

MedAdNews

THE MAGAZINE OF PHARMACEUTICAL BUSINESS AND MARKETING • MEDADNEWS.COM • FEBRUARY 2008

EIGHTH ANNUAL REPORT • FUTURE BLOCKBUSTERS

FUTURE BLOCKBUSTERS

These 10 medicines are expected to eventually garner FDA approval and break the annual billion-dollar sales barrier.

By Andrew Humphreys

2008 is not anticipated to be a year filled with many blockbuster approvals in what would be an extension of a two-year trend. Some industry analysts expect sales from the U.S. pharmaceutical market will not rise more than 5% this year. That performance would reportedly represent the smallest annual growth for the U.S. market in at least several decades.

This cloudy forecast partially reflects recent years in which some billion-dollar medicines have lost patent life while fewer potential blockbusters have been approved due to a weakened industry pipeline. Significant late-stage clinical-trial failures and growing FDA drug-approval safety scrutiny have helped result in stagnant new drug development.

Industry observers believe that a lack of new drug innovation is another contributing factor to a slowing sales market. Other causes include less growth from Medicare Part D, more pressure from payers to control costs and limit access to certain medicines, and big brands being switched from prescription to OTC status.

Patents for branded medicines accounting for an estimated \$12 billion in sales will expire in 2008. The blockbusters losing patent protection will include **Merck**

& Co.'s osteoporosis medicine **Fosamax**, **Johnson & Johnson's** antipsychotic drug **Risperdal**, and **GlaxoSmithKline's** (gsk.com) migraine product **Imitrex**.

Pfizer Inc.'s (pfizer.com) prescription megabrands **Zyrtec** and **Zyrtec-D 12 Hour** (zyrtec.com) lost significant patent life at year-end 2007. In January 2008, the allergy medications were launched by **McNeil Consumer Healthcare** as over-the-counter drugs.

There has been a lack of potential blockbuster medicines approved during the past two years. On the other hand, a new wave of significant products is expected to come out in the 2009-2011 period following the 2006-2008 transition.

For the past few years, this annual special report has focused on medicines anticipated to gain FDA clearance within the current year and eventually attain blockbuster status. Due to the reasons above that have made forecasting such results more uncertain, this year's Future Blockbusters special report reviews 10 drugs that are in late-stage development and may be approved by FDA in 2008 or beyond. The 10 medicines are **bapineuzumab** for Alzheimer's disease, **IPP-201101** for lupus, **ketoprofen/Diractin** for osteoarthritis, **laropiprant/Cordaptive** for cholesterol, **MC-1** for cardiovascular disease, **Multi-**

kine for cancers, **naproxinod** for osteoarthritis, **RhuDex** for rheumatoid arthritis, **SinuNase** for chronic sinusitis, and **Xarelto/rivaroxaban** for venous thromboembolism.

Bapineuzumab

Bapineuzumab could become the first biologic agent to reach the market for treating Alzheimer's disease. This humanized monoclonal antibody against A-beta peptide is known by the product code AAB-001. Joint-developers **Elan Corp.** and **Wyeth** in December announced the initiation of patient dosing in a global Phase III clinical program for bapineuzumab in patients with mild-to-moderate Alzheimer's disease.

Data from Phase III studies are expected to be announced in mid-2008. Phase I trials for a subcutaneous formulation of the product began in second-quarter 2007.

Bapineuzumab is a therapeutic antibody that binds to and clears beta amyloid peptide. The drug is designed to provide antibodies to beta amyloid directly to the patient, rather than requiring the patient to mount their own individual response. This method may eliminate patient need to mount an im-

mune response to beta amyloid.

Animal studies have demonstrated that this method is equally effective in clearing beta amyloid from the brain as traditional active immunization approaches. By providing such a "passive immunization" approach for treating Alzheimer's disease, safety concerns should be greatly reduced or eliminated due to the absence of stimulation of the patient's immune response to beta amyloid.

Elan (elan.com) and **Wyeth** (wyeth.com) announced in May 2007 the initiation of the Phase III clinical program of bapineuzumab for treating mild-to-moderate Alzheimer's disease. This decision was based on the seriousness of the disease and the totality of what the companies have learned from their immunotherapy programs. This includes a scheduled interim review of data from a continuing Phase II blinded study. No conclusion about the Phase II study can be drawn until the study is finished and final data are analyzed and released in 2008.

Bapineuzumab received FDA fast-track designation for mild-to-moderate Alzheimer's disease. Fast-track designation facilitates development and may expedite regulatory review of drugs that the U.S. regulatory agency recognizes as potentially addressing an unmet medical

need for serious or life-threatening conditions.

Two Phase II studies for bapineuzumab are under way. The first is the randomized, double-blind, placebo controlled, multiple-ascending dose study of four cohorts of 240 patients with mild-to-moderate Alzheimer's disease. The primary objective of the trial is to assess the immunotherapeutic candidate's safety. Assessments of cognitive and functional status are being made, with each patient's participation lasting 18 months. The key end points include: ADAS-Cog (assesses cognition), Neuropsychological Test Battery (NTB) and DAD score (measures quality of life). The second Phase II trial is an Alzheimer's beta-amyloid imaging study in 30 patients being conducted in Europe.

The Alzheimer's Immunotherapy Program (AIP) between Elan and Wyeth is a 50/50 collaboration to research, develop, and commercialize an immunotherapeutic approach that may be used for treating mild-to-moderate Alzheimer's disease and possibly for preventing disease onset. Other AIP programs include AAB-001 SubQ, ACC-001, and AAB-002. Wyeth and Elan equally share all costs and potential revenue from this collaboration.

According to the Alzheimer's Association (alz.org), there are more than 5 million Americans living with Alzheimer's disease. The direct and indirect costs of Alzheimer's and other dementias amount to more than \$148 billion per year.

The lack of effective treatments for Alzheimer's disease and an aging population open up an enormous opportunity for disease-modifying medicines, according to analysis from Decision Resources Inc. (dresources.com). Competition to develop new drugs for Alzheimer's disease is fierce, and the efficacy bar for current Alzheimer's disease therapies is low. Therefore, Decision Resources analysts believe that market penetration will hinge on safety profiles.

Pharmacogenomics may cause Alzheimer's disease patients to be turned away from certain therapies. Pharmacogenomics may lead to better dosing and reduce the possibility of side effects and adverse drug interactions.

"Regardless, the soaring disease prevalence, the anticipated increase in early diagnosis and treatment, and the price premium a novel agent could command ensure that an approved Alzheimer's disease disease-modifying drug will become a blockbuster," Decision Resources analysts say.

These analysts expect bapineuzumab to spur the Alzheimer's disease drug market to more than triple by 2016, reaching \$8.8 billion. With a 2011 market introduction in the United States and Europe, the product could generate more than \$5 billion annually by 2016. Another monoclonal antibody, Eli Lilly and Co.'s LY-2062430, may be introduced by 2016 and contribute

to market expansion. The Lilly (lilly.com) drug compound is in Phase II clinical trials for mild-to-moderate Alzheimer's disease. The analysis report does note that significant safety concerns may restrict the overall sales potential of bapineuzumab.

"The launch of bapineuzumab will be the most-important factor driving growth in the Alzheimer's disease drug market," says Nitasha Manchanda, Ph.D., analyst, Decision Resources. "Despite being priced considerably lower than monoclonal antibodies in other markets, we expect bapineuzumab to enter the market priced nearly eightfold higher than current small-molecule therapies. Nevertheless, we anticipate significant uptake of this agent — particularly in patients with mild Alzheimer's disease — despite the safety concerns."

IPP-201101

IPP-201101 specifically modulates the immune system of lupus patients by modifying the behavior of some of the key cells involved in the pathogenesis of the disease. There is no cure or specific treatment for lupus, a chronic, potentially life-threatening autoimmune disease. An estimated 1.6 million

people are affected by the inflammatory disease in the United States, European Union, and Japan. Lupus attacks multiple organs, including the skin, joints, kidneys, blood cells, heart, and lungs.

