

Pharmaceuticals

The Pharmaceuticals Division of Novartis is recognized worldwide for the innovative medicines we provide to patients, physicians and healthcare organizations. This growing business develops and markets patent-protected prescription drugs for important health needs. Our products are concentrated in major therapeutic areas including:

- Cardiovascular and Metabolism
- Oncology and Hematology
- Neuroscience and Ophthalmics
- Respiratory
- Immunology and Infectious Diseases

The current product portfolio includes more than 50 key marketed products, many of which are leaders in their respective therapeutic areas. In 2008 a total of 11 positive regulatory decisions were received in the United States and Europe.

The product development pipeline has 152 projects in various stages of clinical development, including potential new products as well as potential new indications or formulations for existing products.

Key marketed products

Diovan (valsartan) and *Diovan HCT/Co-Diovan* (valsartan and hydrochlorothiazide) together comprise the world's best-selling brand of high blood pressure medicines. *Diovan* is the only agent in its class approved to treat all of the following: patients with high blood pressure, high-risk heart attack survivors and patients with heart failure. The efficacy and safety profile of *Diovan* has been well-established by a large body of evidence. *Diovan* inhibits a hormone, angiotensin II, from binding to a receptor that causes arteries to tighten and narrow, an action that can cause high blood pressure. The single-pill combination product *Co-Diovan* includes the diuretic hydrochlorothiazide and provides additional efficacy for patients needing a greater reduction in blood pressure. In July 2008, the US Food and Drug Administration (FDA) approved *Diovan HCT* as a first-line therapy. First launched in 1996, *Diovan* is available in more than 100 countries.

Innovative products in five major therapeutic areas

Strong pipeline of new medicines to help drive future growth

Best-selling brand of high blood pressure medicines

Exelon (rivastigmine tartrate) is a treatment for mild to moderate Alzheimer's disease and the only approved product for the treatment of mild to moderate dementia associated with Parkinson's disease. First approved in 1997, *Exelon* is available in more than 70 countries. In 2007 *Exelon* Patch (rivastigmine transdermal system), the only transdermal patch for mild to moderate Alzheimer's disease and Parkinson's disease, was approved in the United States and Europe. *Exelon* Patch has now been launched in more than 40 countries.

Only approved product for treatment of mild to moderate dementia associated with Parkinson's disease

Famvir (famciclovir) is an antiviral agent for the treatment of recurrent genital herpes, recurrent herpes labialis (cold sores) and herpes zoster (shingles). Other indications include the treatment of herpes simplex (a virus that can cause blisters on the skin or mucous membranes) in HIV-infected patients. *Famvir* was first launched in 1994 and is registered in more than 70 countries. *Famvir* faces generic competition in the United States and Europe.

Antiviral drug for treatment of herpes

Femara (letrozole tablets/letrozole) is a once-daily oral aromatase inhibitor for the treatment of early-stage or advanced breast cancer in postmenopausal women. First launched in 1996, *Femara* is currently available in more than 90 countries. *Femara* has received US and EU regulatory approval for a number of indications, most recently for use as an adjuvant treatment (post-surgery) in women with early-stage breast cancer. In 2006 *Femara* also received regulatory approval in Japan.

Treatment of early-stage or advanced breast cancer in postmenopausal women

Gleevec/Glivec (imatinib mesylate/imatinib) is a signal transduction inhibitor approved to treat certain forms of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST). First launched in 2001, *Gleevec/Glivec* is available in more than 80 countries. It is one of the first oncology drugs that validates rational drug design based on an understanding of how some cancer cells work. A signal transduction inhibitor interferes with the pathways that stimulate the growth of tumor cells. In the United States, *Gleevec/Glivec* is used to treat newly diagnosed adult and pediatric patients with a form of CML. This condition is a rare form of cancer but one of the most common adult leukemias, and it usually tests positive for the presence of the Philadelphia (Ph) chromosome. *Gleevec/Glivec* is also indicated for the treatment of patients with certain forms of GIST and, in the United States, *Gleevec/Glivec* is also approved for aggressive systemic mastocytosis. In 2008 *Gleevec/Glivec* received US regulatory approval for an adjuvant treatment of patients with

