

PIPELINE TRENDS is produced by the University of Massachusetts Medical School's Clinical Pharmacy Services division and distributed to our clients twice yearly.

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Promising New Agents

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NDA submitted for COPD



Projected Generic Entry

Ambien CR™

Prevacid®

Acular®

Valtrex®



Investigational Indications

Gardasil® for HPV prevention in boys

Nuvigil™ for jet lag

Clinical Pearl

Pulmonary Hypertension

A serious condition affecting cardiopulmonary circulation, pulmonary hypertension requires early and intense medical therapy. It is an illness that represents a unique challenge to managed care organizations.

Promising New Agents

Drug Name: Treprostinil
 Manufacturer: United Therapeutics
 Indication: Pulmonary hypertension
 Formulation: Nebulized inhalation

As an inhaled formulation of treprostinil indicated in the treatment of pulmonary arterial hypertension (PAH), Tyvaso™ is a pulmonary and systemic arterial vasodilator and inhibitor of platelet aggregation. United Therapeutics currently markets the subcutaneous (SC) and intravenous (IV) continuous infusion formulations of treprostinil under the tradename Remodulin®.

The safety and efficacy of inhaled treprostinil was established in a Phase III trial of PAH patients (N=235) stabilized on background therapy of bosentan or sildenafil. After 12 weeks, inhaled treprostinil was associated with an increase in median six-minute walk distance of 20 meters compared to background therapy alone (P<0.0005). In addition, a crossover study (N=44) comparing treprostinil to iloprost found a comparable decrease in pulmonary vascular resistance (PVR), with treprostinil exhibiting a delayed onset (18 ± 2 min versus 8 ± 1 min, respectively; P<0.0001) but a more sustained effect on PVR (P<0.0001) and fewer systemic side effects.

The FDA has delayed the decision on this drug until July 30, 2009, to review additional human-factors study data regarding the nebulized administration instructions. Treprostinil, dosed four times daily, would become the second inhaled PAH treatment. Ventavis® (iloprost), dosed six to nine times daily, was approved in 2004. If approved, treprostinil may provide a more convenient administration schedule.

Drug Name: Denosumab
 Manufacturer: Amgen
 Indication: Osteoporosis
 Formulation: SC Injection

Denosumab is a novel, fully-human, monoclonal antibody. It inhibits the receptor activator of nuclear-factor-κB (RANK) ligand resulting in the prevention of osteoclast-related bone breakdown.

Efficacy for the treatment of postmenopausal osteoporosis (PMO) was established in a Phase III study (N=1,189) evaluating weekly oral doses of 70 mg alendronate compared to twice-yearly SC injections of 60 mg denosumab. After 12 months, patients taking denosumab had a greater increase in bone mineral density (BMD) at the total hip compared to alendronate (3.5 percent versus 2.6 percent, P<0.0001). Denosumab also resulted in greater gains in BMD at the trochanter, one-third radius, lumbar spine, and femoral neck compared to alendronate (P≤0.0002 for all sites). A three-year, Phase III study examined 60 mg of denosumab, twice-yearly, in women with osteoporosis (N=7,868). Denosumab resulted in a 68 percent, 20 percent, and 40 percent reduction in new vertebral (P<0.0001), non-vertebral (P=0.011), and hip fractures (P=0.036), respectively, compared to placebo.

A Biologics License Application (BLA) was filed in February 2009 for the treatment and prevention of bone loss due to PMO or hormone ablation therapy for prostate or breast cancer with an FDA action date of October 19, 2009. Denosumab's infrequent administration, every six months, makes it more convenient than currently available daily, weekly, or monthly-dosed bisphosphonates, competing with zoledronic acid, administered every one to two years.

● Non-Specialty ● Specialty

Promising New Agents

Drug Name: Pegloticase

Manufacturer: Savient
 Indication: Treatment-failure gout
 Formulation: IV Infusion

BLA

As a genetically-engineered formulation of uricase, IV pegloticase converts uric acid to the more soluble and easily excreted allantoin. It is being developed for the management of patients with an inadequate response or contraindication to alternate gout therapy.

