



PharmaNote®

VOLUME 23, ISSUE 6

MARCH 2008

NEW DRUGS APPROVED IN 2007

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Discovering and developing safe and effective new medications is a time-consuming, difficult, and expensive process. On average, it takes 8.5 years to develop a new drug. Starting from early laboratory and animal testing to general public application, the drug review process has 12 separate steps. Included within this process are the preclinical (animal) testing, phase 1 studies (20 to 80 people), phase 2 studies (a few dozen to 300 people), and phase 3 studies (several hundred to about 3,000 people).¹

In 2007, 18 new drugs made their debut, including 16 new molecular entities and 2 new derivatives. Also, there were 30 new drugs approved with significantly new dosage forms from previously approved drugs. A summary of drug names, pharmacokinetic and pharmacodynamic properties, dose and administration, estimated cost, and approval dates are listed in **Table 1**.

This article will discuss the most significant new molecular entities, new derivatives, and new formulations in alphabetical order based on brand names.

Retapamulin (Altabax®) is a topical antibiotic ointment approved for the treatment of impetigo due to methicillin-susceptible *S. aureus* or *S. pyogenes* in patients 9 months of age or older. It inhibits normal bacterial protein biosynthesis by binding to protein

L3 on the ribosomal 50s subunit. The most common adverse reaction associated with the topical application of retapamulin is skin irritation (1.4%).^{2,3}

Parish et al. compared topical retapamulin ointment twice daily to oral cephalexin 500 mg twice daily in 546 patients with secondarily infected dermatitis.⁴ The investigators found that 85.9% of retapamulin-treated patients and 89.7% of patients who received oral cephalexin had similar clinical success. The authors concluded that retapamulin ointment administered twice daily for 5 days was at least as effective as 10 days of twice daily oral cephalexin for the treatment of secondarily infected traumatic skin lesions.

Retapamulin is the first agent in a new pleuromutilin class. It has no cross-resistance with other antibiotics such as beta-lactams, macrolides, fusidic acid and mupirocin. It may be an option in patients where 10 days of oral cephalexin or topical mupirocin are difficult to complete, but it should be avoided in patients with more extensive impetigo and those with systemic symptoms.

Nebivolol (Bystolic®) is a third generation selective β_1 -blocker approved for the treatment of hypertension (HTN). Mechanisms of action include decreased heart rate, decreased myocardial contrac-

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tility, diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, and suppression of renin activity. In addition to the β -blocking activity, nebivolol also modulates the endogenous production of nitric oxide resulting in peripheral vasodilation. The most common side effects of nebivolol include headache (6-9%), dizziness (2-4%), somnolence, and nausea (1-3%).^{2,3}

Van Neuten et al. compared nebivolol 5 mg and atenolol 50 mg to placebo in a randomized, double-blind, parallel-group trial in 364 patients with established HTN and found both active drugs caused significant and similar reduction in systolic and diastolic pressures without orthostatic effect.⁵ Another multicenter, randomized, double-blind trial also conducted by Van Neuten studied nebivolol 5 mg once daily compared to enalapril 10 mg once daily in the treatment of essential HTN.⁶ Nebivolol 5 mg was superior to 10 mg enalapril in changes of sitting diastolic pressure at trough level from baseline. Grassi et al. evaluated nebivolol 5 mg versus atenolol 100 mg.⁷ HCTZ 12.5 mg was added in patients with blood pressure higher than 140/90 mm Hg. The authors concluded that both agents significantly decreased sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline.

Compared to other β -blockers, nebivolol has very high β -1 specificity, favorable side effect profile, and long duration of action. Nebivolol is a once daily medication that can be used alone or in combination with other hypertension treatments.

Doripenem (Doribax[®]) is a broad-spectrum, intravenous, carbapenem antimicrobial agent. It inhibits the third and final stage of bacterial cell wall synthesis and facilitates bacterial cell lyses by inactivating essential penicillin-binding proteins. The most common side effects include headache (4-16%), diarrhea (6-11%), phlebitis (4-8%), and rash (4-8%).^{2,3}

