

NOVARTIS AG  
Form 6-K  
February 11, 2011

# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

## FORM 6-K

**REPORT OF FOREIGN PRIVATE ISSUER  
PURSUANT TO RULE 13a-16 or 15d-16 OF  
THE SECURITIES EXCHANGE ACT OF 1934**

**Report on Form 6-K dated February 9, 2011**

**(Commission File No. 1-15024)**

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(Name of Registrant)

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(Address of Principal Executive Offices)

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Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F:

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Yes:  **No:**

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**- Investor Relations Release -**

**Novartis drug Afinitor® extends progression-free survival in patients with advanced pancreatic NET, study published in NEJM shows**

- *RADIANT-3 trial shows everolimus more than doubled median progression-free survival from 4.6 to 11.0 months versus placebo(1)*
- *No tumor growth after 18 months in 34% of the patients treated with everolimus versus in 9% of those treated with placebo(1)*
- *These data, previously reported at oncology congresses, support worldwide regulatory submissions for treatment of advanced neuroendocrine tumors (NET), which has received priority review designation by US FDA*

**Basel, February 9, 2011** *The New England Journal of Medicine* (NEJM) published a study today that shows Afinitor® (everolimus) tablets plus best supportive care (BSC) more than doubled progression-free survival (PFS), or time without tumor growth, versus placebo plus BSC in patients with advanced pancreatic neuroendocrine tumors (NET)(1).

Data from the study, RADIANT-3 (RAD001 In Advanced Neuroendocrine Tumors), were first presented last year at the 12th World Congress on Gastrointestinal Cancer in Barcelona(2). Regulatory submissions for everolimus to treat this patient population are underway worldwide.

Results from the trial showed that everolimus more than doubled median PFS from 4.6 to 11.0 months when compared with placebo and reduced the risk of cancer progression by 65% (hazard ratio=0.35 [95% confidence interval (CI), 0.27 to 0.45]; p<0.001) in patients with advanced pancreatic NET. After 18 months, 34% of patients treated with everolimus (95% CI, 26 to 43) were alive and progression-free versus 9% of those treated with placebo (95% CI, 4 to 16), showing a more prolonged benefit for patients treated with everolimus(1).

Pancreatic NET originates from the islet cells of the pancreas and can grow aggressively(3). It is a distinct and uncommon disease that is different from what is generally referred to as pancreatic cancer or pancreatic exocrine cancer(4). At time of diagnosis the majority of patients

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have advanced disease, meaning the cancer has spread to other parts of the body and has become more difficult to treat(3),(5). The median survival duration for patients with advanced pancreatic NET is 24 months(6).

A patient diagnosed with advanced NET may have limited treatment options, said James Yao, MD, Associate Professor of Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas. Results from the RADIANT-3 trial are encouraging and demonstrate the potential benefit of treating advanced pancreatic NET with the mTOR inhibitor everolimus.

Everolimus targets mTOR, a protein that acts as an important regulator of tumor cell division, blood vessel growth and cell metabolism(7). Preclinical and clinical data have established the role

of mTOR in the development and progression of several types of tumors, including pancreatic NET.

The US Food and Drug Administration (FDA) has granted everolimus priority review designation for the application of advanced NET of gastrointestinal (GI), lung or pancreatic origin based on results of RADIANT-3 and another Phase III trial, RADIANT-2. Priority review status is granted to therapies that offer major advances in treatment or provide a treatment where no adequate therapy exists(8).

This status accelerates the standard review time for everolimus from 10 to six months(8). Since the data included in the submission may require further discussion, the FDA is likely to call an Advisory Committee meeting, which could result in the FDA extending the review period. Worldwide regulatory filings for everolimus in this indication are also underway.

### **About RADIANT-3**

RADIANT-3 is a Phase III prospective, double-blind, randomized, parallel group, placebo-controlled, multicenter study. The trial examined the efficacy and safety of everolimus plus BSC versus placebo plus BSC in 410 patients with advanced, low- or intermediate-grade pancreatic NET, also known as islet cell tumors. Patients who met the study entry criteria were randomized 1:1 to receive either everolimus 10 mg once-daily (n=207) or daily placebo (n=203) orally, both in conjunction with BSC(1).