Two replicate Phase III trials, GOUT1 and GOUT2, evaluated patients with

treatment-failure gout. Patients (N=212) received either pegloticase 8 mg every two weeks (q2w), every four weeks (q4w), or placebo. The primary endpoint was a plasma uric acid (PUA) <6.0 mg/dL for 80 percent of the time at months three and six. Significantly more patients reached the primary endpoint with pegloticase versus none observed with placebo; for the q2w group, 47 percent (P<0.001) and 38 percent (P=0.001), and for the q4w group, 20 percent (P=0.044) and 49 percent (P=0.001) in GOUT1 and GOUT2 trials, respectively. There were

eight cases of serious cardiac events in these two trials, including two deaths. It is unclear if these events were a result of treatment with pegloticase.

The target FDA action date for this BLA is August 1, 2009. If approved, pegloticase will be the first uricase enzyme for the treatment of gout, joining the available uricosuric agents. The infrequent IV dosing provides a convenient second-line alternative to the daily oral administration of allopurinol, probenecid, and Uloric® (febuxostat).

Drug Name: Vigabatrin

Manufacturer: Ovation
 Indication: Seizures
 Formulation: Oral tablet, powder

NDA

Sabril® (vigabatrin), a novel oral anti-epileptic, irreversibly inhibits gamma-aminobutyric acid transaminase (GABA-T), increasing neuronal GABA levels, thereby reducing the probability of seizures. Submitted in December 2007, an amended New Drug Application (NDA) is under review for adjunctive treatment of refractory complex partial

seizures (rCPS) in adults. Previous submissions were denied due to the risk of a peripheral visual field defect (pVFD).

In clinical trials, treatment with vigabatrin resulted in significantly more patients experiencing a ≥50 percent decrease in seizure frequency, compared to placebo [1 g (24 percent; P≤0.05), 3 g (51 percent; P<0.0001), and 6 g daily (53 percent; P<0.0001)]. Safety data showed that mild to moderate pVFD occurred in 25 percent of adults and 15 percent of children; however, an FDA Advisory Committee stated that the benefits could

outweigh these risks.

Available in over 50 countries, vigabatrin represents an alternative to current anti-epileptic drugs for patients with rCPS. Given the risk of pVFD, this agent will likely be reserved for patients unable to respond to first-line treatments. Ovation has also submitted an NDA for the indication of infantile spasms. If approved, vigabatrin would become the only available treatment for this indication.

Drug Name: Ustekinumab

Manufacturer: Centocor, Inc.
 Indication: Psoriasis
 Formulation: SC Injection

BLA

Ustekinumab is a human monoclonal antibody in development for the treatment of adults with moderate to severe plaque psoriasis. It works via a novel mechanism of action, targeting interleukins 12 (IL-12) and 23 (IL-23), resulting in the inhibition of key pathways implicated in the immunopathogenesis of psoriasis.

In the first comparator trial of

biologic therapies for psoriasis (N=903), ustekinumab 45 mg and 90 mg achieved significantly higher response rates than Enbrel® (etanercept) 50 mg in patients with moderate to severe psoriasis. Compared to 58 percent of etanercept patients, 67.5 percent (P=0.012) and 73.8 percent (P<0.001) of the 45 mg and 90 mg ustekinumab groups, respectively, achieved a Psoriasis Area and Severity Index 75 at week 12.

The BLA for ustekinumab was submitted in 2007, and the FDA issued a Complete Response letter in December 2008. Centocor is currently in the

process of developing a Risk Evaluation and Mitigation Strategy containing a Medication Guide and corresponding communication plan, as requested by the FDA in that letter.

Administered as a SC injection, ustekinumab is dosed by weight for days 1 and 28, followed by maintenance dosing every 12 weeks thereafter. Its mode of action, along with a more convenient administration schedule, make it different from existing biologic therapies, with dosing frequencies ranging from weekly to every eight weeks.