Solomkin et al. compared doripenem (n=486) to meropenem in a randomized trial with an option for oral step-down therapy with amoxicillin/clavulanate in the treatment of complicated intra-abdominal infections (cIAI).⁸ The authors concluded that doripenem was generally safe and non-inferior to meropenem in cIAI. Naber and colleagues evaluated IV doripenem versus IV levofloxacin in the treatment of complicated urinary tract infections (cUTI) in DORI-5 trial.⁹ The authors concluded that doripenem was non-inferior to levofloxacin in cUTI and the use of doripenem was generally well toler-

ated. Rea-Neto et al. found doripenem was therapeutically non-inferior to piperacillin/tazobactam in the treatment of hospitalized patients with nosocomial pneumonia.¹⁰

The efficacy and coverage of doripenem are similar to meropenem with the possible exception of enhanced pseudomonal coverage based on *in vitro* activity (1 MIC dilution lower). Due to potential resistance, doripenem should be reserved for the treatment of complicated urinary tract infections, complicated intra-abdominal infections, and in multi-drug resistant infection where bacteria are more susceptible to doripenem.

Sapropterin (Kuvan[®]) is an orphan drug approved to slow the effects of a rare genetic, metabolic disorder in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4) responsive phenylketonuria (PKU). It works by activating residual phenylalanine hydroxylase (PAH) enzymes and reducing blood phenylalanine (Phe) levels. The most common adverse events are headache, diarrhea, abdominal pain, upper respiratory tract infection, and throat pain.^{2,3}

Burton et al. concluded that sapropterin was well tolerated and reduced blood Phe levels across all PKU phenotypes based on an 8-day course of sapropterin (10 mg/kg per day) in 490 patients with PKU.¹¹ Levy et al. conducted a multicentre, randomized, double-blind, placebo-controlled trial in 89 patients with PKU.¹² The mean blood Phe in control group fluctuated only slightly from baseline over 6 weeks; whereas in the sapropterin group, the mean blood phenylalanine concentration fell from 843 mmol/l to 619.9 mmol/l after one week of treatment with sapropterin (10 mg/kg/day); the reduced concentration remained throughout the 6 weeks of sapropterin treatment.

With the combination of a phenylalanine-restricted diet, sapropterin is an effective therapy in selected patients with HPA and mild-to-moderate PKU who responded to a BH4 loading test. Patients being treated with sapropterin must have their blood Phe levels monitored frequently.

Ambriasantan (Letairis[®]) is an endothelin receptor antagonist (ERA) indicated for the once daily oral treatment of pulmonary arterial hypertension (PAH) in patients with WHO class II or III symptoms. It blocks vasoconstriction and cell proliferation effects of endothelin-A in vascular smooth muscle and endothelium, which in turn relaxes the blood

vessels and reduces right atrial pressure in patients with PAH. The most common side effects are peripheral edema (17%), headache (15%), and decreased hemoglobin (7-10%).^{2,3}

Oudiz and colleagues conducted a 12-week study (ARIES-1) which compared daily doses of 5 mg and 10 mg ambrisentan to placebo in 202 patients with PAH.¹³ ARIES-2, investigated by Olschewski et al, was conducted in 192 patients with PAH for 12 weeks.¹⁴ The study compared daily doses of 2.5 mg and 5 mg ambrisentan to placebo. Both studies showed that treatment with ambrisentan resulted in a significant improvement in 6-minute walking distance for each dose and the dose-response relationship became apparent after 12 weeks of treatment. Moreover, there was a significant delay in the time to clinical worsening for patients receiving ambrisentan compared to placebo. The long-term follow-up of patients who were treated with ambrisentan in the two pivotal studies and their open-label extension (N=383) showed that 95% were still alive at one year and 94% were still receiving ambrisentan monotherapy.

Compared to bosentan, ambrisentan is well tolerated with a lower incidence and severity of liver function test abnormality. However, because of the possibility of liver injury and birth defects, ambrisentan is available only through the Letairis[®] Education Access Program (LEAP) by calling 1-866-664-LEAP (5327) or by logging on to www.letairis.com.

Rotigotine (Neupro[®]) is the first transdermal non-ergolinic dopamine agonist, indicated once-daily for the treatment of early-stage Parkinson's disease (PD). The exact mechanism is unknown, but it may stimulate D2 receptors within the caudate-putamen in the brain.^{2,3}

Watts et al. evaluated the efficacy of rotigotine in a randomized, double-blind, multinational study on 277 early-stage idiopathic PD patients. They found a statistically significant difference in Unified Parkinson's Disease Rating Scale (UPDRS) scores between the placebo and rotigotine.¹⁵ The Parkinson Study Group conducted an international, randomized, double-blind trial with 242 early-stage PD and found the minimum effective dose was 4-6 mg/24 hours.¹⁶ Poewe and colleagues compared the efficacy of transdermal rotigotine to pramipexole (Mirapex[®]) in levodopa-treated advanced PD patients (N=506) in a randomized, double-blind, controlled trial.¹⁷ Rotigotine was non-inferior to

pramipexole in change of absolute off-time from baseline.

