titration appeared to reduce the overall incidence of nausea. The authors concluded that varenicline significantly improved short- and long-term abstinence rates compared to placebo.

Summary

As shown in these clinical trials, varenicline is an effective smoking cessation aid with a unique mechanism of action. It offers clinicians an additional option to assist motivated smokers to quit smoking. However, it is not a cure-all. It was moderately more effective than bupropion in clinical trials; however, there was greater weight gain with varenicline in some studies. Abnormal dreams were also more common in the varenicline group. Dropout rates were similar to those in other smoking cessation trials. Limitations of the trials included the use of intention-to-treat analysis, which may have introduced bias in favour of varenicline, and strict exclusion and inclusion criteria (as is the case in most clinical trials), which may limit applicability to the general population. Further study is needed to determine if smokers who have previously been treated with bupropion may benefit, and whether longer-term treatment with varenicline would provide additional benefit. The efficacy of varenicline compared to nicotine replacement therapies is unknown. Studies of combination therapy with other smoking cessation aids would also be desirable. Despite its limitations, the additional treatment option of varenicline may benefit even a small proportion of smokers, which should lead to greater health benefit for the smokers, those close to them, and society in general.

Table 1: Cost comparison of smoking cessation aids available in Canada

Drug and strengths	Usual dose	Approx. cost/month*
Bupropion SR 150 mg tablets	300 mg/day in divided doses	\$34 (generic)
Bupropion SR (Zyban®) 150 mg tablets	150 mg twice daily	\$53
Bupropion XL (Wellbutrin® XL) 300 mg tablets	300 mg once daily	\$33
Nicotine oral inhaler (Nicotrol®) 10 mg cartridge	6 – 16 cartridges/day	\$145
Nicotine gum (Nicorette®) 2 and 4 mg/piece	3 – 24 pieces	\$95
Nicotine transdermal (Nicoderm®) 7, 14, or 21 mg/patch	1 patch/day	\$104
Varenicline (Champix™) 0.5, 1 mg tablets	1 – 2 mg/day in divided doses	\$95

* Adapted from *The Medical Letter* 2006; 48(1241/1242): 67.

Telbivudine (Sebivo[®] - Novartis)

- antiviral agent

Pharmacology

- a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase
- phosphorylated by cellular kinases to the active triphosphate form

Indications

- for the treatment of chronic hepatitis B in adults 16 years and older with compensated liver disease with evidence of viral replication and active liver inflammation
- this indication is based on a single 52-week, phase 3 trial in nucleoside-naïve patients with HBeAg positive or HBeAg negative chronic HBV infection with compensated liver disease; the primary endpoint was based on virological, serological and biochemical data; there are no available data on telbivudine in patients harbouring lamivudine-resistant virus nor in patients with decompensated chronic hepatitis B, co-infected patients (with HIV or hepatitis C or D), or in liver transplant patients

Pharmacokinetics

Absorption	Peak plasma concentrations in 1-4 h (median 2 h)
Effect of food on absorption	No effect; may be taken with or without food
Effective half-life	~ 15 h (steady-state in 5-7 days)
Plasma protein binding	Low (3.3%)
Metabolism	No metabolites detected; not a substrate, inhibitor or inducer of CYP450 enzyme system
Excretion	Primarily via urinary excretion of unchanged drug
Pediatrics/geriatrics	No pharmacokinetic studies
Hepatic impairment	No significant effect; no dose adjustment needed
Renal impairment	Adjustment of dose interval recommended if CrCl < 50 mL/min, including patients on hemodialysis (see Dosage and Administration section)
Hemodialysis	Reduces systemic telbivudine exposure by ~ 23%; dose should be administered after hemodialysis
CAPD	No studies