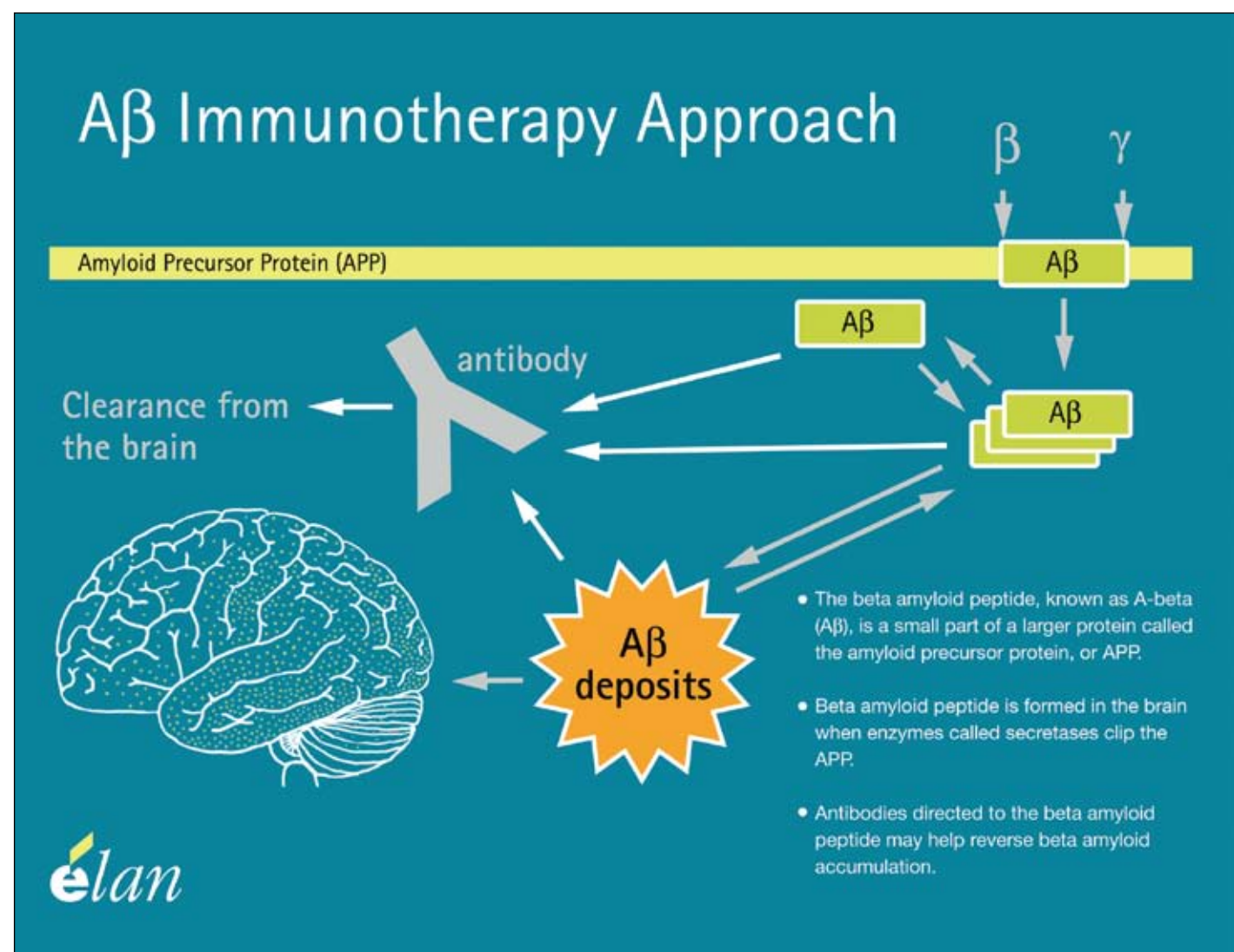
IPP-201101 has the potential to halt the progression of lupus in a substantial proportion of individuals. The drug's novel mechanism of action is directed at modulating the body's immune system.

IPP-201101 is being developed by ImmuPharma Plc., a specialist drug-discovery and drug-development company. In December, the company announced FDA feedback that refines the drug's Phase II/III program for patients with systemic lupus erythematosus. The outcome was the segmenting of the development program into separate Phase IIb and Phase III trials. ImmuPharma (immupharma.com) management had previously expected a single Phase II/III trial in 240 patients over 12 months. The revision allows the company to acquire additional Phase II data, which has the potential to enhance IPP-201101's commercial attractiveness, earlier than previously expected. This process will continue with a simpler Phase III trial in third-quarter 2008 and is broadly in line with previous development time lines. In the near term, ImmuPharma expects the first patients to be dosed into Phase IIb

trials.

As part of an initial investigational new drug application, in July 2007 ImmuPharma filed with U.S. regulators a protocol for a Phase II/III double blind, randomized, placebo-controlled, multicenter study in 240 patients to be treated for 12 months. Following the FDA meeting, the company is conducting a Phase IIb study in 200 patients in Europe and Latin America. This study is a randomized, placebo-controlled, three-arm dose ranging study in patients treated for three months with an additional three-month follow-up. Patients from this trial are expected to be rolled into a one-year open-label safety and efficacy study with results expected to be reported by third-quarter 2009. In third-quarter 2008, a similar but pivotal Phase III study will commence in an additional 200 patients in the United States, Europe, and Latin America for six months. Results from the Phase III study are expected to be announced by third-quarter 2009. In conjunction with the Phase IIb trial, ImmuPharma will complete a long-term preclinical toxicology study as part of regulatory requirements.

"Essentially, we are dividing the Phase II/III program in two parts, which reduces the risk for ImmuPharma and provides data much earlier than previously planned," says



Bapineuzumab binds to and clears beta amyloid peptide; the drug is designed to provide antibodies to beta amyloid directly to the patient, rather than requiring the patient to mount their own individual response.

Dimitri Dimitriou, CEO, ImmuPharma. “This will provide patients with a much-needed drug where there are no specific drugs available today. From a commercial perspective, the refined Phase II/III program has the potential to enhance the commercial attractiveness of our most-advanced drug candidate earlier than anticipated once the data from our Phase IIb are available.”

According to ImmuPharma, IPP-201101 has significant sales potential as well as low marketing costs and a relatively low risk of development failure. The drug compound has the potential to be fast-tracked by FDA and could therefore obtain U.S. regulatory clearance by 2010. Industry analysts expect a license partner will be secured by year-end 2008. Various analyses peg estimated peak yearly sales for IPP-201101 to exceed \$4 billion.

“IPP-201101 is a promising product candidate emerging from a globally recognized lupus team, based at the prestigious CNRS in Strasbourg,” according to a Landsbanki (landsbanki.com) Research Group report. “Lupus is an autoimmune disease of the connective tissues, and Landsbanki estimates it affects 1.6 million people in the United States, Europe, and Japan. This is a chronic debilitating disease. Although survival rates have recently increased, a high level of unmet need still exists. The underlying cause of the disease is unknown, although the cause is most likely an interaction between genetic and environmental factors. Diagnosis is difficult, and treatment currently focuses on management of symptoms, rather than treatment that targets the underlying disease.”

As a result, Landsbanki analysts believe that a successful treatment for the disease is likely to be well received in a market with potential for a high level of sales. IPP-201101 acts as an immunomodulator, down-regulating a specific class of immune cells — the CD4T or T-helper cells, responsible for activating and directing other immune cells — that in Lupus patients are responsible for initiating the autoimmune reaction, and ultimately the symptoms, associated with the disease.

Assuming pricing in line with interferon therapy for multiple sclerosis and market introduction by 2011, Landsbanki analysts project 2017 sales of £3 billion (\$6.1 billion). Net royalties to ImmuPharma would total £338 million (\$681.4 million). This estimate assumes 20% market penetration.

Ketoprofen/ Diractin

Ketoprofen is a carrier-based, targeted local analgesic for osteoarthritis. The drug is being developed incorporating Idea AG’s novel proprietary Transfersome technology. Transfersome ves-

icles are designed to penetrate the skin barrier, bypass the blood capillaries and reach the targeted underlying tissue where the drug exerts the prolonged localized effect. Expected to be marketed in Europe as Diractin, this medicine represents blockbuster potential in the peripheral pain market.

In August 2006, Idea AG (idea-ag.de) reported the positive outcome of a Phase III efficacy and safety trial of knee osteoarthritis. In May 2007, the company filed a regulatory submission to the European Medicines Agency for approval of the short-term and long-term treatment of osteoarthritis. This filing was based in part on data from Phase II and Phase III clinical studies in more than 2,000 patients.

