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MedMetrics HealthPartners

PIPELINE TRxENDS

PIPELINE TRxENDS is a publication produced by the University of Massachusetts Medical School (UMMS) Clinical Pharmacy Services (CPS) and distributed twice yearly.

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Prevacid®
Cozaar®

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Enbrel® for Alzheimer's disease

PegIntron™ for stage III melanoma

Clinical Pearl

Fibromyalgia Syndrome

A chronic condition characterized by widespread pain that affects 3.4% of women and less than 0.5% of men in the United States.

Promising New Agents

NDA

Drug Name: Rivaroxaban
Manufacturer: Johnson & Johnson/Bayer
Indication: VTE prophylaxis
Formulation: Oral tablet

Rivaroxaban is a novel oral anticoagulant which exerts its effect through the direct inhibition of coagulant factor Xa. Rivaroxaban was also studied for treatment of venous thromboembolism (VTE) in Phase III trials; however, a new drug application (NDA) was submitted to the FDA in July of 2008 for only the prevention of VTE in adults undergoing elective hip or knee replacement surgery.

The NDA was supported by data from the pivotal RECORD3 trial. In this trial, rivaroxaban was compared to enoxaparin in 2,531 patients who underwent knee replacement surgery. The primary efficacy outcome was the composite of any deep vein thrombosis, nonfatal pulmonary embolism, or death from any cause within 13 to 17 days after surgery. Patients were followed for 30 to 35 days after the last dose of the study medication. The primary outcome occurred in 9.6% who received rivaroxaban and in 18.9% who received enoxaparin ($P<0.001$).

Administered orally as a once daily dose, rivaroxaban allows for complete 24-hour inhibition of factor Xa and thrombin. Due to predictable pharmacokinetics, a wide therapeutic window, and few drug interactions associated with rivaroxaban, no routine monitoring of coagulation parameters is required. Rivaroxaban will be competing with current agents (such as low-molecular-weight heparin, Arixtra®(fondaparinux) or vitamin K antagonists), which are used as the standard of care for VTE prophylaxis after surgery.

NDA

Drug Name: Prasugrel
Manufacturer: Eli Lilly/Daiichi Sankyo
Indication: Acute coronary syndrome
Formulation: Oral tablet

Prasugrel is an oral platelet inhibitor which exerts its effect by blocking the $P2Y_{12}$ adenosine diphosphate receptor, thereby inhibiting platelet activation and aggregation. Prasugrel is being developed for the management of acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI).

An NDA was submitted to the FDA in December 2007. This application was supported by studies of prasugrel in more than 13,000 patients. The landmark Phase III clinical trial, TRITON-TIMI 38, compared prasugrel to Plavix® (clopidogrel), both in combination with aspirin, in treating ACS in patients post-PCI. Preliminary results showed that prasugrel decreased the risk of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarctions and non-fatal stroke) by 19% more than clopidogrel. Patients in the prasugrel arm experienced six more serious bleeding events per 1,000 patients, compared to clopidogrel ($P=0.03$).

The FDA action date for prasugrel was September 26, 2008; however, more time has been requested to review the application.If approved, prasugrel will bring active competition to clopidogrel as the second oral platelet aggregation inhibitor available for the treatment of ACS in patients post-PCI. Prasugrel appears to have the same mechanism of action as clopidogrel with a similar once-daily dosing regimen.

Non-Specialty Specialty

Promising New Agents

NDA

Drug Name: Sertindole
Manufacturer: H. Lundbeck A/S
Indication: Schizophrenia
Formulation: Oral tablet

An antipsychotic indicated for the treatment of schizophrenia, sertindole targets the dopamine-D_2, serotonin-5-HT_{2A}/5-HT_{2C}, and α-1 adenoreceptors. Extensively metabolized by the hepatic cytochrome P450 2D6 and 3A4 systems, it does not require a renal dosing. On September 15, 2008, the FDA accepted the NDA for sertindole.

In Phase II/III trials lasting six weeks to one year, 3,107 patients were treated with sertindole. The greatest overall improvements, based on rating scales, were demonstrated during the first two months of sertindole therapy and persisted for at least one year. Sertindole showed greater improvements in negative symptoms compared to haloperidol and risperidone ($P \leq 0.05$). Improvements in positive symptoms were similar with all three agents compared to placebo.