Compared to other dopamine agonists, rotigotine offers a valuable therapeutic alternative as monotherapy for early-stage PD patients and possible combination therapy with levodopa/carbidopa in advanced PD patients by providing constant blood levels over a 24-hour period.

Aliskiren (Tekturna[®]) is a direct renin inhibitor indicated for the once-daily, oral treatment of HTN. It binds to a pocket in the renin molecule, blocking angiotensinogen cleavage. Aliskiren appears to be well tolerated. Some side effects associated with aliskiren include rash (1%) and cough (1.1%).^{2,3}

Mitchell et al. demonstrated a statistically significant change from baseline in 24-hour mean ambulatory DBP and SBP with aliskiren 150 mg, 300 mg, or 600 mg compared to placebo in a randomized trial with 2776 patients \geq 18 years of age with mild-to-moderate HTN.¹⁸ Villamil et al. concluded that aliskiren monotherapy was superior to placebo in reducing mean sitting diastolic blood pressure (MSDBP) and mean sitting systolic blood pressure (MSSBP). In combination with HCTZ, aliskiren provided significant additional blood pressure reduction.¹⁹ Pool et al. showed that coadministration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone, comparable in magnitude to the effect of valsartan/hydrochlorothiazide.²⁰ O'Brien et al. also concluded that the addition of 75 or 150 mg of aliskiren to 150 mg of irbesartan alone, for 3 weeks, resulted in significantly lower nighttime pressures compared with irbesartan monotherapy.²¹

Based on these published trials, aliskiren appears to be effective for the treatment of hypertension.

Fluticasone furoate (Veramyst[®]) is a newly approved corticosteroid nasal spray for seasonal and perennial allergic rhinitis. Compared to fluticasone propionate (Flonase[®]), fluticasone furoate is indicated for patients as young as 2 years old, has once-daily dosing, is scent-free, and delivers a consistent dose in a gentle-fine mist. However, fluticasone furoate costs more than generic fluticasone propionate, and no evidence supports fluticasone furoate is more efficacious than fluticasone propionate.^{2,3}

Lisdexamfetamine (Vyvanse[®]) is an amphetamine derivative prodrug used for treating attention-

deficit/hyperactivity disorder (ADHD). It is rapidly absorbed and converted to dextroamphetamine by intestinal or first-pass liver metabolism. The exact mechanism of dextroamphetamine is unknown, but it may block the reuptake of norepinephrine and dopamine. The most common side effects of lisdexamfetamine are loss of appetite (39%), insomnia (19%), and headache (12%).^{2,3}

In a randomized, double-blind, placebo- and active-controlled crossover study comparing the efficacy and safety of lisdexamfetamine with placebo in 52 children ages 6 to 12 years with ADHD, Lopez et al. found 74% of lisdexamfetamine patients and 72% of mixed amphetamine salts extended-release patients "very much improved" or "much improved" using the Clinical Global Impressions score.²² Both drugs showed similar improvement and adverse events versus placebo. In a multi-center, placebo-controlled trial, Biederman et al. assessed the efficacy and tolerability of lisdexamfetamine in 290 school-aged children with ADHD.²³ The treatment with lisdexamfetamine 30 to 70 mg for 4 weeks resulted in improvement in ADHD Rating Scales and Conner's Parent Rating Scale.

Lisdexamfetamine is a Schedule II controlled

substance. There's no evidence that lisdexamfetamine is more effective or causes fewer side effects than Adderall XR[®].