In September 2007, **Alpharma** Inc. agreed to license from Idea AG exclusive U.S. rights to ketoprofen in Transfersome gel. This prescription topical non-steroidal anti-inflammatory drug, known by the product code Idea-033, is in Phase III clinical trials. The license includes access to Idea AG’s Transfersome technology platform that delivers drugs locally to targeted areas.

Based in Munich, Germany, Idea AG is a privately held biopharmaceutical company. Idea AG develops and commercializes non-invasive, targeted therapeutics applied through the skin. The basis of the technology platform are proprietary carriers that are typically applied on skin and can be engineered to achieve high drug concentration at or near the site of application, diminish local or systemic adverse side effects, and often increase drug potency. Alpharma is a worldwide specialty pharmaceutical company with leadership positions in products for humans and animals. The company is active in more than 60 countries with an increasing branded pharmaceutical franchise in the pain market with the morphine-based extended-release **Kadian**.

The first regulatory application regarding ketoprofen was approved by SwissMedic authorities in June 2007 for treating inflammation and pain related to osteoarthritis. This clearance was based on the first pivotal European trial, which showed that ketoprofen in Transfersome gel and **Celebrex** improved patients’ conditions comparably and progressively during the six-week study period and are statistically superior to placebo. Celebrex, comprising celecoxib, is Pfizer’s blockbuster painkiller. The much broader European Medicines Agency filing package included a long-term open-label safety and efficacy trial with patients treated with ketoprofen in Transfersome gel for up to 18 months. Two pivotal European trials, including a 12-week duration study in osteoarthritis, showed that ketoprofen in Transfersome gel delivered a statistically significant improvement in pain, function, and patient global response.

Marketing authorizations obtained by means of the centralized application procedure are valid for an initial five-year period. These are renewable on the basis of an European Medicines Agency re-evaluation. Diractin was eligible for submission as an application for the Community Marketing Authorization under Article 3(2)b (Significant Technical Innovation) of Regulation (EC) No 726/2004. Marketing authorizations issued according to 726/2004 typically provide eight years of data protection and 10 years of marketing protection to the approved medicine. Idea AG management believes that this is the first time an established product in a novel formulation used for a common indication is being dealt with by the European Medicines Agency according to Regulation (EC) No 726/2004.

Idea AG executives anticipate gaining European Medicines Agency marketing clearance in 2008, followed by approvals from Canadian and other regulatory authorities. The company is conducting two clinical studies to support a new drug application filing with FDA for ketoprofen. The drug candidate is targeted for filing for U.S. approval by late 2009. A U.S. product launch is expected in early 2011. In 2006, Idea AG reacquired U.S. and Canadian rights from McNeil Consumer

& Specialty Pharmaceuticals, a unit of Johnson & Johnson (jnj.com).

“Ketoprofen in Transfersome gel is an ideal addition to our product pipeline,” says Dean Mitchell, president and CEO, Alpharma (alpharma.com). “Idea’s unique, proprietary topical ketoprofen gel formulation, which has (had) reported strong clinical results in Europe, complements our recent acquisition of the Flector Patch, offering therapeutic solutions to different segments of the market. The Flector Patch addresses acute pain in a patch delivery system, while ketoprofen in Transfersome gel is a novel topical formulation that is being developed to target chronic pain associated with osteoarthritis. Both of these non-steroidal anti-inflammatory drugs are formulated to treat pain with minimal systemic exposure, a feature that may help address certain safety concerns in the market and provide physicians with expanded options to treat pain. These latest additions to our pharmaceutical product pipeline, combined with our abuse deterrent products currently under development, are expected to result in new product launches in each of 2008, 2009, 2010, and 2011. These product launches could substantially increase top-line growth and profitability, drive synergies across the product lines, and estab-

Lupus facts and figures

- The Lupus Foundation of America estimates that 1.5 million Americans have a form of lupus.
- Although lupus can strike men and women of all ages, 90% of individuals diagnosed with the disease are women; 80% of those afflicted with systemic lupus develop the disease between 15 years old and 45 years old.
- Seventy percent of lupus cases are systemic; in about 50% of these cases, a major organ will be affected.
- Twenty percent of people with lupus will have a parent or sibling who already has or may develop the disease.
- About 5% of children born to individuals with lupus will develop the illness.
- Lupus is two to three times more prevalent among people of color, including African Americans, Hispanics/Latinos, Asians, and Native Americans.
- Several studies indicate that the annual average cost to provide medical treatment for a person with lupus ranges between \$6,000 and \$10,000. For some individuals with lupus, however, medical costs may exceed several thousand dollars per month.
- In a national poll of 1,000 adults conducted for the Lupus Foundation of America, 38% responded that they are somewhat or very familiar with lupus, 39% have only heard of the name of the disease, and 22% have not heard of lupus.
- In a different survey, only four out of 10 young adults 18 years old to 24 years old claimed to be aware of lupus, even though the disease often strikes during the childbearing years.
- Four in 10 lupus patients are treated by three or more physicians and take six or more medicines to treat disease symptoms.

Source: Lupus Foundation of America (lupus.org)

lish AlphaPharma as a leading provider of innovative pain products.”

Terms of the license accord between AlphaPharma Ireland Ltd. and Idea AG include a \$60 million closing payment. Besides the initial payment, AlphaPharma expected \$5 million (or 10 cents earnings per share) in deal-related expenses for third-quarter and fourth-quarter 2007. The transaction includes three clinical and regulatory progress milestone payments amounting to \$77 million that were expected to be made in 2007 or 2008 based on Idea AG's achievement of contractually specified conditions.

Another milestone payment of either \$45 million or \$65 million, depending on the results of one of the drug's clinical trials, is conditioned on U.S. marketing clearance. Idea AG has agreed to pay the costs of specified studies being undertaken to garner FDA clearance. AlphaPharma expects to incur minimal R&D costs before marketing approval.

“We are exceptionally pleased to have AlphaPharma as our commercialization partner,” says Gregor Cevc, Ph.D., founder and CEO, Idea AG. “We believe that AlphaPharma has the focus and commitment to make ketoprofen in Transfersome gel a success in the U.S. marketplace.”

Idea AG intends to fund and conduct two additional late-stage clinical studies: a second pivotal, placebo-controlled, U.S. Phase III study in osteoarthritis patients, and a multi-arm, placebo-controlled, Phase III European study. The latter study will compare ketoprofen in Transfersome gel to Celebrex in a sub-study. This study is expected to help evaluate ketoprofen in Transfersome gel as a viable alternative to oral non-steroidal anti-inflammatory drugs, including cox-2 products.

Non-steroidal anti-inflammatory drugs may result in a growing risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may rise with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Non-steroidal anti-inflammatory drugs also cause an increased risk of serious gastrointestinal adverse events such as bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can happen any time during use and without warning symptoms. Elderly patients are at more of a risk for serious gastrointestinal events. Topically applied non-steroidal anti-inflammatory drugs, such as ketoprofen in Transfersome gel, are designed to minimize systemic exposure and may provide doctors with expanded options to treat pain.

According to Idea AG, most non-steroidal anti-inflammatory drug molecules diffuse well across the primary skin barrier and into peripheral blood vessels, spurred by the drug concentration gradient. Non-steroidal anti-inflammatory drugs proceed this way by first mi-

Ketoprofen in Transfersome Gel

- Topical non-steroidal anti-inflammatory drug product candidate being investigated for the treatment of chronic pain of osteoarthritis
- Novel Transfersome technology
- Target Launch: 2011
- Status: SPA submitted and under review at FDA

Flector Patch

- First FDA approved topical non-steroidal anti-inflammatory drug patch to U.S market
- For the topical treatment of acute pain due to minor strains, sprains, and contusions
- Accelerates expansion of sales force and internal structure to support abuse deterrent product launch; minimal R&D investment
- Status: currently ramping up for an early 2008 launch



grating along hydrophobic intercellular lipid layers in the skin barrier followed by through the blood vessel walls, with total area at least twice that of the skin surface.

Free non-steroidal anti-inflammatory drug molecules are consequently cleared efficiently near the skin surface. This process prevents practically meaningful drug transport to a depth greater than a few millimeters below the skin surface.

In contrast, non-steroidal anti-inflammatory drug molecules included into Idea-033 are predominantly associated with the ultradeformable Transfersome carriers. For example, after an epicutaneous application of Idea-033, more than 95% of the drug molecules are estimated to be associated with such carriers. Therefore, when Idea-033 is used on the skin, the active ingredient does not diffuse through the barrier.