The primary endpoint of RADIANT-3 is PFS. Secondary endpoints include safety, objective response rate (confirmed according to RECIST), duration of response and overall survival(1).

In the study, everolimus maintained a safety profile consistent with the prescribing information and previous studies of the drug. The most frequent all grade, drug-related adverse events ( $\geq 20\%$ ) were stomatitis/oral mucositis/ulcers (64% everolimus vs. 17% placebo; includes stomatitis, aphthous stomatitis, mouth ulceration and tongue ulceration), rash (49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), infections (23% vs. 6%), nausea (20% vs. 18%), peripheral edema (20% vs. 3%) and decreased appetite (20% vs. 7%); most were grade one or two. Grade three and four adverse events ( $\geq 5\%$ ) include stomatitis/oral mucositis/ulcers (7% vs. 0%; includes stomatitis, aphthous stomatitis, mouth ulceration and tongue ulceration), anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%). Median exposure to everolimus was 2.3-fold longer than exposure to placebo (38 vs. 16 weeks)(1).

### **About RADIANT-2**

RADIANT-2 is a Phase III randomized, double-blind, placebo-controlled, multicenter study. The trial examined the efficacy and safety of everolimus plus Sandostatin® LAR® (octreotide acetate for injectable suspension) versus placebo plus octreotide LAR in 429 patients with advanced carcinoid tumors. Patients who met the study's entry criteria were randomized 1:1 to receive either oral everolimus (10 mg daily) plus octreotide LAR (30 mg intramuscularly every 28 days) or placebo daily plus octreotide LAR. Patients had radiological documentation of disease progression within 12 months prior to randomization(9).

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The study did not meet its primary endpoint of PFS as assessed by independent radiological review ( $p=0.026$  vs.  $p=0.0246$  predefined) (hazard ratio=0.77 [95% CI, 0.59 to 1.00]). Secondary endpoints from the trial include safety, overall response rate and overall survival(9).

In the initial review of the data an imbalance in baseline characteristics was observed between the two treatment arms, including prior treatment with chemotherapy, primary tumors located in the lung and a poorer World Health Organization (WHO) performance status (an assessment of each patient's functional/physical performance). Further, inconsistencies were found between analyses of radiology scans, which resulted in censoring of patients from the trial. These imbalances and the censoring of data seem to favor the control arm and may have impacted the outcome of the study. Additional analyses to adjust for imbalances in the treatment arms show

everolimus plus octreotide LAR significantly reduced risk of disease progression (hazard ratio=0.60 [95% CI, 0.44 to 0.84])(9).

In the study, the most frequent all grade drug-related adverse events with everolimus plus octreotide LAR were stomatitis, rash, fatigue, diarrhea, nausea and infections; most were grade one or two. Grade three and four adverse events ( $\geq 5\%$ ) with everolimus plus octreotide LAR were stomatitis (7%; includes stomatitis, aphthous stomatitis, mouth ulceration and tongue ulceration), fatigue (7%), diarrhea (6%), infections/infestations (5%) and hyperglycemia (5%)(9).

#### **About neuroendocrine tumors (NET)**

Neuroendocrine tumors arise from cells that can produce and secrete a variety of hormones that regulate bodily functions(10). There are many types of NET that can occur throughout the body; however, most are found in the GI tract, pancreas and lungs(6),(11). Many patients with NET have no symptoms or nonspecific symptoms, such as flushing and diarrhea, which often lead to delays in diagnosis of five to seven years(12),(13). As a result, many patients with NET often have advanced disease when diagnosed, meaning the cancer has spread to other parts of the body and has become more difficult to treat(3),(5). Approximately 64% of patients with pancreatic NET are diagnosed in advanced stages(6).

#### **About Afinitor (everolimus)**

Afinitor® (everolimus) tablets is approved in the European Union (EU) for the treatment of patients with advanced renal cell carcinoma (RCC) whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy and also in the US for the treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib.