Warnings and Precautions

- **severe acute exacerbations of hepatitis B** – reported in patients who have discontinued anti-hepatitis B therapy; hepatic function must be monitored closely, with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy; if appropriate, re-initiation of hepatitis B therapy may be warranted
- **lactic acidosis and severe hepatomegaly with steatosis, including fatal cases** have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals
- **musculoskeletal** – cases of **myopathy** [persistent unexplained muscle aches and/or muscle weakness in conjunction with increases in creatine kinase (CK) values] have been reported with telbivudine several weeks to months after starting therapy (also reported with some other drugs in this class); patients should be advised to report promptly unexplained muscle aches, pain, tenderness or weakness; telbivudine therapy should be interrupted if myopathy is suspected, and discontinued if myopathy is diagnosed; it is not known if risk of myopathy is increased with

- concurrent administration of other drugs associated with myopathy (e.g., corticosteroids, HMG CoA reductase inhibitors, etc.)
- **lamivudine resistant patients** – available evidence does not support use of telbivudine in patients with established lamivudine-resistant hepatitis B infection; there have been no clinical studies in these patients
 - **adefovir resistant patients** – there are no adequate and well controlled studies of telbivudine treatment in patients with established adefovir-resistant hepatitis B infection
 - **liver transplant recipients** – safety and efficacy unknown; if telbivudine treatment is considered necessary in a liver transplant recipient who is receiving an immunosuppressant that may affect renal function (e.g., cyclosporine, tacrolimus), renal function must be monitored both before and during treatment with telbivudine
 - **cardiovascular** – no evidence of cardiotoxicity; no effect observed on QT intervals (after multiple daily doses up to 1800 mg)
 - **co-infected patients** (e.g., with HIV, HCV or HDV) – not investigated
 - **pregnancy** – no adequate and well-controlled studies; should be used during pregnancy only if benefit to mother outweighs potential risk to fetus; to monitor fetal outcomes in pregnant women exposed to telbivudine, healthcare providers are encouraged to register such patients in the **AntiRetroviral Pregnancy Registry** by calling 1-800-258-4263
 - **labour and delivery** – no data on effect of telbivudine on transmission of HBV from mother to infant; therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV infection
 - **lactation** – not known if drug is excreted in human milk; manufacturer advises against breastfeeding while taking telbivudine
 - **pediatrics** – safety and effectiveness in patients below age 16 have not been established
 - **geriatrics** – insufficient numbers of patients ≥ 65 years of age in clinical trials; caution should be exercised and renal function monitored

Drug Interactions

- **general** – since telbivudine is eliminated primarily by renal excretion, co-administration with substances that affect renal function may affect plasma concentrations of telbivudine and/or the co-administered substance
- potential for CYP 450-mediated interactions is low, since telbivudine is not an inhibitor or inducer of CYP isoenzymes and is not metabolized by CYP 450
- **lamivudine** – no significant interactions with a subtherapeutic dose of telbivudine (200 mg) in combination with lamivudine (100 mg) in healthy subjects
- **adefovir dipivoxil** – no significant interaction in healthy subjects (telbivudine 600 mg and adefovir 10 mg)
- **peginterferon alfa-2a** – no significant effect of single 180 mcg SC dose of peginterferon on steady-state pharmacokinetics of telbivudine
- **cyclosporine A** – steady-state pharmacokinetics of both drugs appeared to be unaltered following multiple dose administration of telbivudine and cyclosporine (4 mg/kg/day in two divided doses) in healthy subjects; no information on higher doses of cyclosporine
- **other renally eliminated drugs/drugs affecting renal function** – no information on co-administration

Adverse Effects

- generally well tolerated; most adverse effects are mild to moderate in severity
- most frequently reported: upper respiratory tract infection (12%), nasopharyngitis (10%), fatigue (10%), headache (10%), dizziness (4%) and myalgia (3%)

- **lab abnormalities** – most commonly reported: creatine kinase (CK) elevation; usually asymptomatic; may decrease while still on treatment; some CK elevations were associated with myopathy and muscle weakness
- refer to Product Monograph for other reported adverse reactions

Dosage and Administration

- recommended dose is 600 mg orally once daily, taken with or without food
- optimal duration of treatment has not been established
- **hepatic impairment** – no dose adjustment needed
- **elderly** – insufficient data to support a specific dose recommendation for patients over age 65
- **impaired renal function** – no dose adjustment is necessary in patients with CrCl \geq 50 mL/min; adjust dose interval in patients with CrCl < 50 mL/min including those with end stage renal disease (ESRD) on hemodialysis, as follows:

Creatinine clearance (mL/min)	Recommended dose
\geq 50	600 mg once daily
30 – 49	600 mg once every 48 hours
< 30 (not requiring dialysis)	600 mg once every 72 hours
ESRD	600 mg once every 96 hours (after dialysis)

Availability and Cost

- supplied as film-coated tablets containing telbivudine 600 mg - \$476.00/28 tablets
- refer to Product Monograph for list of excipients

Place in Therapy

Chronic hepatitis B virus (HBV) infection is usually treated with weekly injections of pegylated interferon alfa, or once-daily orally with a nucleoside analogue such as lamivudine or entecavir, or the nucleotide analog, adefovir. Although the oral preparations are much better tolerated than interferon, resistance has been a problem, particularly with lamivudine therapy. Adefovir is active against lamivudine-resistant strains, and is now commonly used in combination with lamivudine, if resistance is present. Entecavir is much more active than lamivudine against HBV in treatment-naïve patients, but less active against lamivudine-resistant strains. Telbivudine, another nucleoside analogue, has been approved in Canada for the treatment of patients \geq 16 years of age with active chronic HBV infection. Unlike lamivudine and adefovir, telbivudine has no known activity against HIV or other viruses. See Table 1 below for a cost comparison of oral drugs available in Canada for chronic HBV infection.

The approval of telbivudine was based on an unpublished, randomized, double-blind trial (007 GLOBE Study; summarized in Product Monograph), which compared telbivudine 600 mg once daily with lamivudine 100 mg once daily in 1367 nucleoside-naïve patients with active chronic HBV. The primary endpoint was therapeutic response (a composite of HBV DNA suppression, and either loss of serum HBeAg or ALT normalization) at week 52. In HBeAg-positive patients, telbivudine was superior to lamivudine (75.3% vs. 67% responders; $p = 0.0047$). In HBeAg-negative patients, telbivudine was non-inferior to lamivudine (75.2% vs. 77.2% responders; $p = 0.0047$).

A one-year, phase II trial compared telbivudine monotherapy, lamivudine monotherapy and telbivudine/lamivudine combination therapy in 104 nucleoside-naïve HBeAg-positive patients with compensated liver disease (Lai C-L, et al, and the Telbivudine Phase II Investigator Group. *Gastroenterology* 2005; 129: 528-36). Telbivudine monotherapy was superior to lamivudine

monotherapy in clearing HBV DNA (61% vs. 32%) and normalizing ALT levels (86% vs. 63%). However, the difference between the two drugs in HBeAg seroconversions (31% vs. 22%) was not statistically significant. The combination of both drugs was not more effective than telbivudine monotherapy.

In a randomized, comparative trial in 135 HBeAg-positive adults (published in abstract form only), mean HBV DNA reduction was significantly greater with telbivudine (600 mg/d for 24 weeks) than with adefovir (10 mg/d for 24 weeks). After 24 weeks, patients on adefovir were randomized to either continue treatment or switch to telbivudine for another 28 weeks. At 52 weeks, patients continuing or switched to telbivudine had greater reductions in HBV DNA (but not statistically significant).

In summary, telbivudine appears to be at least as effective as lamivudine in treatment-naïve patients with HBV infection. However, its use in treatment-experienced patients will be limited by cross-resistance with lamivudine. Efficacy compared to entecavir remains to be established. Telbivudine appears to suppress HBV DNA more than adefovir during the first year of treatment but resistance emerges more frequently with telbivudine. After two years of treatment, 21.6% of HBeAg-positive and 8.6% of HBeAg-negative telbivudine-treated patients developed resistance mutations. Telbivudine is generally well tolerated and has minimal potential for drug interactions. Creatine kinase elevations have been more common in patients taking telbivudine than in those taking lamivudine (72% vs. 42%); symptomatic myopathy has been reported with telbivudine. As with other drugs for HBV infection, severe disease exacerbations can develop when telbivudine is discontinued.