Instead ketoprofen is transported across the barrier by the carriers and is then mainly released from them deep below, rather than in the skin, throughout many hours. Idea AG managers say conventional transdermal drug-delivery methods are inferior to Transfersome technology at attaining such goals.

Laropiprant/ Cordaptive

Laropiprant is a novel flushing pathway inhibitor that is designed to reduce the flushing associated with niacin. This investigational compound is being developed by Merck as an active ingredient within two separate drug

candidates. Known by the product code MK-0524A, laropiprant in combination with niacin is awaiting FDA approval for treating elevated LDL-cholesterol, low HDL-cholesterol, and elevated triglyceride levels. This product would be approved under the brand name Cordaptive. Additionally this year, Merck anticipates submitting a U.S. new drug application for MK-0524B, which combines laropiprant with simvastatin and extended-release niacin.

Cordaptive was accepted for standard FDA review according to a Merck Aug. 29 announcement. FDA action is expected by mid-2008 for extended-release niacin/laropiprant for elevated LDL cholesterol, low HDL cholesterol and elevated triglycerides.

About 55 million Americans have high LDL cholesterol, 55 million have low HDL cholesterol, and 28 million have high triglycerides. Merck plans to submit marketing filings in other countries as well.

In September, Merck reported that Cordaptive was demonstrated in a clinical trial to lower bad cholesterol and raise good cholesterol while alleviating an uncomfortable side effect associated with a similar treatment. The combination drug is intended to prevent patients from experiencing flushing, a reddening of the skin often on the face and neck that may be coupled with a warm or burning feeling.

Industry analysts believe that Cordaptive will attain blockbuster status because sales of existing niacin-based drugs have been limited due to their strong tendency to cause flushing. Included among these products is Abbott Laboratories Inc.'s Niaspan, which has been

on the U.S. market since 1997. In April 2007, FDA cleared for approval a new-coated extended-release tablet for the medicine. Niaspan is the only U.S.-approved, once-a-day extended-release prescription niacin form for treating lipid disorders with an ability to significantly raise HDL cholesterol. Niaspan is the leading drug for elevating HDL cholesterol.

MK-0524B combines the novel approach to raising HDL cholesterol and lowering triglycerides from extended-release niacin along with laropiprant and the proven benefits of simvastatin in one combination medicine. Simvastatin has been marketed by Merck since 1991 as the cholesterol-modifying medicine Zocor. The yearly multibillion-dollar sales generator is used in addition to diet to modify cholesterol levels after diet and other non-drug measures have failed to achieve target levels.

In November, Merck (merck.com) presented results at the American Heart Association 2007 Scientific Sessions in Orlando, Fla., for a double-blind, parallel, 12-week study with seven treatment arms in almost 1,400 patients. Cordaptive coadministered with simvastatin had significant additive effects on reducing LDL cholesterol, increasing HDL cholesterol, and reducing triglyceride levels in a Phase III study with patients with primary hypercholesterolemia or mixed dyslipidemia.

In the study, two 1-gram tablets of Cordaptive coadministered with simvastatin (pooled across 20-milligram or 40-milligram doses) reduced LDL cholesterol 48%, increased HDL cholesterol 28%, and reduced triglyceride levels 33% fol-

lowing 12 weeks of treatment. The primary study endpoint was LDL-cholesterol reduction; secondary endpoints included increased HDL cholesterol, triglyceride reduction, and effects on other lipoproteins. A 1-gram tablet of Cordaptive contains 1 gram of Merck-developed extended-release niacin and 20 milligrams of laropiprant.

Niacin-induced flushing is primarily caused by the prostaglandin PGD(2). This chemical causes vasodilation in the skin and flushing symptoms, acting through the DP(1) flushing pathway. Laropiprant selectively blocks the binding of PGD(2) to its DP(1) receptor. Research has demonstrated that blocking DP(1) reduces flushing associated with niacin.

“It has been shown that niacin-based therapies reduce the risk of cardiovascular events,” says John Paolini, M.D., Ph.D., clinical research, cardiovascular disease, Merck Research Laboratories. “But even though niacin has broad lipid effects, the flushing side effect has been a barrier to many patients reaching the maximum 2-gram dose.”

Dyslipidemia is the elevation of LDL cholesterol and/or triglycerides or a low HDL-cholesterol level that contributes to atherosclerosis development. Atherosclerosis is the leading cause of death among men and women and the primary reason for loss of quality of life in Western countries. Major modifiable risk factors for atherosclerotic disease include hypertension, diabetes, obesity, smoking, and high levels of total cholesterol or LDL cholesterol. Low levels of HDL cholesterol increase an individual’s chances of developing atherosclerosis. Epidemiologic studies have demonstrated that for every 1-milligram/deciliter rise in HDL cholesterol, the risk of developing cardiovascular disease decreases 2% to 3%.

Cardiovascular disease is a general term referring to diseases that affect the heart or blood vessels. Coronary heart disease, or coronary artery disease, is one of the most-common forms of cardiovascular disease and the No. 1 cause of death worldwide. Major risk factors for cardiovascular disease include abnormal lipids, meaning not only high LDL-cholesterol and triglyceride levels, but low levels of HDL cholesterol. Researchers believe that HDL takes part in the reverse transport of cholesterol from peripheral tissues in the body back to the liver for elimination. Additionally, HDL suppresses vascular inflammation associated with atherosclerosis and may potentially reduce the risk of injury to blood vessels through an anti-oxidative effect. Sixty-six percent of patients on current lipid-lowering therapy have at least one lipid outside current recommendations.

Cowen & Co. (cowen.com) analysts have forecasted a Cordaptive and MK-0524B market introduction for 2008. Sales of \$700 million have

been projected for 2012 by the analysts.

MC-1

MC-1 is a cardioprotective medicine that has demonstrated potential for treating various forms of cardiovascular disease in clinical studies. The properties of this naturally occurring molecule were discovered by researchers more than a decade ago. MC-1 represents a major potential first-to-market drug in a new class of cardioprotective products for treating acute cardiovascular events, including coronary artery bypass graft surgery, acute coronary syndrome, and angioplasty.

MC-1 is a novel cardioprotective compound being evaluated in the prevention of cardiac damage. The biopharmaceutical company **Medicure Inc.** has completed two Phase II studies with MC-1 demonstrating the drug’s cardioprotective effects. MC-1 received FDA fast-track designation in June 2007 to reduce cardiovascular events associated with ischemic and/or ischemic reperfusion injury in patients experiencing percutaneous coronary interventions, coronary artery bypass graft surgery, and acute coronary syndrome. Medicure intends to develop MC-1 for the coronary artery bypass graft surgery and acute coronary syndrome markets. These markets have a combined annual incidence of 2 million people in the United States.

In August 2007, Medicure announced that following the second and final planned meeting of the independent Data Safety Monitoring Board, the company had received

another recommendation to continue the Phase III Mend-CABG II trial as planned. Medicure was able to complete study enrollment in late September 2007, two months ahead of schedule.

“This second positive recommendation by the Data Safety Monitoring Board further substantiates the safety profile of MC-1, and confirms the rapid progress being made in this 3,000 patient Phase III registration study,” says Albert D. Friese, Ph.D., president and CEO, Medicure (medicure.com). “We are also pleased to report that enrollment has exceeded our expectations ... We feel the rapid pace of enrollment reflects positively on the medical need for MC-1 and its acceptance by the thoracic surgery and interventional cardiology communities.”

The Data Safety Monitoring Board is primarily responsible for monitoring the safety of patients participating in the study and for reviewing safety data throughout the duration. The Mend-CABG II study is evaluating the safety and efficacy of MC-1 in up to 3,000 patients undergoing coronary artery bypass graft surgery. The Data Safety Monitoring Board consists of independent medical experts and was established by Medicure, in coordination with Duke Clinical Research Institute (dcri.duke.edu) and Montreal Heart Institute (icm-mhi.org), as part of the company’s compliance with good clinical practice guidelines.