Promising New Agents

Drug Name: Indacaterol

Manufacturer: Novartis
Indication: COPD
Formulation: Inhaled dry powder

NDA

A novel once-daily, ultra-long-acting β_2 -agonist (uLABA), indacaterol is under FDA review as a 24-hour bronchodilator for chronic obstructive pulmonary disease (COPD).

In a Phase III study (N=1732), indacaterol 300 μg and 600 μg once-daily produced clinically significant bronchodilation, >120 mL, in trough FEV₁

post-dose, compared to placebo, at week 12 (indacaterol 300 μg and 600 μg , 1.48 L; placebo, 1.31 L; P<0.001). Indacaterol 300 μg and 600 μg also produced significantly greater differences in trough FEV₁ versus placebo, compared to that seen with formoterol 12 μg twice-daily, at weeks 12 and 52, in exploratory endpoints.

In another trial (N=416), after 12 weeks of treatment, indacaterol 150 μg once-daily resulted in nine percent fewer days of poor control in COPD patients compared to placebo (P<0.001). Results

of an active comparison to tiotropium will be released later this year.

Indacaterol has an onset of action similar to short-acting β_2 -agonists and a sustained effect. If approved, it would provide a dosing advantage, in COPD treatment, over the current long-acting β_2 -agonists, which require twice-daily dosing. Indacaterol is additionally undergoing clinical trials for the treatment of asthma, as monotherapy, and also in a fixed dose combination with mometasone. A response from the FDA regarding this application is expected in October 2009.

Drug Name: Fampridine-SR

Manufacturer: Acorda Therapeutics
Indication: Multiple sclerosis
Formulation: Oral tablet

NDA

Fampridine-SR is a sustained release agent being developed to improve walking ability in patients with multiple sclerosis (MS). In May 2009, an NDA was submitted to the FDA for this indication. It exerts its effect by blocking slowly inactivating or nonactivating voltage-gated potassium channels and allowing an increased calcium influx

into the presynaptic terminals, thereby enhancing neuronal communication. These actions improve impulse conduction in damaged nerve fibers.

A double-blind, placebo-controlled, 14-week, Phase III trial (N=301) evaluated the efficacy of fampridine-SR 10 mg twice-daily. The primary endpoint, an improvement in walking speed in at least three of the four follow-ups, was measured by the Timed 25-Foot Walk Test. Fampridine-SR resulted in significantly more patients exhibiting improvement compared to

placebo, 34.8 percent versus 8.3 percent (P<0.001), respectively. In another 8-week Phase III trial (N=240), 42.9 percent of the fampridine-SR group compared to 9.3 percent of the placebo group (P<0.001) demonstrated an improvement on the Timed 25-Foot Walk Test.

Fampridine-SR joins other agents currently used to treat MS symptoms. While not disease-modifying, it would become the first agent indicated for improving walking ability in patients with MS. An FDA response to this application is expected on October 22, 2009.

Drug Name: Dronedaron

Manufacturer: Sanofi Aventis
Indication: Atrial fibrillation
Formulation: Oral tablet

NDA

Dronedaron, a new antiarrhythmic, exerts its rhythm-controlling effect by blocking calcium, potassium, and sodium channels. An NDA was submitted to the FDA in July 2008 for the treatment of patients with atrial fibrillation and atrial flutter. In March 2009, an FDA Advisory Panel voted 10-3 in favor of approval.

In the placebo-controlled, double-

blind, landmark ATHENA trial (N=4,628), the use of dronedaron was examined in patients with atrial fibrillation or flutter without severe heart failure. Results demonstrated that dronedaron, 400 mg twice-daily, significantly reduced the risk of first cardiovascular (CV) hospitalization or death by 24 percent (P<0.001) over 21 months, compared to placebo. Dronedaron also reduced the risk of CV death by 29 percent (P=0.03) and arrhythmia-related death by 45 percent (P=0.01). Another study, conducted in patients with advanced

heart failure, was stopped early due to increased mortality in the dronedaron group. This indicates that dronedaron may not be safe to use in patients with severe heart or left ventricular failure.

