


PIPELINE TR_x ENDS is produced by the University of Massachusetts Medical School's Clinical Pharmacy Services division and distributed twice yearly.

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Promising New Agents



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Projected Generic Entry



Mirapex®
Aldara®
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Investigational Indications



Cymbalta®
(duloxetine):
for chronic pain

Low-dose
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for fibromyalgia

FDA Updates



Denosumab:
Receives complete response letter

Fampridine-SR:
Review period extended

Indacaterol:
Receives complete response letter

Promising New Agents

NDA

Drug Name: Cladribine

Manufacturer: Merck KGaA
Indication: Multiple sclerosis
Formulation: Oral tablet

An oral formulation of the purine analog cladribine is being investigated for the treatment of relapsing forms of multiple sclerosis (MS). Cladribine acts by hindering the action and proliferation of lymphocytes that are associated with the pathological process of MS.

A 96-week, double-blind, placebo-controlled Phase III trial (N=1,326) evaluated the efficacy of oral cladribine for the treatment of relapsing-remitting MS. Participants were randomized to one of three treatment groups. Patients treated with low- and high-dose cladribine tablets experienced a 58 and 55 percent relative reduction, respectively, in annualized MS relapse rates versus placebo (P<0.001). Lymphopenia occurred more frequently in the cladribine groups, with 22 percent in the low-dose and 31 percent in the high-dose, possibly due to the drug's inhibitory effect on lymphocytes. However, the rate and incidence of infections were similar among the treatment groups. Cladribine is also being studied for its role in long-term use, as a preventative agent, and as add-on therapy with Rebif® (interferon beta-1a).

Cladribine has been granted fast track status by the FDA, but the New Drug Application (NDA) was denied in November 2009. The company is currently working with the FDA to design a plan for resubmission. If approved, cladribine tablets would be the first orally administered disease-modifying therapy available for relapsing forms of MS. This presents a new treatment option for those who have needle phobias and/or dexterity concerns.

NDA

Drug Name: Insulin (rDNA origin)

Manufacturer: MannKind Corporation
Indication: Type 1, type 2 diabetes
Formulation: Inhalation powder

An ultra-rapid-acting prandial insulin, Afresa® is formulated as an inhalation powder and delivered through MannKind's Technosphere® Insulin (TI) inhaler. Upon dissolving in the lungs, TI particles release insulin into the bloodstream within 12 to 14 minutes, similar to mealtime insulin release.

Efficacy of TI was established in a Phase II study of patients with type 2 diabetes (N=126) suboptimally managed with oral antidiabetic agents. After 12 weeks, reductions in A1C from a mean baseline of 7.9 percent were greater with TI compared to placebo (-0.72 percent versus -0.30 percent, P=0.003). A reduction of 43 percent in maximal postprandial glucose levels was observed in the TI group compared with placebo (34 mg/dl versus 60 mg/dl, P<0.0001). Incidences of hypoglycemia and hyperglycemia were similar in both groups. A 52-week Phase III trial (N=565) demonstrated non-inferiority of TI, measured by changes in A1C, versus insulin aspart in type 1 diabetes. A four-year Phase III study (N=229) showed that changes in lung function were similar in patients treated with injectable and/or oral diabetes medications compared to TI, indicating good long-term safety.

An NDA was accepted by the FDA in May 2009 with an FDA review date of Jan. 16, 2010, for the treatment of hyperglycemia in adults with type 1 or type 2 diabetes. The approval of Afresa® may improve glycemic control via faster suppression of postprandial glucose levels and increase adherence by sparing patients multiple daily injections.

● Non-Specialty ● Specialty

Promising New Agents

NDA

Drug Name: Lorcaserin

Manufacturer: Arena Pharma.
Indication: Weight management
Formulation: Oral tablet

Developed for weight management, lorcaserin exerts its effect by selectively activating the serotonin 2C receptor, which is strongly associated with feeding behavior and satiety.