Treatment for certain forms of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST)

GIST and is awaiting approval in Europe. *Gleevec/Glivec* is also approved in the United States and Europe for the treatment of Philadelphia-positive acute lymphoblastic leukemia (ALL) and in certain markets for use in various rare cancers. *Gleevec/Glivec* Global Access Programs comprise a range of flexible models through which Novartis Oncology partners with national and provincial governments, other payors, and charitable organizations to bring this critical drug to the broadest number of patients possible. The full donation program, the *Gleevec/Glivec* International Patient Assistance Program (GIPAP), is available in 80 countries and to date has provided treatment at no charge to almost 35 000 patients worldwide who otherwise would not have access to this innovative therapy.

Neoral (cyclosporine) is an immunosuppressant to prevent organ rejection following a kidney, liver or heart transplant. *Neoral* is one of the world's most commonly used primary immunosuppressants, largely replacing its predecessor *Sandimmun/Sandimmune*, which revolutionized organ transplantation when it was introduced by Novartis in 1982. First launched in 1995, *Neoral* is also used in treating select autoimmune disorders such as psoriasis and rheumatoid arthritis. *Neoral* faces generic competition in certain markets.

One of world's most commonly used primary immunosuppressants

Sandostatin LAR/Sandostatin SC (octreotide acetate) is used for the treatment of patients with acromegaly, a chronic disease in adults caused by over-secretion of pituitary growth hormone. It is also approved for use to treat certain symptoms associated with carcinoid tumors and other types of gastrointestinal neuroendocrine and pancreatic tumors. *Sandostatin* is a synthetic protein that mimics the action of somatostatin, a naturally occurring hormone. *Sandostatin SC* faces generic competition in the United States. However, patent protection for *Sandostatin LAR* continues in major markets.

Treatment for patients with acromegaly

Trileptal (oxcarbazepine) is an anti-epileptic drug for the treatment of partial seizures, as adjunctive or monotherapy, in adults and children age four and above. In the United States, *Trileptal* has also been approved for adjunctive therapy for children age two and above. First approved in 1990, *Trileptal* acts by stabilizing neuronal functions, thereby controlling and limiting the spread of seizures. *Trileptal* is available in more than 60 countries but faces generic competition in the United States.

Anti-epileptic drug for treatment of partial seizures

Voltaren/Cataflam (diclofenac sodium/potassium) is a leading non-steroidal anti-inflammatory drug (NSAID) for the relief of symptoms in rheumatic diseases such as rheumatoid arthritis and osteoarthritis and for various other inflammatory or pain conditions. This product, which faces generic competition, is available in a wide variety of dosage forms including tablets, drops, suppositories, ampoules and topical therapy. In various markets, low-dose oral forms of *Voltaren* and topical therapy are available as over-the-counter products.

Leading non-steroidal anti-inflammatory drug (NSAID)

Xolair (omalizumab) is the first humanized monoclonal antibody approved for the treatment of moderate to severe allergic asthma in the United States and for severe allergic asthma in Europe in adolescents (aged 12 and above) and adults. It has been approved in 61 countries, including the United States in 2003 and Europe in 2005. In 2008 Novartis received a positive CHMP opinion for a liquid formulation for European approval and filed for use of *Xolair* in pediatric patients in Europe. *Xolair* was submitted for use in children aged six to under 12 years old in the United States by Genentech, Inc. *Xolair* is manufactured by Novartis Pharma AG. In the United States, it is co-promoted by Novartis Pharmaceuticals Corporation and Genentech, Inc.

First humanized monoclonal antibody for treatment of severe allergic asthma

Zometa (zoledronic acid for injection/zoledronic acid 4 mg) is a treatment for certain cancers that have spread to the bones. First approved in 2001, *Zometa*, a third-generation bisphosphonate, is available in more than 80 countries. *Zometa* is approved in most key markets for the treatment of skeletal-related events in patients with cancer involving bone, including prostate, breast, lung and multiple myeloma, as well as hypercalcemia of malignancy (tumor-induced excessive levels of calcium). The active ingredient is also approved under the brand name *Aclasta/Reclast* for use in other indications.