The Phase III Mend-CABG II trial is double-blind, randomized, and placebo-controlled. Up to 3,000 patients are being enrolled to undergo coronary artery bypass graft surgery at 130 cardiac surgical centers in North America and Europe. Some

of these major cardiovascular centers are located in New York; Boston; Chicago; Los Angeles; Montreal; Toronto; Vancouver, British Columbia; and Hamburg and Bonn in Germany. Study patients will be randomized to receive placebo or MC-1 250 milligrams before surgery and for 30 days post-operatively (POD 30). The primary efficacy endpoint of Mend-CABG II is the incidence of cardiovascular death or non-fatal myocardial infarction up to and including POD 30. Study patients will be followed for 60 days after treatment (90 days post-operatively) for further safety and efficacy analysis. Study enrollment commenced in November 2006. Four positive Phase II trials were completed with MC-1. A Phase II clinical trial was finished combining MC-1 and lisinopril (MC-4232).

Millions of patients have discovered that drug-coated stents used as part of their heart operations may be having more of a detrimental effect on their health than medical experts have publicly acknowledged. Medical-journal articles suggest that unless patients who receive drug-eluting stents continue to take blood thinners, they could more than double their risk of heart attack or death.

This emerging safety controversy around drug-coated stents has experts forecasting a resurgence in heart-bypass operations. The bypass operations, although more invasive and dangerous, are believed to have longer-lasting benefits versus stents.

Medicure may be able to improve bypass outcomes for patients with MC-1. Clinical trials have shown that MC-1 can reduce the threat of post-operative heart attacks in bypass patients nearly in half.

CORDAPTIVE: Investigational extended-release niacin combined with a novel flushing pathway inhibitor

- Statins are proven therapy for cardiovascular disease management, however residual risk remains
- Niacin has broad lipid effects and unsurpassed in raising HDL cholesterol
- Target 2-gram dose of niacin routinely available
 - Proven cardiovascular benefits associated with niacin treatment
 - Early outcome study demonstrated benefit in heart disease¹
 - Atherosclerosis studies indicated vascular improvement^{2,3}
- Niacin-induced flushing (NIF) is major barrier to use
- Laropiprant, a potent/selective DP receptor antagonist, reduces NIF at initiation of therapy and with sustained use
- ER niacin/laropiprant provides an opportunity to change the paradigm of niacin dosing and maximize the therapeutic potential of niacin
- Long-term use of niacin is necessary to achieve and sustain lipid efficacy and persistent outcomes benefit



¹Canner PL, et al. JACC 1986, 8 (6):1245-55

²Brown B.G, et al. NEJM 2001, 345:1583-1592

³Taylor A.J, et al. Circulation 2004, 110 (23):3512-3517

Atherosclerosis is the leading cause of death among men and women; major modifiable risk factors for atherosclerotic disease include hypertension, diabetes, obesity, smoking, and high levels of total cholesterol or LDL cholesterol.

Along with the clinical-development efforts of MC-1, Medicure commenced the company's first commercialization efforts in August 2006 with the acquisition of the U.S. rights to Aggrastat. This GP IIb/IIIa inhibitor generated 2006 sales of \$85 million for Merck. This transaction provided Medicure with immediate revenue and a commercial presence in advance of MC-1's potential marketing clearance.

Aggrastat was first approved by FDA May 14, 1998. In combination with heparin, Aggrastat treats acute coronary syndrome, including patients who are to be medically managed and those undergoing percutaneous transluminal coronary angioplasty or atherectomy. The product has been demonstrated to decrease the rate of a combined endpoint of death, new myocardial infarction, or refractory ischemia/repeat cardiac procedure. Aggrastat has been studied in a setting that included aspirin and heparin.

In 2006, Merck acquired the non-North American right of first refusal on future product opportunities combining MC-1 with Aggrastat. Merck initially developed Aggrastat and maintains non-U.S. rights to the medicine, including Europe.

Multikine

Multikine is the only cancer immunotherapy that kills cancer cells in a targeted fashion and activates the general immune system to destroy cancer. A different kind of weapon in the fight against cancer, this drug unleashes and empowers the body's own anti-tumor immune response. Multikine is a patented defined mixture of naturally derived cytokines.

This is the first immunotherapeutic agent that belongs to a new class of medicines known as immune simulators. These drugs simulate the way a person's natural immune system acts in defense against cancer. Whereas other immunotherapies are designed to target a single or limited number of specific antigens or molecules, immune simulators are multi-targeted. These drugs simultaneously cause a direct and targeted killing of the specific tumor cells and activate the immune system to produce a stronger anti-tumor attack on multiple fronts.

This is the first immunotherapeutic agent that is being developed as a

first-line standard of care for the treatment of cancer. Multikine is administered before any other cancer therapy because that is the period when the anti-tumor immune response can still be fully activated.

Once a patient has advanced disease, or had surgery or has received radiation and/or chemotherapy, the immune system is severely weakened and is less able to mount an effective anti-tumor immune response. Other immunotherapies are administered after a patient has received chemotherapy and/or radiation therapy, thereby limiting effectiveness.

The biotechnology company Cel-Sci Corp. (cel-sci.com) is developing Multikine. In Phase II clinical trials, the compound was demonstrated to be safe and well-tolerated, improving patient overall survival 33% at a median of three-and-a-half years following surgery. Multikine advanced into a Phase III clinical trial in January 2007. Phase III trials are being conducted in the United States and Canada. The product was granted orphan-drug status by FDA in May 2007 for the neoadjuvant therapy of squamous cell carcinoma of the head and neck.

Cel-Sci's goal is to receive worldwide marketing approval for Multikine as a first-line standard of care drug for advanced primary head and neck cancer patients. Cel-Sci executives are not aware of any other biotechnology company that has ever gone for first-line standard of care in cancer as its first indication. Typically drugs are developed and approvals have been sought for treating advanced-stage, recurrent or metastatic disease. Getting to the Phase III trial stage for a first-line indication takes a very long time, and only drugs that have a very good safety profile have a chance to qualify.

Multikine is multi-targeted. The drug acts on multiple targets (antigens) on the cancer cell; directly kills cancer cells; signals the immune system to mount an effective and sustainable anti-tumor immune response by changing the type of cells that infiltrate and attack the tumor from the usual CD-8 cells to the CD-4 cells; and renders the remaining cancer cells much more susceptible to radiation and chemotherapy treatment, thereby making these treatments more effective.

Because Multikine simulates a healthy immune response, the drug is anticipated to be effective in treating many other tumors. Multikine will be developed for use in treating breast cancer, skin cancer and cervical cancer. Studies will be conducted to confirm observations made during Phase II clinical studies that Multikine has the ability to increase radiation and chemotherapy effectiveness. This could eventually result in the drug's ability to reduce amounts of radiation and chemotherapy given to patients.

In August 2007, Cel-Sci announced a \$15 million acquisition of long-term use of a dedicated man-

ufacturing facility for Multikine. Located near Baltimore, this facility was leased for 20 years from the biomedical real-estate group BioRealty Inc. (biorealty.com). The manufacturing site will produce Multikine for Phase III clinical trials for head and neck cancer as well as other cancers, and for sale following marketing clearance.

According to the National Cancer Institute (cancer.gov), head and neck cancers, including in the buccal cavity, head and neck subset, larynx, pharynx, thyroid, salivary glands and nose/nasal passages, account for 6% of all malignancies in the United States. An estimated \$3.2 billion is spent in the United States annually on the treatment of head and neck cancers.

Cel-Sci management anticipates eventual multibillion-dollar sales from Multikine on an annual basis. Within the oncology market, company executives estimate that revenue from the head and neck cancer market for Multikine could reach about \$1.2 billion in the United States and Canada and \$3 billion in Europe, according to a report compiled by Cel-Sci and Crystal Research Associates LLC (crystalra.com), with stats from the Mouth Cancer Foundation (mouthcancerfoundation.org). These values are based on the company's internal metrics, assuming a value of about \$30,000 for each of the about 40,000 head and neck cancer patients in the United States and Canada and roughly 100,000 patients in Europe.

Naproxcinod

NicOx SA's lead product is in Phase III clinical development for treating the signs and symptoms of osteoarthritis. According to NicOx management, naproxcinod has the potential to become the drug of choice for osteoporosis, with no detrimental effect on blood pressure and a solid gastrointestinal tolerability. Known by the product code HCT 3012, naproxcinod is a unique nitric oxide-donating anti-inflammatory. Naproxcinod represents the first of the CINOD class (Cox-Inhibiting Nitric Oxide Donators).