Lorcaserin has been studied in three Phase III trials that enrolled a total of 7,800 patients. The two-year BLOOM trial (N=3,182) studied twice-daily dosing

of lorcaserin. Overall average weight loss from baseline with lorcaserin 10 mg twice-daily was 8.2 percent compared to 3.4 percent with placebo (P<0.0001). Once- and twice-daily dosing of lorcaserin 10 mg was evaluated in the one-year BLOSSOM trial (N=4,008). Average weight loss from baseline was 6.5 percent with once-daily and 7.9 percent with twice-daily dosing of lorcaserin compared to 3.9 percent with placebo (P<0.0001). The third trial, BLOOM-DM, was designed to focus on the use of lorcaserin in patients with type 2 diabetes; however, the results

have not yet been released. These trials included a standardized diet and exercise program for all patients.

Lorcaserin was well tolerated in both the BLOOM and BLOSSOM trials. Arena expects to submit an NDA in December 2009. If approved, lorcaserin would be the first selective serotonin drug developed for weight management. Since clinical trials have not shown adverse cardiac effects or risk of valvulopathy, a major concern with weight management drugs, lorcaserin could provide patients with a new weight loss option.

BLA

Drug Name: Motavizumab

Manufacturer: MedImmune, Inc.
Indication: RSV prophylaxis
Formulation: IM injection

Derived from recombinant DNA technology, motavizumab is an investigational, humanized monoclonal antibody indicated for the prevention of respiratory syncytial virus (RSV) infection in high-risk infants. Motavizumab targets the F-protein of the virus and inhibits the entry of RSV into the lung cells of the host.

In one placebo-controlled Phase

III study (N=1,410), the motavizumab group showed an 83 percent reduction in hospitalizations due to RSV compared to placebo in full-term Native American infants less than 6 months of age (1.4 percent versus 8.3 percent, P<0.001). In another Phase III study, motavizumab was compared with the standard of care, Synagis® (palivizumab), in high-risk infants. This study showed motavizumab was non-inferior to palivizumab in reducing RSV-related hospitalizations and superior in reducing RSV-related outpatient visits. Currently, motavizumab

is also being evaluated in Phase II studies for the early and late treatment of RSV infection in children age 1 and younger.

A Biologics License Application (BLA) was filed by MedImmune in January 2008. In a complete response letter issued in November 2008, the FDA requested additional information. MedImmune plans to resubmit the BLA in December 2009. Due to improved potency and RSV neutralizing activity as compared to palivizumab, motavizumab may be able to provide more effective RSV prophylaxis in high-risk infants.

NDA

Drug Name: Naproxcinod

Manufacturer: NicOx
Indication: Osteoarthritis
Formulation: Oral capsule

With approval expected in the third quarter of 2010 for an NDA accepted by the FDA in November 2009, naproxcinod, a first-in-class cyclooxygenase-inhibiting nitric oxide donator, is being studied for the treatment of inflammation due to osteoarthritis (OA).

In two Phase III trials (N=918, N=1020), patients with OA of the knee were randomized to receive either

naproxcinod 375 mg or 750 mg, naproxen 500 mg, or placebo, all given twice-daily. Co-primary endpoints include change in WOMAC pain/function subscales and the subject's overall rating of disease status. At 13 weeks, both doses of naproxcinod were associated with a greater improvement in all primary endpoints compared to placebo (P<0.001). Similar findings were reported in a Phase III trial (N=810) evaluating naproxcinod in OA of the hip. According to a pooled analysis (N=2,734), naproxcinod significantly lowered, on average, both systolic (SBP) and diastolic blood pressure (DBP) when each regimen

was compared to naproxen 500 mg twice-daily (SBP and DBP for naproxcinod: 375 mg, -1.2 and -0.8 mmHg (P<0.05); 750 mg, -2.2 and -1.2 mmHg (P<0.001)).

Compared with COX-2 inhibitors and NSAIDs used in OA, naproxcinod could be a safer alternative. It may be associated with fewer gastrointestinal side effects based on initial findings and may improve rather than worsen blood pressure due to its production of vasodilatory nitric oxide. Favorable effects on blood pressure are valuable in the treatment of OA since approximately 50 percent of patients also suffer from hypertension.

Promising New Agents

Drug Name: Roflumilast

NDA

Manufacturer: Nycomed

Indication: COPD

Formulation: Oral tablet

Daxas[®] (roflumilast), a phosphodiesterase (PDE) 4 inhibitor, is a once-daily oral treatment for chronic obstructive pulmonary disease (COPD). Roflumilast exhibits its anti-inflammatory action by inhibiting the PDE-4 enzyme, which targets inflammatory markers believed to be important in the underlying disease process of COPD.