Treatment for certain cancers that have spread to bones

Recently launched products

Aclasta/Reclast (zoledronic acid 5 mg) is the first once-yearly infusion for postmenopausal women with osteoporosis, approved in more than 80 countries to reduce the risk of fractures in areas of the body typically affected by osteoporosis, including the hip, spine and other bones. *Aclasta/Reclast* is also approved to treat osteoporosis in men and to reduce the risk of new clinical fractures in patients who recently suffered a low-trauma hip fracture. *Aclasta/Reclast* was first approved in 2005 for Paget's disease of bone. This active ingredient is also marketed under the brand name *Zometa* for use in oncology indications.

First once-yearly infusion for postmenopausal women with osteoporosis

Exforge (valsartan and amlodipine besylate) is the first single-pill combination of the two best-selling antihypertensives in their respective classes: angiotension receptor blocker (ARB) and calcium channel blocker (CCB). *Exforge* was approved in 2007 for the treatment of high blood pressure in the United States and Europe. In July 2008, the US FDA approved *Exforge* as a first-line therapy. Clinical trial data have shown that *Exforge* is a powerful medication, getting nine out of 10 patients to treatment goals. It works across all grades of high blood pressure and offers powerful blood pressure drops of up to 43 mmHg in some patients.

First single-pill combination of the two best-selling anti-hypertensives

Exjade (deferasirox) is the first once-daily oral iron chelator approved to remove excess iron caused by blood transfusions in patients who have a wide range of underlying anemias. Iron overload is a cumulative, potentially life-threatening consequence of frequent blood transfusions. *Exjade* is the first significant breakthrough therapy for this condition in more than 40 years, offering an alternative therapy for many patients who currently take deferoxamine and undergo up to 12-hour infusions for five to seven nights per week. *Exjade* is approved in more than 90 countries, including the United States, Europe and Japan.

First once-daily oral iron chelator approved to remove excess iron caused by blood transfusions in patients with wide range of underlying anemias

Extavia is a version of interferon beta-1b branded by Novartis, approved in Europe to treat a broad range of multiple sclerosis (MS) patients, from the first signs of active disease to more advanced relapsing stages. Formerly known as NVF233, *Extavia* is the same medicinal product as Betaferon®, an interferon beta-1b, which is marketed by Bayer Schering and was the first beta interferon treatment for MS. Novartis gained rights to its own branded version of interferon beta-1b in an agreement with Bayer Schering. Interferon beta-1b has a well-characterized efficacy and safety profile, with more than 700 000 patient years' experience and a 17-year track record of clinical use – the longest for any interferon beta in the treatment of MS. The January 2009 launch of *Extavia* in a number of European countries marks the beginning of a long-term commitment by Novartis to meeting the therapeutic needs of the MS community. *Extavia* has also been filed in the United States.

Treatment for broad range of multiple sclerosis (MS) patients

Galvus (vildagliptin), a new oral treatment for type 2 diabetes, and *Eucreas*, a single-pill combination of vildagliptin and metformin, have shown promising results during the rollout in Europe following approvals in early 2008. Data show *Galvus* is better tolerated by patients with type 2 diabetes, with no weight gain, a favorable cardiovascular profile and equal efficacy

New oral treatments for type 2 diabetes patients

compared to widely used thiazolidinediones (TZDs). *Eucreas* was the first single-pill combination of a DPP-IV inhibitor to be launched in Europe. *Galvus* and *Eucreas* are approved as oral treatments for type 2 diabetes patients in all 27 European countries, Norway and Iceland. *Galvus* is currently available in 25 countries and is approved in more than 50 countries. *Eucreas* is available in 16 countries.

Lucentis (ranibizumab) is the first approved treatment for “wet” age-related macular degeneration (AMD) shown to improve vision. AMD is considered the leading cause of blindness in people over age 50. *Lucentis* binds and inactivates vascular endothelial growth factor (VEGF), a protein that plays a role in angiogenesis (formation of new blood vessels). *Lucentis* has been shown in Phase III studies in AMD to improve vision and restore the ability to do everyday activities. In a Phase II study called RESOLVE, *Lucentis* significantly improved vision compared to placebo in patients with diabetic macular edema (DME), an eye condition linked with high blood sugar that causes blindness. The Phase III RESTORE study was started in May 2008 in DME, with submission in Europe planned for 2010. *Lucentis* is approved in more than 70 countries, including Europe, Canada, Australia and the United States. *Lucentis* is developed in collaboration with Genentech, Inc., which retains the rights in the United States.