Top-line results from the first Phase III study were successful, according to company executives. This performance represents a significant step toward biopharmaceutical company NicOx's (nicox.com) goal of making naproxcinod the drug of choice for osteoarthritis patients.

Millions of people rely on non-steroidal anti-inflammatory medicines for the treatment of chronic pain and inflammation relating to a range of conditions, such as osteoarthritis. Cox-2 selective non-steroidal anti-inflammatory drugs and non-selective non-steroidal anti-inflammatory drugs have been linked to an increased risk of serious cardiovascular events. These events include heart attack and stroke, creating a

necessity for new medicines with better safety profiles. This demand is particularly crucial for patients with coexisting cardiovascular risk factors, such as hypertension, who represent about 40% of osteoarthritis sufferers.

NicOx announced in October 2006 top-line results from the first pivotal Phase III clinical trial for naproxcinod. This study is known as the 301 trial. The results confirmed that naproxcinod is superior to placebo in relieving the signs and symptoms of osteoarthritis. Naproxcinod demonstrated a clear and sustainable effect of lowering blood pressure and had good safety and tolerability.

The following month NicOx announced top-line results of a non-

MC-1 represents a major potential first-to-market drug in a new class of cardioprotective products for treating acute cardiovascular events, including coronary artery bypass graft surgery, acute coronary syndrome, and angioplasty.

pivotal study, using the Ambulatory Blood Pressure Monitoring technique in 131 hypertensive subjects. This Ambulatory Blood Pressure Monitoring trial showed a differentiated and favorable 24-hour blood-pressure profile for naproxcinod compared with naproxen after two weeks of treatment.

NicOx management believes that naproxcinod will generate significant market potential if the drug's non-negative blood-pressure profile in contrast to existing non-steroidal anti-inflammatory drugs is confirmed. This is based on the fact that the blood-pressure increase evident with existing non-steroidal anti-inflammatory drugs is considered one of the potential factors responsible for the apparent heightened risk of serious cardiovascular events observed with these agents.

The Phase III efficacy program for gaining regulatory approval for naproxcinod in the United States and Europe consists of three pivotal Phase III studies. The 301 study was the first clinical trial in the program. This study produced top-line results in October 2006. The 13-week, double-blind, placebo and naproxen-controlled trial for 918 patients with knee osteoarthritis was conducted in 120 U.S. clinical sites. Eligible patients were randomized to one of four treatment groups: naproxcinod 375 milligrams twice daily, naproxcinod 750 milligrams twice daily, naproxen 500 milligrams twice daily, or placebo twice daily. Naproxcinod demonstrated good overall safety. The number of serious adverse events was low and evenly spread among treatment groups. Blood-pressure data for both naproxcinod

doses demonstrated a sustained reduction compared with baseline and naproxen at all time points. The number of adverse hypotensive events was low across all treatment groups. The 301 study has a long-term extension that will provide additional safety data.

NicOx completed enrollment in the second pivotal Phase III study for naproxcinod in December 2007. Begun in April 2007, the 302 study is a 53-week, randomized, double-blind, efficacy and safety trial in which 1,020 patients with knee osteoarthritis have been enrolled at 150 U.S. clinical centers. Efficacy results are anticipated during third-quarter 2008.

Patients have been randomized to one of these treatment groups: naproxcinod 375 milligrams twice daily (52 weeks), naproxcinod 750 milligrams twice daily (52 weeks), naproxen 500 milligrams twice daily (52 weeks) and placebo twice daily during the first 13 weeks. Following 13 weeks, the placebo-treated patients are being randomized to either naproxcinod 375 milligrams twice daily or naproxcinod 750 milligrams twice daily for the trial remainder (39 weeks). The two doses of naproxcinod will be compared to placebo on the three co-primary efficacy endpoints that are the same as those used in the other pivotal Phase III studies. A secondary trial endpoint will compare the efficacy of naproxcinod and naproxen at 26 weeks. The general safety and tolerability of naproxcinod will be assessed until week 52, and the clinical trial has a one-week post-treatment safety period.

NicOx launched the third and fi-

nal pivotal Phase III trial for naproxcinod in June 2007. The 303 study is a 13-week, double-blind, placebo and naproxen controlled trial in patients with hip osteoarthritis. This efficacy and safety clinical trial is expected to enroll 800 patients at 100 clinical centers in the United States, Canada, and Europe. Efficacy results are anticipated by year-end 2008. Eligible patients will be randomized to three arms: naproxcinod 750 milligrams twice daily, placebo twice daily, and naproxen 500 milligrams twice daily.

NicOx will conduct a statistical analysis according to a predefined plan on the pooled office blood-pressure measurements data from the three Phase III studies following completion of the 302 and 303 trials. Company management anticipates filing a new drug application with FDA for naproxcinod during first-quarter 2009.

In October 2007, France-based NicOx opened U.S. headquarters in Warren, N.J. The 6,000-square-foot facility serves as the base for NicOx's commercial affairs and U.S. clinical operations departments.

"As NicOx transitions from a pure research and development organization to a fully integrated commercial company, we recognized the need to open NicOx' U.S. headquarters," says Damian Marron, VP of corporate development for NicOx. "As we move closer to our anticipated new drug application filing for naproxcinod, we will need to build our sales and marketing infrastructure."

Most of NicOx' clinical trials are planned and will be conducted in the United States. This process will help implement the company's U.S.

clinical strategy and provide strong support and management for the CROs working for NicOx.

"We selected Warren because many leading global pharmaceutical firms, biotech companies, universities, and hospitals are located in New Jersey, making this a highly attractive location as we build the skills and infrastructure we need in the United States," says Sanjiv Sharma, VP of commercial affairs for NicOx. "Furthermore, we are in close proximity to the global headquarters of Pfizer Inc. and Merck & Co., our collaborators in ophthalmology and hypertension, as well as the contract research organizations that are assisting with naproxcinod's pivotal studies."

RhuDex

RhuDex is a T-cell co-stimulation modulator for treating rheumatoid arthritis. The drug is the first oral CD80 interactor and blocks the activation of CD4 T cells. This anti-arthritic agent works as an immunosuppressant with an anti-inflammatory effect. By specifically blocking T-cell activation, RhuDex reduces the release of inflammatory cytokines involved in the autoimmune disease rheumatoid arthritis.

The novel, orally available compound is being developed by **MediGene AG**. The initial program leading to the isolation of RhuDex originates from **Active Biotech AB's** (activebiotech.com) patented CD80 antagonists. This program was out-licensed to MediGene's subsidiary

Avidex Ltd. (avidex.com) in 2002.

A Phase IIa clinical trial was initiated during the early part of 2007. MediGene management expected the conclusion of the clinical part of the Phase IIa trial by year-end 2007. Data are expected to be announced in first-half 2008.

Upon completion of this trial, another Phase II trial with more than 200 patients is planned for this year. MediGene is responsible for the clinical program and related costs.

The U.S. Patent Office granted a central patent for RhuDex in October 2007. This protects the pharmaceutical application of the drug candidate's substance.

Rheumatoid arthritis is a debilitating and degenerative autoimmune disease. Rheumatoid arthritis affects 1% of the global population and about 2.1 million Americans.

Traditional rheumatoid arthritis treatments consist of fast-acting, oral, first-line drugs. These include non-steroidal anti-inflammatory drugs such as ibuprofen, corticosteroids, and slow-acting second-line drugs known as disease-modifying antirheumatic drugs or DMARDs.

With all of these drugs, however, in time irreversible joint destruction and disease progression occur. Long-term treatment with all of these drugs can result in unwanted side effects and toxicity.

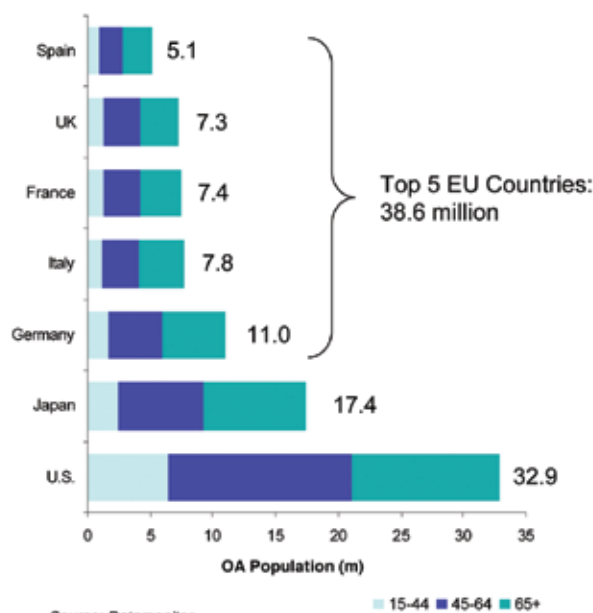
More recently, antibody-based medicines to block inflammatory cytokines such as tumor necrosis factor, were introduced to the marketplace, but these have to be parenterally administered.