Levocetirizine (Xyzal[®]) is an oral antihistamine approved for the relief of symptoms associated with idiopathic urticaria and seasonal and perennial allergic rhinitis in adults and children age 6 years and older. Levocetirizine, the R-enantiomer of cetirizine, is a selective piperazine H₁ – receptor antagonist. Clinical data has not demonstrated that levocetirizine is more efficacious than other antihistamines. Levocetirizine may be helpful for patients whose allergic symptoms are not controlled by other antihistamines.^{2,3}

References

1. The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective <http://www.fda.gov/>
2. Clinical pharmacology. Gold Standard Inc. 2008.
3. Micromedex Healthcare Series.
4. Parish LC, Jorizzo JL, Breton JJ, et al. Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis. *J Am Acad Dermatol* 2006;55:1003-13.
5. Van Neuten L, Taylor FR, and Robertson JIS. Ne-

Table 1. Summary of the most significant new molecular entities, new derivatives, and new formulations^{2,3}

Brand	Generic	PK ^a /PD ^b	Dose/Administration	Estimated Cost ^g	Approval Date
<i>New molecular entities</i>					
Altabax [®]	retapamulin	A ^c : increased when applied to abraded skin D ^d : 94% protein binding M ^e : hepatic via CYP 3A4 No significant effect on QT interval	Apply a thin layer topically twice daily for 5 days	5 g tube: \$41.02 10 g tube: \$69.52 15 g tube: \$68.60	4/07
Bystolic [®]	nebivolol	A ^c : 12% bioavailability in extensive metabolizers (EMs) to 96% bioavailability in poor metabolizers (PMs), food has insignificant effect D ^d : 98% protein binding M ^e : hepatic via direct glucuronidation and N-dealkylation and oxidation by CYP2D6 E ^f : 38% in urine and 44% in feces (EMs), 67% in urine and 13% in feces (PMs)	HTN: 5 mg orally daily, titrate at 2-week intervals to 40 mg daily Heart failure: 1.25 mg orally daily titrated to a maximum of 10 mg daily (non-FDA approved indication)	2.5 mg (30- day): \$66.59 5 mg (30- day): \$58.59 10 mg (30- day): \$58.59	12/07
Doribax [®]	doripenem	D ^d : 8.1% protein binding M ^e : non-hepatic, 15% converted to inactive metabolites in kidney E ^f : 70% unchanged drug in kidney	IV, 500 mg Q 8 hours, administer over 1 hour	AWP ^h of 500 mg vial: \$47.91	10/07
Kuvan [®]	sapropterin	A ^c : Food increases AUC by 87% and C _{max} by 84% t _{1/2} is 6.7 hours	Oral, 10 mg/kg/day to 20 mg/kg/day	For 70kg, 700mg (30-day): \$7,617.50 and 1400mg (30-day): \$15,200 ⁱ	12/07

Table 1 (continued).

Brand	Generic	PK ^a /PD ^b	Dose/Administration	Estimated Cost ^g	Approval Date
<i>New molecular entities</i>					
Letairis [®]	ambrisentan	A ^c : unknown bioavailability, food has no effect D ^d : 99% protein binding M ^e : hepatic through CYP3A4, CYP2C19, UGT-1A9S, 2B7S E ^f : Non-renal: predominant No significant QT prolongation	Oral with or without food Initial: 5 mg daily; if tolerated, may increase to maximum of 10 mg daily	5 mg (30-day): \$4829.99 10 mg (30-day): \$4829.99	6/07
Neupro [®]	rotigotine	A ^c : food has no effects D ^d : 89.5% protein binding M ^e : N-dealkylation and conjugation at liver E ^f : 70% renal	Transdermal, 2 mg/24hours to 6 mg/24 hours	2 mg/24 hour (30-day): \$120.89 4-6 mg/24 hour (30-day): \$369.90	5/07
Tekurna [®]	aliskiren	A ^c : poorly absorbed, decreased with high fat meal D ^d : protein binding 49.5% M ^e : in vitro via CYP3A4 E ^f : 91% eliminated unchanged through feces	Take consistently with or without food Initial 150 mg/day orally, may increase to 300 mg/day	150 mg (30-day): \$69.99 300 mg (30-day): \$87.99	3/07
Vyvanse [®]	lisdexamfetamine	A ^c : fast absorption D ^d : CNS, plasma, and breast milk M ^e : intestinal/hepatic: first-pass metabolism E ^f : Renal 96%	All patients > 6 yrs start at 30 mg orally daily, may increase by 20 mg/day at weekly intervals to a maximum of 70 mg/day	30 mg (30-day): \$135.99 50 mg (30-day): \$135.99 70 mg (30-day): \$135.99	2/07
<i>New derivatives</i>					
Flector [®]	Diclofenac epolamine		Apply one 1.3% topical patch (180 mg) to the most painful site BID	\$ 10.99 per 1.3% topical patch	1/07
Veramyst [®]	Fluticasone furoate		For 12 yrs and older, 110 mcg daily, delivered as two sprays to each nostril. For children 2 to 11 yrs, 55 mcg daily, delivered as one spray to each nostril	\$ 108.99 per bottle	4/07
<i>New formulations</i>					
Xyzal [®]	Levocetirizine		For 12 yrs and older, 5 mg once every evening. For children 6 to 11 yrs, 2.5 mg once every evening.	5 mg (30-day): \$97.59	5/7