In a comparison with amiodaron (N=504), dronedaron resulted in fewer adverse events (P=0.1291). This improved safety profile is likely related to the lack of an iodine group. Amiodaron-related thyroid or pulmonary toxicity is associated with the iodine group, which prolongs the half-life and increases accumulation in tissues.

Projected Generic Entry*

- **Ambien CR™ (zolpidem extended release)**
6/2009
- **Glyset® (miglitol)**
8/2009
- **Prandin® (repaglinide)**
10/2009
- **Prevacid® (lansoprazole)**
11/2009
Novartis planning to release OTC Prevacid® prior to this date
- **Acular® (ketorolac)**
12/2009
- **Valtrex® (valacyclovir)**
12/2009
- **Clarinet® and Clarinet-D® (desloratadine & desloratadine/pseudoephedrine)**
12/2009
Planned OTC switch prior to patent expiration
- **Optivar® (azelastine HCl)**
12/2009
- **Astelin® (azelastine HCl)**
3/2010
- **Cozaar® (losartan)**
4/2010
- **Flomax® (tamsulosin)**
4/2010
- **Epivir® (lamivudine)**
5/2010
- **Arimidex® (anastrozole)**
7/2010
- **Teveten® (eprosartan)**
8/2010
- **Xalatan® (latanoprost)**
3/2011
- **Aricept® (donepezil)**
4/2011

*Dates are estimates, current as of 6/15/09, and are subject to change due to any patent litigation or additional patents.

Investigational Indications

Gardasil® (human papillomavirus quadrivalent vaccine)

The FDA is reviewing an application submitted by Merck & Co., Inc., seeking approval for the use of the human papillomavirus (HPV) vaccine, Gardasil®, in males ages 9 to 26 for the prevention of external genital lesions caused by HPV types 6, 11, 16, and 18. In a pivotal Phase III study with approximately 4,000 males ages 16 to 26, Gardasil® was 90.4 percent effective at reducing external genital lesions when compared to placebo (P<0.001).

Information available at www.merck.com

Nuvigil® (armodafinil)

Cephalon, Inc., recently announced it will submit a request to the FDA, by third quarter 2009, for an additional indication for Nuvigil® (armodafinil) to treat jet lag. Efficacy for this indication was evaluated in a three-day, double-blind, placebo-controlled study (N=427) of patients traveling eastbound from the U.S. to France. Patients taking 150 mg of Nuvigil® reported significant improvement over placebo in both the Multiple Sleep Latency Test (P<0.0001) and the Patient Global Impression of Severity (P<0.05).

Information available at www.cephalon.com



Clinical Pearl

PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH), a serious, life-threatening, medical condition characterized by elevated pressure within the pulmonary circulation, is associated with a poor prognosis if left untreated. Treatment may require the involvement of specialists from a variety of settings including rheumatology, respiratory medicine, and cardiology.

The National Institutes of Health Registry on Primary Pulmonary Hypertension defines PAH as a mean pulmonary artery pressure >25 mmHg with a pulmonary capillary or left arterial

pressure <15 mmHg. Patients may initially experience exertional dyspnea, lethargy, and fatigue related to the inability to increase cardiac output with an increase in physical activity. A progression to right ventricular failure, resulting in chest pain, syncope, and peripheral edema, can occur.

Therapy is highly individualized and based on the patient's functional classification, as determined by either the New York Heart Association or World Health Association's functional assessment. Pharmacological interventions focus on vasodilation to reduce

pulmonary pressure. Treatment options for PAH include the following: endothelin-receptor antagonists, such as oral Tracleer® (bosentan); prostanoids such as IV Flolan® (epoprostenol); IV and SC infusions of Remodulin® (treprostinil); and, more recently, inhaled Ventavis® (iloprost). Patients with an inadequate response may also consider treatment with a phosphodiesterase inhibitor, such as Revatio® (sildenafil). This class of agents represents a challenge to managed care organizations due to the high cost of these treatments, generic availability limited only to IV epoprostenol, and the complexity of treating PAH.