To minimize the risk of orthostatic hypotension, sertindole should be titrated every fourth day beginning with a starting dose of 4 mg/day; clinically effective doses ranged from 12 to 24 mg/day. The incidence of extrapyramidal symptoms (EPS) with sertindole (22%) is comparable to placebo (29%) but lower than with haloperidol (56%). Unlike other antipsychotics, sertindole is non-sedating. Weight gain of ≥7% from baseline was observed in 13% of sertindole-treated patients as opposed to patients treated with risperidone (9%), quetiapine (17%), and olanzapine (26%).

NDA

Drug Name: Asenapine
Manufacturer: Schering-Plough
Indication: Schizophrenia/Bipolar
Formulation: Sublingual tablet

Asenapine, formulated as a fast-dissolving sublingual tablet, is a newly developed 5-HT_{2A} and D_2 receptor antagonist. This psychopharmacologic agent has a higher affinity for serotonin, dopamine, histaminic and adrenoreceptors and a lower affinity for muscarinic receptors, compared to the other available atypical antipsychotics. Schering-Plough filed an NDA for asenapine in November 2007 seeking FDA approval for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder.

According to Phase III bipolar I studies ranging from 3 to 26 weeks, asenapine was shown to be safe and effective. Compared to placebo, asenapine produced greater score reduction from baseline in the Young Mania Rating Scale. In two of these studies, asenapine was observed to have a two-fold lower incidence of weight gain compared to olanzapine.

In schizophrenia studies, asenapine was also shown to have a significantly lower rate of long-term relapse compared to placebo (12% versus 47%, $P<0.0001$). A separate safety analysis concluded that asenapine has minimal affect on the QT interval.

If approved, asenapine may represent another therapeutic choice for patients who have not tolerated or benefited from the currently available atypical antipsychotics.

NDA

Drug Name: Milnacipran
Manufacturer: Forest/Cypress Biosci.
Indication: Fibromylagia
Formulation: Oral tablet

Milnacipran, an oral dual-reuptake inhibitor, selectively inhibits the reuptake of both serotonin and norepinephrine in a balanced 1:3 ratio. In February 2008, an NDA was submitted to the FDA for its use in the treatment of fibromyalgia. Milnacipran is being used in other countries to treat major depression; this use is supported by clinical trials consisting of 1,032 patients with milnacipran dosed 50 mg twice-daily.

Phase III trials evaluated the efficacy of milnacipran in improving a composite of fibromyalgia symptoms. This composite included an improvement in pain and in global perception of disease status as well as increased physical functioning. A pain response was defined as a decrease in pain of at least 30% and an improved global perception of disease. Milnacipran resulted in 33% of patients achieving a pain response. A syndrome response was classified as an improvement on all three parameters. Milnacipran 100 mg and 200 mg resulted in 44% and 45%, respectively, of patients having a syndrome response compared to 28% of placebo patients. Studies showed these effects were sustained after one year of therapy.

The FDA action date for milnacipran was October 18, 2008; however, the application is still being reviewed. If approved, milnacipran would become the third medication FDA-approved for the treatment of fibromyalgia, joining Lyrica® (pregabalin) and Cymbalta® (duloxetine).

Promising New Agents

BLA

Drug Name: Golimumab
Manufacturer: Centocor
Indication: Rheumatoid arthritis
Formulation: SC injection

Golimumab is a human anti-tumor necrosis factor (TNF)-alpha monoclonal antibody administered as a monthly subcutaneous (SC) injection for the treatment of adults with active forms of rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis.

In June 2008, a biologics license application (BLA) was submitted to the FDA for golimumab. Efficacy and safety data from five pivotal Phase III studies (N=1,400) support the BLA.

After 24-weeks of treatment in the GO-REVEAL Phase III trial (N=405), more patients receiving either 50 mg or 100 mg of golimumab showed improvement according to American College of Rheumatology scores (ACR 20, ACR 50, ACR 70), Disease Activity Scores (DAS 28), and Psoriatic Area and Severity Index scores (PASI 75) compared to patients receiving placebo (P<0.001). Through one year of treatment, ACR 20, DAS 28, and PASI 75 scores were all maintained in all golimumab-treated patients.

Patients receiving golimumab also experienced improvements in physical function and health-related quality of life measures (P<0.05).

If approved, golimumab would become the fourth anti-TNF agent indicated for the treatment of RA joining Enbrel® (etanercept), Remicade® (infliximab), and Humira® (adalimumab).

NDA

Drug Name: Liraglutide
Manufacturer: Novo Nordisk
Indication: Type 2 diabetes
Formulation: SC injection

Liraglutide (NN2211) is a once-daily SC injection studied in the treatment of type 2 diabetes. Liraglutide is a long-acting glucagon-like peptide (GLP-1) analog that works by enhancing glucose-dependent insulin secretion and increasing satiety after meals.