Table 1: Oral drugs for chronic HBV infection available in Canada

Drug	Recommended dosage (normal renal function)	Approx. cost/30 days*
Adefovir (Hepsera®)	10 mg once daily	\$696.00
Entecavir (Baraclude®)	0.5 mg once daily	\$696.00
Lamivudine (Heptovir®)	100 mg once daily	\$139.00
Telbivudine (Sebivo™)	600 mg once daily	\$510.00

*Cost based on manufacturer's listed price/McKesson Canada; prices may vary based on individual institutional contracts, etc.

NEW PRODUCTS AND DOSAGE FORMS

Testosterone Gel (Testim® - Auxilium Pharmaceuticals via Paladin Labs)

- indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
- safety and efficacy for use in children < 18 years of age
- designed to provide consistent transdermal absorption of testosterone over 24 hours after a single dose
- **adverse effects** – most commonly reported: application site erythema (4.1%), increased PSA (4.3%), increased hematocrit (3.9%) and increased hemoglobin concentration (3.7%)
- **dosage and administration** – recommended starting dose is 5 g of gel (one tube) containing 50 mg of testosterone applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders or upper arms; should NOT be applied to genitals or to the abdomen

- morning serum testosterone levels should be measured approximately 7-14 days after initiation of therapy to ensure proper serum testosterone levels are achieved; if serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved, the dose may be increased to 10 g (two tubes); the duration of treatment and frequency of subsequent testosterone measurements should be determined by the physician
- maximum recommended dose is 100 mg/day
- upon opening the tube, the entire contents should be squeezed into the palm of the hand and immediately applied to shoulders and/or upper arms; application sites should be allowed to dry for a few minutes prior to dressing; hands should be washed thoroughly with soap and water after application
- in order to maintain serum testosterone levels in the normal range, the sites of application should not be washed for at least two hours after application
- **supplied as** 5 g tubes containing testosterone 1% in a clear to translucent hydroalcoholic topical gel

PRODUCT NEWS

Rosiglitazone Maleate (Avandia[®] - GlaxoSmithKline)

- **important safety information – cardiac safety** - an article published recently in the *New England Journal of Medicine* (May 21, 2007) has generated significant public attention – based on a meta-analysis of 42 clinical studies, a statistically significant increased risk of myocardial infarction (OR 1.43, CI 1.10 – 1.98, $p = 0.03$) and statistically non-significant increase in the risk of cardiovascular death (OR 1.64, CI 0.98 – 2.74, $p = 0.06$) was associated with use of rosiglitazone in comparison with placebo or other anti-diabetic therapies
- conclusions reached from this meta-analysis require confirmation; analysis of all currently available data is ongoing
- some of the studies highlighted in the *NEJM* article included patients using rosiglitazone in combination with metformin AND a sulfonylurea (not approved in Canada) or rosiglitazone plus insulin (also not approved in Canada)
- when considering treatment decisions, physicians are advised to carefully weigh the overall benefit versus risk of rosiglitazone
- patients should be advised not to stop taking rosiglitazone without first consulting their healthcare provider
- note: rosiglitazone is contraindicated in patients with NYHA Class III and IV cardiac status, and should be used with caution in patients with Class I and II cardiac status; all patients should be monitored for signs and symptoms of fluid retention, edema, and rapid weight gain
- the dose of rosiglitazone used in combination with a sulfonylurea should not exceed 4 mg daily

Pioglitazone Hydrochloride (Actos[®] - Eli Lilly)

- **important safety information – increased risk of fractures in female patients** who have received long-term treatment with pioglitazone for type 2 diabetes mellitus
- manufacturer has recently received an analysis of the pioglitazone trial database with a special focus on fractures reported as adverse events – 19 randomized, controlled, double-blind clinical trials comparing patients treated with pioglitazone to a non-thiazolidinedione (non-TZD) comparator (placebo, metformin, or sulfonylureas) were reviewed
- **note:** none of the studies was designed to study effects of pioglitazone on bones