Efficacy for roflumilast was established in four Phase III studies. Two 12-month trials, HERMES and AURA (N=3,091), evaluated the once-daily use of roflumilast 500 µg. Roflumilast met the primary end points by reducing exacerbation rates (P<0.0003) and increasing pulmonary function (P<0.0001) in severe and very severe COPD patients. In two six-month trials, EOS and HELIOS (N=1,676), roflumilast was evaluated when used concomitantly with tiotropium or salmeterol in patients with moderate to severe COPD. In these studies, roflumilast

met the primary endpoint of mean change in pre-bronchodilator pulmonary function from baseline for both the salmeterol and tiotropium groups (P<0.001).

Roflumilast offers several advantages over theophylline, an oral non-selective PDE inhibitor, including (1) no required monitoring of plasma levels, (2) simplified dosing, (3) no known drug interactions, and (4) improved cardiac and neurological safety. Roflumilast may represent a valuable add-on therapy, because it was shown to improve lung function in COPD patients treated with current standard of care.

Drug Name: Ticagrelor

NDA

Manufacturer: AstraZeneca

Indication: Acute coronary syndrome

Formulation: Oral tablet

Brilinta[™] (ticagrelor) reversibly binds to the P2Y₁₂ adenosine diphosphate receptor and subsequently inhibits platelet activity. Ticagrelor is being studied for the reduction of major cardiovascular (CV) events in patients with acute coronary syndrome (ACS).

A Phase III trial (N=18,624) evaluated the efficacy of ticagrelor compared to

Plavix[®] (clopidogrel), both in combination with aspirin, for the prevention of CV events and death in patients with ACS. The composite primary endpoint, including CV death, myocardial infarction, or stroke, occurred in fewer patients taking ticagrelor versus clopidogrel over 12 months (9.8 percent versus 11.7 percent, P<0.001). Both groups demonstrated similar rates of major bleeding; however, an analysis of life-threatening or fatal bleeding events demonstrated that ticagrelor resulted in a greater rate of fatal intracranial bleeds when compared to clopidogrel (0.1 percent

versus 0.01 percent, P=0.02).

Ticagrelor is initiated with a loading dose of 180 mg followed by 90 mg twice-daily for maintenance. Due to ticagrelor's short half-life and reversible binding at the P2Y₁₂ receptor, it may represent a better option, compared to clopidogrel or Effient[®] (prasugrel), for patients who require rapid reversal of anti-platelet effects prior to invasive procedures. However, both clopidogrel and prasugrel have the benefit of once-daily dosing. The NDA for ticagrelor was submitted to the FDA in November 2009.

Drug Name: Tocilizumab

BLA

Manufacturer: Chugai, Roche

Indication: Rheumatoid arthritis

Formulation: IV infusion

Actemra[®] (tocilizumab) is an interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody being studied in adult patients with moderate to severe rheumatoid arthritis (RA). Tocilizumab acts by inhibiting the pro-inflammatory activities of IL-6, which have been shown to be correlated with disease severity in RA.

RADIATE was a 24-week Phase III trial (N=499) designed to evaluate the efficacy and safety of tocilizumab 4 mg/kg and 8 mg/kg IV every four weeks plus methotrexate versus placebo plus methotrexate in patients with active RA and prior anti-tumor necrosis factor (anti-TNF) failure. The percentage of patients achieving an American College of Rheumatology 20 response in the placebo, 4 mg/kg, and 8 mg/kg arms was 10.1, 30.4, and 50.0, respectively. Both treatment arms were statistically significant compared to placebo (P<0.0001). The number of

patients achieving disease remission, defined by a Disease Activity Score-28 of <2.6, was 30.1 percent in the 8 mg/kg arm versus 1.6 percent in the placebo arm (P=0.0001).

The BLA for tocilizumab, which includes data from five Phase III trials, was accepted by the FDA in July 2009 with a review date scheduled for January 2010. Administered intravenously every four weeks, tocilizumab offers an alternative to patients that have previously failed anti-TNF therapy or other drugs targeting the inflammatory response.