^aPK= pharmacokinetics; ^bPD= pharmacodynamics; ^cA = absorption; ^dD= distribution; ^eM= metabolism; ^fE = elimination; Estimated Cost^g obtained from the average of 5 different retail pharmacy stores; ^gAWP=average wholesale price from the Red Book, manufacturer's information and the McKesson database. Kuvan[®] price¹ obtained from Fairview specialty pharmacy, one of the specialty pharmacies distributes Kuvan[®]

- bivolol vs atenolol and placebo in essential hypertension: a double-blind randomized trial. *J Hum Hypertens* 1998;12:135-140.
6. Van Neuten L, Schelling A, et al. Nebivolol vs enalapril in the treatment of essential hypertension: a double-blind randomized trial. *J of Hum Hypertens* 1997;11:813-19.
 7. Grassi G, Trevano FQ, et al. Efficacy and tolerability profile of nebivolol vs atenolol in mild-to-moderate essential hypertension: results of a double-blind randomized multicentre trial. *Blood Press Suppl* 2003;2:35-40.
 8. Solomkin J, Umeh O, Jiang J, et al. Doripenem versus meropenem with an option for oral step-down therapy in the treatment of complicated intra-abdominal infections. [Poster] Presented at the 47th ICAAC, Chicago, IL, September 17-20, 2007.
 9. Naber K, Redman R, Kotey P, et al. IV therapy with doripenem vs. levofloxacin with an option for oral step-down therapy in the treatment of complicated urinary tract infection and pyelonephritis. [abstract 1733-331]. Presented at the 17th ECCMID, Munich, Apr 1-4, 2007.
 10. Rea-Neto A, Niederman M, Lee M, et al. Efficacy and safety of intravenous doripenem vs. piperacillin/tazobactam in nosocomial pneumonia [Poster]. Presented at the 47th ICAAC; Chicago, IL; Sept.17-20, 2007.
 11. Burton BK, Grange DK, et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): a phase II, multicentre, open-label, screening study. *J Inher Metab Dis* 2007;30: 700-7.
 12. Levy HL, Milanowski A, et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. *Lancet* 2007;370: 504-10.
 13. Oudiz RJ, Torres F, Frost AE et al. ARIES-1: A placebo-controlled, efficacy and safety study of ambrisentan in patients with pulmonary arterial hypertension. *Chest* 2006;130: 121S.
 14. Olschewski H, Galie N, Kramer M et al. Ambrisentan Improves Exercise Capacity and Time to Clinical Worsening in Patients with Pulmonary Arterial Hypertension: Results of the ARIES-2 Study. San Diego, CA: American Thoracic Society, 2006.
 15. Watts RL, Jankovic J, Waters C, et al. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology*. 2007;68:272-6.
 16. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol* 2003;60:1721-8.
 17. Poewe WH, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. *Lancet Neurology* 2007;6:513-20.
 18. Mitchell J, Oh B, Herron J, et al. Once-daily aliskiren provides effective, smooth 24-hour control in patients with hypertension. *J Clin Hypertension*. 2006;8:A93. Abstract P-209.
 19. Villamil A, Chrysant SG, Calhoun D, et al. Renin Inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with HCTZ. *J Hypertension* 2007; 25: 217-26
 20. Pool J, Schmieder R, et al. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. *Am J Hypertension* 2007;20:11-20.
 21. O'Brien E, et al. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin converting enzyme inhibitor, or an angiotensin receptor blocker. *Hypertension* 2007;49:1-9.
 22. Lopez FA, Boellner SW, Childress A, et al. ADHD improvement in children treated with lisdexamfetamine dimesylate (LDX; NRP 104) and MAS XR. Program and abstracts of the 19th U.S. Psychiatric & Mental Health Congress; November 15-19, 2006; New Orleans, LA. Abstract 103.
 23. Biederman, J, Krishnan, S, Zhang, Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther* 2007;29:450.

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