- findings from analysis of 19 trials showed that significantly more pioglitazone-treated female patients experienced at least one event of bone fracture than patients treated with non-TZD comparator drugs (2.6% vs. 1.7%, respectively)
- fracture incidence calculated was 1.9 fractures per 100 patient-years in the pioglitazone group and 1.1 fractures per 100 patient years in the comparator group; therefore, the observed excess risk of fractures for women on pioglitazone is 0.8 fractures per 100 patient-years of use
- the majority of fractures observed in female patients on pioglitazone were in the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula and tibia); these fractures are in different sites from those typically associated with postmenopausal osteoporosis (e.g., hip, spine)
- there was no increased risk of fracture identified in men
- risk of fracture should be carefully considered in the care of female patients with type 2 diabetes mellitus who are currently being treated with pioglitazone, or when initiation of treatment is being considered; bone health should be assessed and maintained according to current standards of care

Alglucosidase alfa (Myozyme[®] - Genzyme)

- **reports of black particles after reconstitution** – the manufacturer has received isolated complaints of black gelatinous particles after reconstitution of 50 mg vials of alglucosidase alfa; following an investigation, it was discovered that when certain types of needles are used to penetrate the rubber stopper on the vials, black gelatinous particles may appear in the product, on the stopper or on the needle
- the black particles were found to be composed of gel-like silicone (silicone is commonly used as a lubricant on needles) with inclusions of microscopic stainless steel particles, both of which appear to have come from the needle; this gelatinous material has not been observed in products or on stoppers that have not been penetrated by a needle for reconstitution; based on investigations to date, the formation of the black particles is the result of insertion of the needle through the stopper during vial reconstitution and is not related to the product
- this phenomenon has the potential to occur with any stainless steel needle; if black gel-like particles are noticed after reconstitution, consider using a plastic needle or a plastic spike for reconstitution, or an alternative brand of needle; however, if an alternative is not available, reconstituted solution should be visually examined for the presence of any foreign particles
- it is also recommended that the same needle be used once, as multiple uses of the same needle can lead to stopper coring and other problems
- **do not use a product with black particles after reconstitution**
- an **inline low-protein-binding 0.2-micron filter** should be used to filter the reconstituted product during administration

Levonorgestrel (Plan B[®] - Paladin Labs)

- **new dosing regimen** – one-step regimen – two tablets (each containing levonorgestrel 0.75 mg) can be taken together within 72 hours (3 days) following unprotected intercourse or a contraceptive accident
- this new one-step dosing will allow women to take both tablets at the same time, thereby increasing ease of use, without any increase in side effects or loss of efficacy

PUBLICATIONS OF INTEREST

1. Wilson W, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; (downloaded May 8, 2007; www.circulationaha.org).
2. Campbell CL, et al. Aspirin dose for the prevention of cardiovascular disease. A systematic review. *JAMA* 2007; 297:2018-24.
3. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review). *Neurology* 2007; 69 (published ahead of print on May 23, 2007; www.neurology.org)
4. Francis CW. Prophylaxis for thromboembolism in hospitalized medical patients. *N Engl J Med* 2007; 356: 1438-44.
5. Chen LH. Controversies and misconceptions in malaria chemoprophylaxis for travelers. *JAMA* 2007; 297: 2251-63.
6. Khosla S, et al. Osteopenia. *N Engl J Med* 2007; 356:2293-300.
7. Ellison DH, et al. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; 356: 2064-72.
8. Mannucci PM, et al. Prevention and treatment of major blood loss. *N Engl J Med* 2007; 356: 2301-11.

New drug reviews in upcoming issues of *Current Drug Topics*:

Triptorelin Pamoate (Trelstar™ - Paladin Laboratories)
Lanthanum Carbonate (Fosrenol® - Shire BioChem)
Interferon alfacon-1 (Infergen® - Valeant Canada)
Dasatinib (Sprycel™ - Bristol-Myers Squibb)
Acamprosate Calcium (Campral® - Prempharm)
Lanreotide (Somatuline® Autogel® - Tercica via McKesson)
Posaconazole (Spriafil™ - Schering-Plough)

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