Rheumatoid arthritis is caused by abnormal T-cell activation resulting in an immune response that damages the synovial membrane of the articular capsules. T-cell activation occurs in two steps. The first step is an interaction between the antigen-

Naproxcinod - Market opportunity in Osteoarthritis



Osteoarthritis Population



Over 70 million OA sufferers in the US and in Europe

Market Opportunity

- Worldwide NSAID market worth over \$12 billion/year
- 40% of OA sufferers are estimated to be hypertensive
- 2004/2005: Vioxx (\$2.7 billion estimated 2004 sales) and Bextra (\$1.3 billion estimated 2004 sales) were withdrawn
- 2007: Arcoxia and Prexige received a non approval letter from FDA; Celebrex is the only product actively promoted in US
- All NSAIDs in the US and EU now carry a blood pressure warning

Significant need for a safer treatment with no impact on blood pressure

Multikine is the first immunotherapeutic agent developed as a first-line treatment for cancer. Multikine is administered before any other cancer therapy because that is the period when anti-tumor immune response can still be fully activated. Once a patient has had surgery or received radiation and/or chemotherapy, the immune system is severely weakened and is less able to mount an effective anti-tumor immune response. Other immunotherapies are administered later in cancer therapy, such as after radiation, chemotherapy, and surgery.

presenting cell and a T cell via the MHC complex. The second part is the binding of the CD80 and CD28 proteins on the surface of the two cells.

RhuDex inhibits the second step, thereby blocking T-cell activation. Consequently, the disease-causing mechanism is stopped very specifically and at an early stage. Marketed rheumatoid arthritis medicines intervene in the later steps during this process.

As the first oral inhibitor of the drug's well-defined target, MediGene management believes that RhuDex offers a clearly competitive therapeutic advantage compared with marketed rheumatoid arthritis medicines. Annual peak sales potential of RhuDex has been projected at more than €1.5 billion (\$2.18 billion).

SinuNase

SinuNase is anticipated to become the first product to be approved for the fungal-induced inflammation chronic sinusitis. This debilitating disease affects more than 60 million people in the United States and Europe. Chronic sinusitis is the most-common chronic respiratory disease with a commercial market double that of asthma.

SinuNase is an amphotericin B suspension that is self-administered into a patient's nasal cavity for treating chronic rhinosinusitis. Rhinosinusitis is an inflammatory condition of the paranasal sinuses that leads to symptoms such as nasal congestion, facial pain and pressure, nasal discharge, and headaches. Rhinosinusitis affects an estimated 35 million Americans, with a projected 90% of cases being chronic. Up to 500,000 people with chronic rhinosinusitis receive sinus surgery every year.

SinuNase is the first product candidate from **Accentia Biopharmaceuticals Inc.**'s pipeline. A vertically integrated

biopharmaceutical company, **Accentia** (accentia.net) is focused on the development and commercialization of drug candidates in late-stage clinical development. These products typically are based on active pharmaceutical ingredients that have been previously approved by U.S. regulators for other indications.

In October, Accentia completed patient enrollment for a Phase III clinical trial of SinuNase for treating chronic sinusitis. The randomized, double-blind, placebo-controlled clinical trial for severe chronic sinusitis patients is being conducted at more than 50 U.S. sites. This is reportedly the first Phase III trial for chronic sinusitis. The initial study population is severe chronic sinusitis patients who have undergone sinus surgery and are struggling with recurrent chronic sinusitis. The trial is expected to be unblinded after 18 weeks, with top-line results being announced in March demonstrating a highly statistically significant outcome for SinuNase. The product is part of FDA's fast-track status program.

According to management, Accentia intends to seek an expedited approval through Subpart H. This FDA pathway enables accelerated, conditional approval of therapeutics for serious unmet clinical indications. This approval would allow SinuNase to be prescribed for the most serious cases of chronic sinusitis. To significantly expand upon that market, the company expects to carry out a second, confirmatory Phase III study. By year-end 2008, Accentia anticipates having completed the confirmatory trial and submitted a new drug application with FDA, seeking broad, unconditional approval for SinuNase.

According to Accentia, chronic rhinosinusitis treatment historically has mainly been targeted at addressing condition symptoms through acute antibiotic therapy, intranasal or oral corticosteroids, and sinus surgery.

Although antibiotics are useful in treating the acute exacerbations

that result from the bacterial invasion of the damaged paranasal tissue of chronic rhinosinusitis patients, no antibiotic has proven effective in eradicating the underlying cause of chronic rhinosinusitis.

Intranasal and oral corticosteroids, which are potent anti-inflammatory hormones, have been used to reduce the inflammation that plays a role in chronic rhinosinusitis, but oral corticosteroids can cause serious side effects and must be avoided or cautiously used with patients that have certain conditions.

These conditions include gastrointestinal ulcers, renal disease, hypertension, diabetes, osteoporosis, thyroid disorders, and intestinal disease. Surgery is frequently used in chronic rhinosinusitis patients to improve the drainage of their sinuses based on the assumption that the disease can be reversed by identifying and correcting the obstruction that caused the condition, but although such surgery usually provides temporary symptom relief, it is typically not curative.

Accentia licensed global, exclusive commercial rights to SinuNase from The Mayo Clinic. Mayo (mayoclinic.org) researchers determined that chronic sinusitis is caused by a mold that is normally innocuous, but which in chronic sinusitis patients induce a destructive, inflammatory response. This result was confirmed by testing for the presence of the toxic protein eosinophilic major basic protein, which is released by inflammatory cells in response to the fungi.

"Mayo's research leads us to believe that most, if not all cases of chronic sinusitis are due to fungal-induced inflammation," says Francis E. O'Donnell Jr., M.D., chairman and CEO, Accentia. "SinuNase is the only intranasal, anti-fungal chronic sinusitis product that has been submitted as an investigative new drug to the FDA. We also continue to strengthen our patent portfolio for SinuNase with key patents being granted in the United States and European Union covering the treatment of chronic sinusitis with intranasal anti-fungals, including the active ingredient in SinuNase."

Accentia has an agreement with **Immco Diagnostics** to commercialize SinuTest, which is a diagnostic used to measure eosinophilic major basic protein in the nasal mucin of suspected chronic sinusitis patients. This diagnostic is expected to provide physicians with a tool to predict those patient candidates best suited to benefit from treatment with SinuNase.

The SinuTest patented technology was developed at the Mayo Foundation for Medical Education and Research. The technology is exclusively licensed to Immco (immco-diagnostics.com). Company management believes that SinuTest will be a useful adjunct for identification of patients who are suspected of having chronic sinusitis and who may be candidates for treatment with SinuNase.

Based on the anticipated unconditional approval of SinuNase, Accentia management has projected the market opportunity for peak annual product sales could top \$1 billion.

Accentia executives anticipate submitting for accelerated, conditional FDA approval in mid-2008. European regulatory approval via the European Medicines Agency registration pathway will also be sought this year. Marketing and sales initiatives are expected to be launched upon conditional approval in late 2008. Upon positive confirmatory trial results, the company would file for unconditional U.S. approval. During this year, Accentia expects to form key commercial license deals for the U.S. and international markets.

Based on the anticipated unconditional approval of SinuNase, Accentia management has projected the market opportunity for peak annual product sales could top \$1 billion. Company officers are additionally hopeful for two other products in the pipeline that could turn into future blockbuster brands: **BiovaxID** and **Revimmune**.

BiovaxID is a personalized cancer vaccine in a pivotal Phase III fast-track trial. Researchers are initially targeting the drug candidate for the treatment of non-Hodgkin's lymphoma, but Biovax ID has the potential to treat many difficult-to-treat B-cell related cancers, including multiple myeloma and chronic lymphocytic leukemia.

During 2007, Accentia acquired the global exclusive license to **Revimmune** for autoimmune diseases. This technology, developed at the Johns Hopkins University School of Medicine (hopkinsmedicine.org), is believed to offer unprecedented benefits for treating up to 80 autoimmune diseases, including multiple sclerosis.