An NDA was submitted to the FDA in May 2008. This application was supported by data from five Phase III trials consisting of more than 5,000 patients.

The 52-week LEAD-3 trial compared liraglutide to glimepiride. Liraglutide was associated with significant changes in HbA_{1c} (0.84 vs. 0.51 point reduction, P=0.0014), weight (-2 kg vs. +1 kg, P=0.001) and systolic blood pressure (3.6 vs. 0.7 point reduction, P=0.0118).

Currently, Byetta® (exenatide) is the only GLP-1 analog approved and is a twice-daily SC injection. Liraglutide's once-daily administration provides a potential dosing advantage.

In the 26-week LEAD-6 Phase 3b trial consisting of patients with existing metformin and/or sulfonylurea therapy, liraglutide exhibited better glycemic control (1.12 versus 0.79 point reduction in HbA_{1c}, P<0.05) with fewer incidences of hypoglycemia (1.9 versus 2.6 events per year, P<0.05) compared to exenatide. Nausea was the most common side effect for both treatments; however, in the liraglutide group, nausea was more transient. Weight reduction was similar for liraglutide and exenatide groups.

NDA

Drug Name: Alogliptin
Manufacturer: Takeda
Indication: Type 2 diabetes
Formulation: Oral capsule

Alogliptin (SYR-322) is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor studied for the treatment of type 2 diabetes. It works by slowing the inactivation of incretin hormones GLP-1 and glucose dependent insulinotropic peptide (GIP). An NDA for alogliptin was submitted in December 2007.

The NDA was supported by six 26-week Phase III studies that evaluated alogliptin in more than 2,000 patients In addition to the single entity product, an NDA was submitted for a combination product of alogliptin/pioglitazone (unspecified dose) in September 2008.

In Phase III clinical trials, the safety and efficacy of alogliptin 12.5 mg and 25 mg was studied as once-daily monotherapy in addition to diet and exercise as well as an adjunct to other antidiabetic medications including sulfonylureas, metformin, thiazolidinediones, and insulin. Alogliptin was well-tolerated, and significant decreases in mean HbA_{1c} from baseline to day 15 were observed for doses of 25 mg (-0.22%, p=0.044), 100 mg (-0.40%, p<0.001) and 400 mg (-0.28%, p=0.018) compared with placebo.

Alogliptin provides a new option in the class of DPP-4 inhibitors for the treatment of type 2 diabetes. If approved, alogliptin would become the second DPP-4 inhibitor available, joining Januvia® (sitagliptin).

Projected Generic Entry*

- **Glyset® (miglitol)**
  2/2009
- **Topamax® (topiramate)**
  4/2009
- **Adderall XR (mixed amphetamine salts)**
  4/2009
- **Ambien CR™ (zolpidem extended release)**
  9/2009
- **Aciphex® (rabeprazole)**
  10/2009
- **Prevacid® (lansoprazole)**
  11/2009
  Novartis planning to release OTC Prevacid® in 2009
- **Acular® (ketorolac)**
  12/2009
- **Valtrex® (valacyclovir)**
  12/2009
- **Cozaar® (losartan)**
  2/2010
- **Flomax® (tamsulosin)**
  4/2010
- **Epivir® (lamivudine)**
  5/2010
- **Arimidex® (anastrozole)**
  7/2010
- **Teveten® (eprosartan)**
  8/2010
- **Aricept® (donepezil)**
  11/2010
- **Xalatan® (latanoprost)**
  3/2011
- **Effexor XR® (venlafaxine)**
  7/2011
- **Lipitor® (atorvastatin)**
  7/2011

*Dates are estimates, current as of 12/2/08, and are subject to change due to any patent litigation or additional patents

Investigational Indications

Enbrel® (Etanercept)

A recent study conducted in Alzheimer's patients showed dramatically improved language recall and memory function after the perispinal administration of Enbrel® (etanercept). These effects were seen within minutes of administration and were sustained throughout the six-month treatment period. These results support the theory that excess TNF-alpha may play a role in the pathogenesis of Alzheimer's disease. Targeting TNF-alpha in the brain offers a novel approach for this debilitating illness.

Tobinick EL et al. BMC Neurology. 2008;8:27.

PegIntron™ (Pegylated Interferon Alpha-2b)

The European Organization for the Research and Treatment of Cancer (EORTC) and Schering-Plough recently released results of a trial investigating the use of PegIntron™ (pegylated interferon alpha-2b) in patients with stage III melanoma. The study found that this agent reduced the risk of cancer recurrence and the risk of death by 18% (P=0.01) compared to observation. These findings have a significant impact as melanoma is considered the deadliest form of skin cancer.