Afinitor is also approved in the US to treat patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of Afinitor is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been shown. Novartis has submitted marketing applications for everolimus to the European Medicines Agency (EMA) and the Swiss Agency for Therapeutic Products (Swissmedic), and additional regulatory submissions are underway worldwide.

In the EU, everolimus is available in different dosage strengths under the trade name Certican® for the prevention of organ rejection in heart and kidney transplant recipients. In the US, everolimus is available in different dosage strengths under the trade name Zortress® for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.

Everolimus is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Not all indications are available in every country. As an investigational compound the safety and efficacy profile of everolimus has not yet been established in NET. Access to everolimus outside of the approved indications has been carefully controlled and monitored in clinical trials designed to better understand the potential benefits and risks of the compound. Because of the uncertainty of clinical trials, there is no guarantee

that everolimus will become commercially available for NET or any additional indications anywhere in the world.

**Important Safety Information about Afinitor (everolimus) tablets**

Afinitor is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives or to any of the excipients.

Cases of non-infectious pneumonitis have been described; some of these have been severe and occasionally fatal. Management of pneumonitis may require dose adjustment and/or interruption, or discontinuation of treatment and/or addition of corticosteroid therapy.

Afinitor is immunosuppressive. Localized and systemic bacterial, fungal, viral or protozoal infections (e.g., pneumonia, aspergillosis, candidiasis, hepatitis B reactivation) have been described; some of these have been severe and occasionally fatal. Pre-existing infections should be treated prior to starting treatment. Patients and physicians should be vigilant for symptoms and signs of infection; in case of emergent infections, appropriate treatment should be promptly instituted and interruption or discontinuation of Afinitor should be considered. Patients with systemic invasive fungal infections should not receive Afinitor.

Hypersensitivity reactions have been observed.

Mouth ulcers, stomatitis and oral mucositis have been seen. Topical treatments are recommended; alcohol- or peroxide-containing mouthwashes should be avoided.

Monitoring of renal function, blood glucose and complete blood counts is recommended prior to initiation and periodically during treatment. Cases of renal failure, some fatal, have been observed.

Afinitor is not recommended in patients with severe hepatic impairment.

Use of live vaccines should be avoided.

Afinitor is not recommended during pregnancy or for women of childbearing potential not using contraception. Afinitor may cause fetal harm in pregnant women. Women taking Afinitor should not breast feed. Male fertility may be compromised by Afinitor.

Avoid concurrent treatment with strong CYP3A4 and PgP inhibitors and use caution with moderate inhibitors. Avoid concurrent treatment with strong CYP3A4 or PgP inducers.

In advanced RCC, the most common adverse reactions ( $\geq 10\%$ ) include stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, cough, infections, peripheral edema, dry skin, epistaxis, pneumonitis, pruritus and dyspnea. Common adverse reactions ( $\geq 1$  to  $<10\%$ ) include headache, dysgeusia, dry mouth, pyrexia, weight loss, hand-foot syndrome, abdominal pain, erythema, insomnia, dyspepsia, dysphagia, hypertension, increased daytime urination, dehydration, chest pain, renal failure, hemoptysis and exacerbation of diabetes mellitus. Uncommon adverse reactions ( $<1\%$ ) include ageusia, congestive cardiac failure, new-onset diabetes mellitus, impaired wound healing, and grade I hemorrhage.

Cases of hepatitis B reactivation and pulmonary embolism have been reported.

In patients with SEGA, the most common adverse reactions ( $\geq 10\%$ ) include infections, hypertriglyceridaemia, cough, stomatitis, diarrhoea, acneiform dermatitis, acne, pyrexia, and decreased white blood cell count. Common adverse reactions ( $\geq 1$  to  $< 10\%$ ) include pharyngeal inflammation, gastritis, vomiting, mucosal inflammation, increased blood triglycerides, anxiety, somnolence, hypertension, respiratory disorders, dry skin, pityriasis rosea, proteinuria, fatigue, peripheral oedema, ocular hyperaemia, and decreased blood immunoglobulin G.