First approved treatment for “wet” age-related macular degeneration shown to improve vision

Tasigna (nilotinib) was launched during the fourth quarter of 2007 in the United States and Europe following regulatory approvals as a new therapy for patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) who are resistant or intolerant to treatment with *Gleevec/Glivec* (imatinib). *Tasigna* is now approved in more than 50 countries and was also submitted for approval in Japan in June 2008. Separate Phase III studies comparing *Tasigna* and *Gleevec/Glivec* in newly diagnosed CML patients are underway. A registration study is also underway in patients with gastrointestinal stromal tumors (GIST) who are resistant or intolerant to prior treatment.

New therapy for patients with Philadelphia chromosome-positive chronic myeloid leukemia who are resistant/intolerant to *Gleevec/Glivec* treatment

Tekturna/Rasilez (aliskiren), the first new type of high blood pressure medicine in more than a decade, continues to grow in the United States and Europe. In addition to providing effective blood pressure reductions that last beyond 24 hours both as monotherapy and in combination, the first-in-class direct renin inhibitor has the potential to protect organs such as the heart and kidneys. *Tekturna/Rasilez* is currently being investigated further in the landmark ASPIRE HIGHER program, the largest

First new type of high blood pressure medicine in more than a decade

ongoing cardio-renal outcomes program worldwide involving more than 35 000 patients in 14 trials. Data from the ALOFT (heart failure) and AVOID (kidney disease) studies, which are part of the ASPIRE HIGHER program, have been added to European product information. *Tekturna/Rasilez* is approved in 65 countries. *Tekturna* was approved in the United States in March 2007 and *Rasilez* in Europe in August 2007. *Rasilez HCT*, which includes the diuretic hydrochlorothiazide, was approved in Switzerland in October 2008 and a European Commission decision is expected for this single-pill combination in early 2009. *Tekturna HCT* was approved in the United States in January 2008. Additional single-pill combinations in the pipeline include a combination of *Tekturna/Rasilez* with *Diovan* (valsartan); *Tekturna/Rasilez* with the calcium channel blocker amlodipine, and a triple-combination therapy with *Tekturna/Rasilez*, amlodipine and a diuretic.

Selected compounds in development

FTY720 (fingolimod), a sphingosine-1-phosphate receptor modulator, has the potential to become the first oral disease-modifying treatment for patients with relapsing multiple sclerosis, a disabling neurological condition estimated to affect approximately 2.5 million people worldwide. Phase II data evidence a profound reduction in relapses and inflammatory disease activity as seen by magnetic resonance imaging, an effect that has since been maintained for three years. The Phase III program started in 2006 and is currently ongoing. First Phase III results from the TRANSFORMS study for FTY720 showed superior relapse-related efficacy at one year compared to interferon beta-1a. FTY720 was generally well-tolerated, and its safety profile was in line with previous clinical experience. Further analysis of the data and results from two other ongoing Phase III studies will help to provide a more comprehensive assessment of FTY720's risk/benefit profile. FTY720 was licensed from Mitsubishi Tanabe Pharma Corporation.

Potential first oral disease-modifying treatment for patients with relapsing multiple sclerosis

ACZ885 (canakinumab) is a human monoclonal antibody which targets interleukin 1 β (IL-1 β), a key chemical messenger that drives inflammation and tissue destruction. ACZ885 is in registration for the treatment of a group of rare genetic lifelong diseases such as cryopyrin-associated periodic syndromes (CAPS), including Muckle-Wells syndrome (MWS), a rare disorder characterized by chronic recurrent urticaria (hives), periodic arthralgia (joint pain) and fever. ACZ885 is also being developed for systemic juvenile idiopathic arthritis (SJIA) and rheumatoid

Human monoclonal antibody in development for treatment of rare genetic lifelong diseases

arthritis. In December 2008, Novartis filed ACZ885 for CAPS in Europe, the United States and Switzerland. It has been granted orphan status for CAPS and SJIA in Europe and the United States.