Projected Generic Entry*

- **Mirapex® (pramipexole)**
1/2010
- **Aldara® (imiquimod)**
2/2010
- **Astelin® (azelastine)**
3/2010
- **Cozaar® (losartan)**
4/2010
- **Flomax® (tamsulosin)**
4/2010
- **Hyzaar® (losartan/HCTZ)**
4/2010
- **Epivir® (lamivudine)**
5/2010
- **Fosamax Plus D™ (alendronate/cholecalciferol)**
6/2010
- **Arimidex® (anastrozole)**
7/2010
- **Effexor® XR (venlafaxine)**
7/2010
- **Aricept® (donepezil)**
11/2010
- **Levaquin® (levofloxacin)**
7/2011
- **Patanol® (olopatadine)**
7/2011
- **Actos® (pioglitazone)**
8/2011
- **Xalatan® (latanoprost)**
9/2011
- **Zyprexa® (olanzapine)**
10/2011
- **Lipitor® (atorvastatin)**
11/2011
- **Femara® (letrozole)**
12/2011

*Dates are estimates, current as of 12/15/09, and are subject to change due to any patent litigation or additional patents.

Investigational Indications

Cymbalta® (duloxetine)

Based on completed studies in chronic pain stemming from osteoarthritis and chronic low back pain, Eli Lilly and Company resubmitted a supplemental NDA for Cymbalta® (duloxetine) to the FDA in June 2009. Efficacy of duloxetine for the management of chronic pain was evaluated in a 13-week, double-blind, placebo-controlled study of 404 patients. Improvements in average weekly pain scores were significant for duloxetine 60 mg and 120 mg beginning at week three; however, the mean change from baseline did not differ significantly from placebo by the end of the study.

Information available at www.lilly.com

Naltrexone

The use of low-dose 4.5 mg naltrexone to reduce symptoms of fibromyalgia was recently investigated in a crossover study in patients (N=10) with moderately severe fibromyalgia. During treatment with naltrexone, patients reported a fibromyalgia symptom severity score 32.5 percent lower than baseline (P<0.0005). Low-dose naltrexone has been shown to suppress the production of proinflammatory cytokines in the central nervous system and exert neuroprotective effects via regulation of mitochondrial apoptotic pathways.

Younger J, et al. *Pain Med.* 2009 May-Jun;10(4):663-72.



FDA Updates

Denosumab

Amgen Inc. received a complete response letter from the FDA regarding the BLA for denosumab (Prolia™) on Oct. 19, 2009. The FDA asked for additional information regarding the planned post-marketing surveillance program for patients being treated for postmenopausal osteoporosis (PMO). Before supporting its use in PMO prevention, the FDA has requested additional clinical trials. The FDA has also determined that a Risk Evaluation and Mitigation Strategy (REMS) will be required for this product, including a medication guide, a communication plan, and a timeline for submissions regarding assessments of this REMS to the FDA.

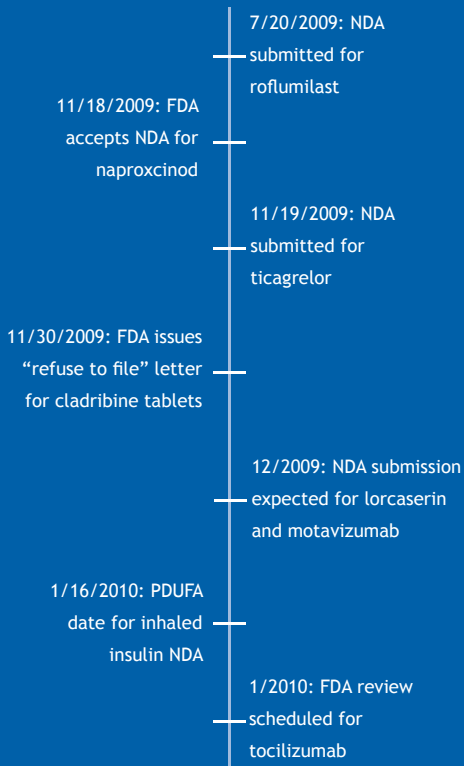
Fampridine-SR

On Oct. 14, 2009, the FDA Peripheral and Central Nervous System Drugs Advisory Committee voted 12-1 that data on fampridine-sustained release (SR) demonstrated efficacy in improving walking ability in patients with multiple sclerosis. However, on Oct. 22, the original target response date for fampridine-SR, the FDA announced an extension of the NDA review period. Acorda Therapeutics recently submitted a major amendment to the NDA containing additional information about the REMS. As a result of this amendment, the FDA announced they are now planning to respond to the NDA by Jan. 22, 2010.