**About Sandostatin LAR (octreotide acetate for injectable suspension)**

Sandostatin® LAR® is a long-acting, injectable depot formulation of octreotide acetate that is indicated for the treatment of patients with acromegaly who are adequately controlled on s.c. treatment with Sandostatin; in whom surgery or radiotherapy is inappropriate or ineffective; or in the interim period until radiotherapy becomes fully effective and for the treatment of patients with symptoms associated with functional GEP-NET in whom symptoms are adequately controlled on s.c. treatment with Sandostatin.

Sandostatin LAR was first approved in France in June 1995 and is currently approved in 85 countries. For more than a decade, Sandostatin LAR has achieved a long-standing track record of sustained efficacy with a well-established safety profile.

Not all indications are approved in every country.

### **Important Safety Information about Sandostatin LAR**

Patients who have a known hypersensitivity to octreotide or to any of the excipients should not take Sandostatin LAR. Dose adjustments of drugs, such as beta-blockers, calcium channel blockers or agents to control fluid and electrolyte balance may be necessary. Caution should be used in patients with insulinomas; patients with diabetes mellitus. Thyroid function should be monitored if receiving prolonged treatment with octreotide. Patients receiving Sandostatin LAR should receive periodic examination of the gallbladder; and patients who have a history of vitamin B12 deprivation should have their vitamin B12 levels monitored. Caution should be used in patients who are pregnant; patients should be advised to use adequate contraception, if necessary. Patients should not breast-feed during Sandostatin LAR treatment. The use of Sandostatin LAR may increase the bioavailability of bromocriptine, impair intestinal absorption of cyclosporin and delay that of cimetidine. Drugs mainly metabolized by CYP3A4 and that have a low therapeutic index should be used with caution.

Very common ( $\geq 1/10$ ) adverse drug reactions in clinical studies with Sandostatin LAR were diarrhea, abdominal pain, nausea, constipation, flatulence, headache, cholelithiasis, hyperglycemia and injection-site localized pain. Common ( $\geq 1/100$ ,  $< 1/10$ ) adverse drug reactions were dyspepsia, vomiting, abdominal bloating, steatorrhea, loose stools, discoloration of feces, dizziness, hypothyroidism, thyroid dysfunction (e.g., decreased thyroid stimulating hormone, decreased Total T4 and decreased Free T4), cholecystitis, biliary sludge, hyperbilirubinemia, hypoglycemia, impairment of glucose tolerance, anorexia, elevated transaminase levels, pruritus, rash, alopecia, dyspnea and bradycardia.

The uncommon ( $\geq 1/1000$ ,  $< 1/100$ ) adverse drug reactions were dehydration and tachycardia. The following adverse reactions have been reported postmarketing: anaphylaxis, allergy/hypersensitivity reactions, urticaria, acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice, arrhythmia, increased alkaline phosphatase levels and increased gamma glutamyl transferase levels.

### **Disclaimer**

The foregoing release contains forward-looking statements that can be identified by terminology such as encouraging, potential, priority review, likely, could, will, or similar or similar expressions, or by express or implied discussions regarding potential submissions or approvals for new indications or labeling for Afinitor, or regarding the potential timing of any such approvals, or regarding potential future revenues from Afinitor. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Afinitor to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Afinitor will be submitted or approved for any additional indications or labeling in any market. Nor can there be any guarantee that Afinitor will achieve any particular levels of revenue in the future. In particular, management's expectations regarding Afinitor could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry and general public pricing pressures; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, and

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other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties

materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

## About Novartis

Novartis provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines, diagnostic tools and consumer health products. Novartis is the only company with leading positions in these areas. In 2010, the Group's continuing operations achieved net sales of USD 50.6 billion, while approximately USD 9.1 billion (USD 8.1 billion excluding impairment and amortization charges) was invested in R&D throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 119,000 full-time-equivalent associates (including 16,700 Alcon associates) and operate in more than 140 countries around the world. For more information, please visit <http://www.novartis.com>.

Novartis is on Twitter. Sign up to follow @Novartis at <http://twitter.com/novartis>.

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**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

**Novartis AG**

Date: February 9, 2011

By: */s/ MALCOLM B. CHEETHAM*

Name: Malcolm B. Cheetham  
Title: Head Group Financial  
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