QAB149 (indacaterol) is a once-daily beta-2 agonist that offers sustained 24-hour bronchodilation with fast onset of action for the treatment of chronic obstructive pulmonary disease (COPD), a progressive respiratory disease. QAB149 was filed in Europe and the United States in December 2008. Phase III studies with QAB149 in a single-dose dry powder device show that it provides fast onset, clinically relevant and sustained 24-hour bronchodilation with no evidence of loss of effect over a 52-week treatment in patients with moderate to severe COPD. QAB149 is also being investigated as a possible fixed-dose combination with the long-acting muscarinic antagonist (LAMA) NVA237. In addition, Novartis and Schering-Plough are jointly developing QMF149, a once-daily fixed dose combination of QAB149 and Schering-Plough's inhaled corticosteroid mometasone (the active ingredient in Asmanex®). QMF149 is currently in Phase II development.

Potential treatment for patients with chronic obstructive pulmonary disease (COPD)

Afinitor/RAD001 (everolimus), a once-daily oral inhibitor of the mTOR pathway that has demonstrated broad clinical activity in multiple tumors, is progressing toward a potential first regulatory approval in 2009. *Afinitor* is under regulatory review in Europe, the United States and other countries based on results from the RECORD-1 trial showing *Afinitor* more than doubled the time without tumor growth in patients with advanced kidney cancer after failure of standard treatment. A decision in the United States is expected by the end of the first quarter of 2009. New data presented in 2008 showed that *Afinitor* controls tumor growth in patients with advanced pancreatic neuroendocrine tumors (NET) when used in combination with octreotide IM or as monotherapy. Registration trials in the first- and second-line setting for this rare and difficult-to-treat form of cancer, as well as a trial in progress in advanced carcinoid tumors, are already under way. The investigational medicine has also shown potential in HER2-positive breast cancer, with a Phase III trial expected to start this year. In cancer cells, *Afinitor* provides continuous inhibition of mTOR, a protein that acts as a central regulator of tumor cell division, cell metabolism and blood vessel growth.

Once-daily oral inhibitor of the mTOR pathway that has demonstrated broad clinical activity in multiple tumors

EPO906 (patupilone) is a novel microtubule stabilizer that has shown broad anticancer activity preclinically, including anti-vascular and antimetastatic activity. The global development program for patupilone includes a Phase III study in resistant/refractory ovarian cancer, and Phase II studies in brain metastases from lung cancer and breast cancer, hormone refractory prostate cancer and in GI malignancies.

Novel microtubule stabilizer that has shown broad anti-cancer activity

SOM230 (pasireotide) is a somatostatin analogue in development for Cushing's disease and acromegaly as first-line medical therapy following surgery and for carcinoid syndrome for patients refractory/resistant to *Sandostatin LAR*. Phase II studies show significant hormone reductions in Cushing's disease and acromegaly patients, and achievement of partial or complete symptom control in patients with refractory/resistant carcinoid syndrome. A Phase III registration study for Cushing's disease, a rare disorder characterized by excessive excretion of the hormone cortisol from a pituitary adenoma (tumor) and a condition for which there is no approved medical therapy is currently enrolling patients. A Phase III trial in acromegaly and a Phase III trial in carcinoid tumors are under way.

Somatostatin analogue in development for Cushing's disease and acromegaly

LCZ696 is a novel dual-acting molecule that blocks the angiotensin receptor blocker (ARB) and inhibits neutral endopeptidase (NEPi). The compound is set to enter Phase III development in 2009 in the treatment of heart failure, an indication in which angiotensin-converting enzyme (ACE) inhibitors are the current standard of care. Phase II studies involving 1 300 patients showed LCZ696 provided superior blood pressure reductions compared with valsartan alone and was well-tolerated with no reported cases of angioedema (swelling).

Dual-acting molecule that blocks angiotensin receptor blocker (ARB) and inhibits neutral endopeptidase (NEPi)

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