Revimmune could be the world's first therapy to propose restoration of neurologic function as the primary endpoint and offer potential for the elimination of autoimmunity. Accentia expects to commence enrollment for a Phase III clinical trial by mid-2008.

Xarelto / rivaroxaban

Rivaroxaban is an investigational, oral, once-a-day direct Factor Xa inhibitor. The drug is the most-promising product in **Bayer HealthCare AG**'s pipeline. Pivotal studies have shown that rivaroxaban significantly reduces the risk of venous thromboembolism in patients undergoing total knee-replacement surgery compared with

MediGene

RhuDex® allows earlier intervention in disease than current therapies or those in development

RhuDex® intervenes before T cell activation and prevents cytokine release

Current therapies and those in development intervene after T cell activation or act on cytokines

ENBREL (Immune)	TNF
REMICADE (Centocor)	IL-10
CCP 019 (Cellectis)	IL-1
HUMIRA (CAT)	IL-2
TACE (BMS)	IL-6
CNTO 148 (Centocor/JLL)	
PEGs TNF11 (Amgen)	
HLAAX (Genmab/Amgen)	
ICE INHIBITORS (Vertex/Avantis)	
KINERET (Amgen)	
E-1 TRAP (Regeneron)	
IL-1/2 (Amgen/Immune)	
JWS (Abbott)	
MRA (Chugai)	

enoxaparin, the standard of care. Rivaroxaban was submitted to the European Medicines Agency in October for the prevention of venous thromboembolism after major orthopedic surgery of the lower limbs. U.S. filing for this indication is expected in 2008.

Venous thromboembolism is a thromboembolic disease caused by obstruction of a blood vessel by a blood clot. An estimated 543,000 deaths in Europe result from venous thromboembolism every year. Individuals undergoing major surgery, particularly total knee or hip replacement, are prone to developing venous thromboembolism due to a combination of factors that include prolonged bed rest, damage to blood vessels, and an increased tendency of blood clotting. An estimated 50% of patients undergoing lower-limb surgery develop venous thromboembolism if they do not receive preventative care.

“The submission of the data for venous thromboembolism prevention to the European Medicines Agency is an important milestone in the development of this new treatment for the prevention of life-threatening blood clots,” says Dr. Kemal Malik, head of global development and a member of Bayer HealthCare’s (bayer-healthcare.com) executive committee. “As an effective and convenient once-daily oral treatment with a reassuring safety profile, we feel confident that rivaroxaban has the potential to set a new standard of care in the preventative treatment of thrombosis in patients undergoing major orthopedic surgery.”

The anticoagulant is in advanced clinical development for the prevention and treatment of thrombosis in acute and chronic settings, allowing for convenient administration in the hospital and at home. Rivaroxaban’s study program already comprises four indications. Another indication, the treatment of hospitalized patients with internal diseases, will be added to this program. About 50,000 patients will take part in these studies, resulting in the largest clinical-study program Bayer has ever undertaken. Rivaroxaban has been the most-studied oral direct Factor Xa inhibitor in development by any company.

“The available results of the first Phase III study on prevention of ve-

nous thromboembolism in knee-replacement surgery have exceeded our own expectations,” says Bayer AG (bayer.com) Management Board Chairman Werner Wenning.

Rivaroxaban is being jointly developed by Bayer and **Johnson & Johnson Pharmaceutical Research & Development LLC** (jnjpharmarnd.com). The trade name of rivaroxaban is expected to be Xarelto. Upon regulatory clearance, rivaroxaban will be commercialized in Europe by **Bayer Schering Pharma** (bayer-scheringpharma.de). A U.S. filing for rivaroxaban for a similar indication is planned for 2008. The product would be marketed in the United States by J&J’s wholly owned subsidiaries, **Ortho-McNeil Inc.** (orthomcneil.com) and **Scios Inc.** (sciosinc.com).

According to Decision Resources analysis, the market entries of oral agents that do not necessitate dose adjustment or monitoring, particularly Xarelto, will spur the anticoagulant drug market to more than double from \$3 billion in 2006 to \$7.4 billion in 2016. Due to the drug’s fixed-dose once-a-day administration, Xarelto will best fulfill the need for a convenient oral anticoagulant in treating major thrombotic indications. These indications, which account for more than half of the total anticoagulant market, include stroke prevention in atrial fibrillation, the prevention and acute treatment of venous thromboembolism, and acute coronary syndrome.

A Decision Resources report indicates that the market introduction of simple-to-use agents, such as Xarelto, other factor Xa inhibitors, and oral thrombin inhibitors, will encourage new prescriptions in lieu of (and the switching of existing patients from) vitamin K antagonists whenever long-term anticoagulation is indicated. The market potential for new premium-priced oral anticoagulants is highest in preventing stroke in atrial fibrillation and in the secondary prevention of venous thromboembolism.

Bayer management believes that the peak annual sales potential of rivaroxaban tops E2 billion (\$2.91 billion). Early reports indicate that short-term use of rivaroxaban in patients undergoing orthopedic surgery has demonstrated promising results compared with **Lovenox**. This inject-

Xarelto (Rivaroxaban) – Potentially Redefining the Market for Anticoagulants



An ideal anticoagulant should have ...

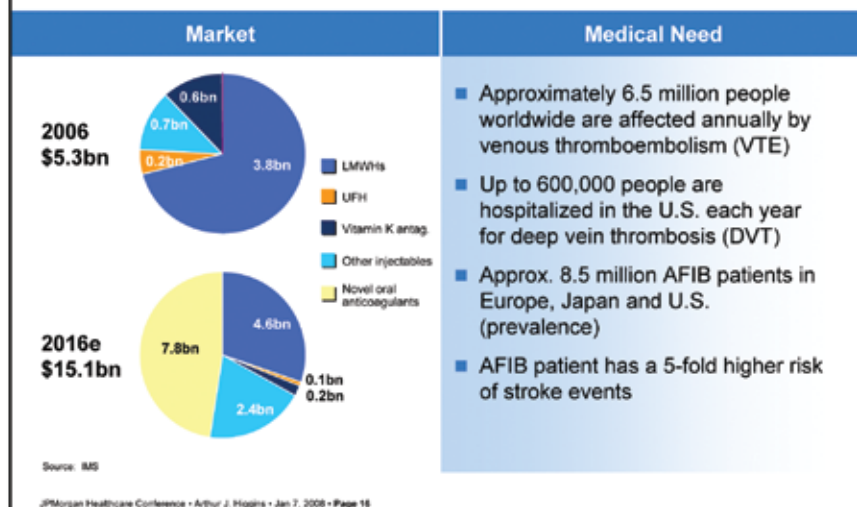
Xarelto has:

Oral administration	Convenient use both in and out of hospital	✓
Once daily dosing	Key issue to enhance compliance in the target population	✓
Predictability	Safe and effective regulation of coagulation from the first dose and throughout therapy	✓
Wide therapeutic window	Broad safety margin at a wide range of effective doses	✓
Minimal food/drug interactions	Ease of use with concomitant medication and diet	✓
No monitoring	No need for laboratory monitoring saves healthcare costs through fewer hospital / physician visits and patients' time	✓

... based on current knowledge

JPMorgan Healthcare Conference • Arthur J. Higgins • Jan 7, 2008 • Page 15

Anticoagulants – A Large Unmet Medical Need



Source: IMS

JPMorgan Healthcare Conference • Arthur J. Higgins • Jan 7, 2008 • Page 16

able blood thinner, marketed since 1993 by **Sanofi-Aventis** (sanofi-aventis.com), has generated annual sales of more than \$3 billion.

Three large studies named Record demonstrated that rivaroxaban was consistently superior in efficacy and comparable to Lovenox in safety after direct analysis. Lovenox is the current standard of care, and the product contains the active ingredient enoxaparin. Rivaroxaban showed the ability to prevent life-threatening blood clots in patients undergoing total hip-replacement surgery

and knee-replacement surgery.

About 700,000 Americans have hip-replacement and knee-replacement surgeries every year. A blood clot is the most-common cause of re-hospitalization for this patient group. Venous thromboembolism is considered the most-frequent preventable serious and potentially fatal complication following major orthopedic surgery.

This article can be accessed online at

PharmaLive.com