Information from Rubin LJ. *CHEST*.2004;126:75-105. & Badesch DB et al. *CHEST*.2004;126:355-625.

Running Timeline

12/08: FDA issued a Complete Response for ustekinumab

3/09: FDA Advisory Committee voted in favor of dronedarone

6/26/09: New PDUFA date for alogliptin NDA

7/30/09: New PDUFA date for saxagliptin NDA & PDUFA date for inhaled treprostinil NDA

8/1/09: PDUFA date for pegloticase BLA

10/09: FDA Response expected for indacaterol NDA

10/19/09: PDUFA date for Denosumab BLA

10/22/09: PDUFA date for fampridine-SR NDA

Additional Promising New Agents*

Drug Name	Manufacturer	Indication	Product Timeline
Fentanyl (buccal)	BioDelivery Sciences International, Inc.	Pain management	Approval expected first half 2009
Oxycodone & niacin	Acura & King Pharmaceuticals, Inc.	Pain management	PDUFA date: 7/30/2009
Cethromycin	Advanced Life Sciences	Community acquired pneumonia	PDUFA date: 7/31/2009
Morphine sulfate & naltrexone	King Pharmaceuticals, Inc.	Pain management	NDA submitted 6/2008; FDA review planned for early 2009
Lasofoxifene	Pfizer, Inc.	Osteoporosis	FDA issued Complete Response letter 1/2009
Gabapentin encarbil	GSK & Xenoport, Inc.	Restless Leg Syndrome	FDA accepted NDA 3/2009
Rosuvastatin & fenofibric acid combination	Abbott & AstraZeneca	Lipid-lowering	NDA expected third quarter 2009
Lorcaserin	Arena Pharmaceuticals, Inc.	Weight loss	NDA expected late 2009
Telcagepant	Merck & Co., Inc.	Migraine	Target NDA submission date for 2009 delayed
Mipomersen (subcutaneous)	Genzyme Corp. and Isis Pharmaceuticals	Lipid-lowering	NDA expected second half 2010
Dapagliflozin	AstraZeneca	Diabetes	NDA expected second half 2010
Darapladib	GSK	Coronary heart disease	Phase III trials ongoing
Dimebon	Pfizer, Inc.	Alzheimer's disease	Phase III trials ongoing
Acidinium bromide (inhalation)	Forest Laboratories & Laboratorios Almirall	COPD	Phase III trials ongoing
Telaprevir	Vertex Pharmaceuticals, Inc.	Hepatitis C	Phase III trials ongoing
Dabigatran	Boehringer Ingelheim	Prevention/treatment of thromboembolism	Phase III trials ongoing

* All agents are administered orally unless otherwise indicated

PDUFA = Prescription Drug User Fee Act

Industry Trends

Agents in Clinical Development



Phase I - 42%
Phase II - 36%
Phase III - 16%
NDA/BLA - 6%

Pipeline Research

Oncology - 24%
CNS - 14%
Infectious - 8%
Cardiology - 7%
Endocrine - 7%
Respiratory - 5%
Other - 34%



Who We Are and What We Do



The University of Massachusetts Medical School's (UMMS) Clinical Pharmacy Services is a comprehensive prescription drug management program developed in 1999 as part of the Medical School's Commonwealth Medicine division, primarily to provide drug utilization review for Massachusetts Medicaid. Today, we bring exceptional depth and experience in the development and implementation of unique, client-customized managed care-related clinical pharmacy functions including, but not limited to, evidence-based formulary support, drug utilization review, medication therapy management, clinical call center support, and provider/patient education. *PIPELINE TRENDS* is an educational resource produced twice yearly to deliver critical information at the highest level of quality to our clients. We hope that you find this resource of value and welcome your suggestions for improvement.

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