Information available at www.pharmalive.com

Clinical Pearl

FIBROMYALGIA

Fibromyalgia Syndrome (FMS) is a chronic condition characterized by widespread pain, fatigue, and excessive tenderness at specific muscle-tendon sites. In the U.S., 3.4% of women and less than 0.5% of men have been diagnosed. Other common symptoms include stiffness, sleep disturbances, headaches, cognitive disorders, and depression. FMS symptoms are not outwardly visible and diagnostic tests do not show a cause for the pain. As a result, FMS is diagnosed when all other potential causes for the symptoms have been ruled out.

Although the exact etiology is unknown, recent data supports the theory that FMS is caused by dysfunctional pain processing in the central nervous system (CNS). Pharmacological treatment consists of CNS active agents, including antidepressants, analgesics, anticonvulsants, and benzodiazepines. Currently two agents have an FDA-approved indication for the treatment of FMS: Lyrica® (pregabalin) and Cymbalta® (duloxetine).

According to the 2005 American Pain Society guidelines, the recommended initial therapy for FMS is a trial of a low-dose tricyclic antidepressant or cyclobenzaprine. Further treatments include trials of a selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), tramadol, and anticonvulsants. Non-pharmacological treatments used include exercise, stress management, and cognitive behavioral therapy.

Currently, the FDA is in the process of evaluating an application for milnacipran, an SNRI, for the treatment of FMS. FDA action on this application is expected in early 2009.

Information from Abeles AM et al. Ann Intern Med. 2007;146(10):726-734., Goldenberg DL et al. JAMA. 2004;292(19)2388-2395., www.FDA.gov, Buckhardt CS et al. American Pain Society. 2005;109.

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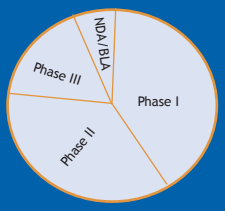
Running Timeline

- 5/08: Liraglutide NDA submitted to FDA
- 6/08: Golimumab BLA submitted to FDA
- 7/30/08: Rivaroxaban NDA submitted to FDA
- 9/08: Alogliptin/pioglitazone combination NDA submitted to FDA
- 9/15/08: Sertindole NDA accepted for FDA review
- 9/26/08: Original FDA action date for prasugrel NDA
- 10/18/08: Original FDA action date for milnacipran NDA

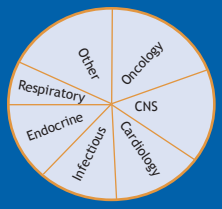
Industry Trends

Agents in Clinical Development



Phase I - 41%
Phase II - 36%
Phase III - 17%
NDA/BLA - 6%

Oncology - 19%
CNS - 16%
Cardiology - 14%
Infectious - 13%
Endocrine - 13%
Respiratory - 7%
Other - 18%



Additional Promising New Agents

Drug Name	Manufacturer	Indication	Phase I	Phase II	Phase III
Mipomersen	Genzyme & Isis	Hypercholesterolemia			
Anacetrapib	Merck	Hypercholesterolemia			
Apixaban	Pfizer & Bristol-Myers Squibb	Anticoagulation			
SCH 530348	Schering-Plough	Anticoagulation			
AZD6140	AstraZeneca	Anticoagulation			
Prulifloxacin	Optimer Pharmaceuticals	Infectious Diarrhea			
Boceprevir	Schering-Plough	Hepatitis C			
Telaprevir	Vertex	Hepatitis C			
Vicriviroc	Schering-Plough	HIV			
Almorexant	Actelion & GlaxoSmithKline	Chronic Insomnia			
Tasimelteon	Vanda	Chronic Insomnia			
Saredutant	Sanofi-Aventis	Depression/Anxiety			
Agomelatine	Novartis	Depression			
Telcagepant	Merck	Migraine			
Semagacestat	Eli Lilly	Alzheimer's disease			
Bapineuzumab	Elan & Wyeth	Alzheimer's disease			

A PARTNERSHIP IN CLINICAL EXCELLENCE

In an effort to deliver the highest possible level of quality and innovation in our clinical programming to our clients, MedMetrics has partnered with University of Massachusetts Medical School (UMMS) Clinical Pharmacy Services (CPS). CPS brings exceptional depth and experience in the development and implementation of unique 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. *'MedMetrics Pipeline Tr$_x$ends'* is an educational resource produced twice yearly to highlight this unique PBM/UMMS relationship. We hope that you find this resource of value and welcome your suggestions for improvement.

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