Indacaterol

The FDA issued a complete response letter on Oct. 19, 2009, to Novartis regarding the NDA for its once-daily bronchodilator, indacaterol. The original NDA for indacaterol was submitted to the FDA in December 2008. The recent FDA letter requests additional information regarding proposed dosing for the treatment of patients with COPD. Working with the FDA, Novartis plans to determine whether additional clinical trials will be necessary by reviewing the information submitted with the NDA, along with any new data for indacaterol.

Running Timeline



Additional Promising New Agents*

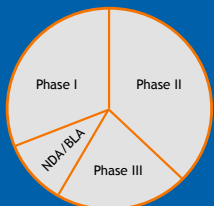
Drug Name	Manufacturer	Indication	Product Timeline
Liraglutide (subcutaneous)	Novo Nordisk	Type 2 diabetes	NDA submitted 5/2008; FDA review planned in 4Q 2009
Azfirocetl-T* (subcutaneous)	Fibrocell Science, Inc.	Moderate to severe nasolabial fold wrinkles	PDUFA date 1/4/2010
Ketorolac (intranasal spray)	ROXRO	Moderate to severe acute pain	NDA accepted 2/2009
Exenatide once-weekly (subcutaneous)	Amylin, Eli Lilly, Alkermes	Type 2 diabetes	NDA submitted 5/2009
Ondansetron (oral dissolving film strips)	MonoSol Rx	Prevention of nausea and vomiting	NDA accepted 6/2009, FDA review planned in 1Q 2010
Tesamorelin* (subcutaneous)	Theratechnologies	HIV-associated lipodystrophy	NDA accepted 8/2009
Rivaroxaban	Johnson & Johnson, Bayer	Prevention of deep vein thrombosis	Complete response letter received 5/2009
Carisbamate	Ortho-McNeil-Janssen, Johnson & Johnson	Epilepsy	Complete response letter received 8/2009
Modified-release clonidine	Adrenex Pharma./ Sciele Pharma, Inc.	ADHD	Supplemental NDA submitted 10/2009
Ceftaroline	Forest Laboratories, AstraZeneca	CABP, cSSSI	NDA submission planned in 4Q 2009
Bupropion SR/naltrexone SR	Orexigen	Obesity	NDA submission planned in first half of 2010
Bapineuzumab* (intravenous, subcutaneous)	Elan Corp., Wyeth	Alzheimer's Disease	Phase III trials ongoing (IV), Phase II trials ongoing (SC)
Phentermine/topiramate	Vivus, Inc.	Obesity, Type 2 diabetes	Phase III trials ongoing
Agomelatine	Novartis	Major Depressive Disorder	Phase III trials ongoing
Teplizumab* (intravenous)	Macrogenics	Type 1 diabetes	Phase III trials ongoing
Zonisamide SR/bupropion SR	Orexigen	Obesity	Phase II trials complete

Note: All agents are administered orally unless otherwise indicated, *Designates Specialty Drug
CABP = community-acquired bacterial pneumonia, cSSSI = complicated skin and skin structure infections, PDUFA = Prescription Drug User Fee Act



Industry Trends

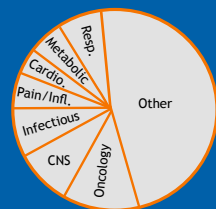
Agents in Clinical Development



Phase I - 31%
Phase II - 37%
Phase III - 21%
NDA/BLA - 11%

Pipeline Research

Oncology - 21%
CNS - 8%
Infectious - 6%
Pain/Inflammation - 5%
Cardiology - 5%
Metabolic - 4%
Respiratory - 4%
Other - 47%



A PARTNERSHIP IN CLINICAL EXCELLENCE

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