

NOVARTIS AG  
Form 6-K  
January 26, 2018

**UNITED STATES**

**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 January 26, 2018**

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

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**Novartis AG**

(Name of Registrant)

**Lichtstrasse 35**

**4056 Basel**

**Switzerland**

(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:

**Form 20-F:** Form 40-F:

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1):

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Indicate by check mark whether the registrant by furnishing the information contained in this form is also thereby furnishing the information to the Commission pursuant to Rule 12g3-2(b) under the Securities Exchange Act of 1934.

Yes: **No:**

Novartis International AG  
Novartis Global Communications

CH-4002 Basel  
Switzerland

<http://www.novartis.com>

**MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG**

**Advanced Accelerator Applications Receives FDA Approval for Lutathera® for Treatment of Gastroenteropancreatic Neuroendocrine Tumors**

- *Lutathera marks first FDA Approval for a Peptide Receptor Radionuclide Therapy (PRRT)*
- *Advanced Accelerator Applications is a newly established subsidiary of Novartis*
- *Lutathera expands Novartis' neuroendocrine tumor portfolio, building on long heritage and leadership*

**Basel, January 26, 2018** - Novartis AG (NYSE: NVS) today announced that Advanced Accelerator Applications, a subsidiary of Novartis Groupe S.A., has received US Food and Drug Administration (FDA) approval of its new drug application (NDA) for Lutathera® (lutetium Lu 177 dotatate\*) for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors, in adults. Lutathera, which received orphan drug designation from the FDA, is a first-in-class drug and the first available FDA-approved Peptide Receptor Radionuclide Therapy (PRRT), a form of treatment comprising of a targeting molecule that carries a radioactive component. The approval was based on a Phase 3 study which demonstrated a 79% reduction in the risk of disease progression or death within the Lutathera plus best standard of care arm (octreotide LAR 30mg every four weeks) compared to 60 mg of octreotide LAR alone (hazard ratio 0.21, 95% CI; 0.13-0.32; p<0.001). Novartis recently completed a successful tender offer for Advanced Accelerator Applications to become a subsidiary within the Novartis Group.

"The approval of Lutathera marks an important achievement and an innovation greatly needed for the NET cancer community," said Susanne Schaffert, Ph.D., Chairperson and President, Advanced Accelerator Applications. "For 30 years, Novartis has supported the NET community with the development of therapeutics in NET and carcinoid syndrome. I cannot think of a better way to commemorate the joining of two organizations and our future together as we advance new nuclear medicine therapeutics in NET as well as across other tumor types."

NETs are rare tumors originating in the neuroendocrine cells of numerous organs, including the gastrointestinal tract, pancreas and lung. Some patients develop symptoms arising from the excessive production of hormones by neuroendocrine tumor cells, while others remain clinically silent for years. The estimated incidence, or rate of new

cases, of NETs in the United States is approximately 6.98/100,000 per year, while the estimated prevalence for 2014, based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, was 171,321.[1] Patient survival with advanced GEP-NETs depends on stage and histology. Patients with well- and moderately-differentiated tumors and distant metastases have a 5-year survival probability of 35%.[2]

The approval of Lutathera is based on results of a randomized pivotal Phase 3 study, NETTER-1 that compared treatment using Lutathera plus best standard of care (octreotide LAR 30mg every four weeks) to 60 mg of octreotide LAR, also dosed every four weeks, in patients with inoperable midgut NETs progressing under standard dose octreotide LAR treatment and overexpressing somatostatin receptors, as well as a subset of efficacy and safety data from an international, single-institution, single-arm, open-label trial conducted by Erasmus Medical Center in Rotterdam, Netherlands in more than 1,200 patients with somatostatin receptor positive tumors.

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The NETTER-1 study met its primary endpoint, showing a 79% reduction in risk of disease progression or death using Lutathera compared to 60 mg octreotide LAR (hazard ratio 0.21, 95% CI: 0.13-0.32;  $p < 0.0001$ ).[3] Median PFS was not reached in the Lutathera arm compared to 8.5 months for the 60 mg octreotide LAR arm.[3] A pre-planned interim overall survival analysis determined that Lutathera treatment lead to a 48% reduction in the estimated risk of death (hazard ratio 0.52, 95% CI: 0.32-0.84) compared to treatment with 60 mg octreotide LAR.[3] The objective response rate, composed of complete and partial responses, was 13% for the Lutathera arm compared to 4% in the Octreotide LAR 60mg arm ( $p < 0.0148$ ).[3]

The most common Grade 3-4 adverse reactions occurring with a greater frequency among patients in the NETTER-1 study receiving Lutathera with octreotide compared to patients receiving high-dose octreotide include: lymphopenia (44%), increased gamma-glutamyl transferase (20%), vomiting (7%), nausea and elevated aspartate aminotransferase (5% each), and increased alanine aminotransferase, hyperglycemia and hypokalemia (4% each).[3]

### **Lutathera® (lutetium Lu 177 dotatate) Important Safety information[3]**

#### **INDICATION**

Lutathera® is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults.

#### **WARNINGS AND PRECAUTIONS**

**Radiation exposure:** Treatment with Lutathera contributes to a patient's overall long-term radiation exposure and is associated with an increased risk for cancer. Radiation can be detected in the urine for up to 30 days following Lutathera administration. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with Lutathera consistent with institutional good radiation safety practices and patient management procedures.

#### **Myelosuppression:**

Due to potential hematological adverse reactions such as anemia, thrombocytopenia, leukopenia, lymphopenia, and

- neutropenia, blood cell counts must be monitored prior to, during, and after treatment. Dose modification or cessation of treatment may be necessary.

#### **•Secondary**

**Myelodysplastic Syndrome and**

**Leukemia:** With a

median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving Lutathera with long-acting octreotide compared to no patients receiving high-dose long-acting octreotide. In a Phase I/II clinical study, 15 patients (1.8%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) and 55 months (32 to 155 months) for acute leukemia.

**•Renal toxicity:**

Treatment with Lutathera will expose kidneys to radiation, which may impair renal function. Monitor serum creatinine and creatinine clearance to assess changes in renal function. A concomitant intravenous infusion of amino acids during Lutathera administration is mandatory for renal protection. Patients with baseline renal impairment may be at greater risk of

toxicity. Perform more frequent assessments of renal function in patients with mild or moderate impairment. Withhold, reduce dose, or permanently discontinue based on severity of reaction.

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**Hepatotoxicity:** In Lutathera clinical trials, <1% of patients were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic

- metastasis may be at increased risk of hepatotoxicity due to radiation exposure. Monitor transaminases, bilirubin, and serum albumin during treatment. Withhold, reduce dose, or permanently discontinue based on severity of reaction.
- Neuroendocrine hormonal crises,** manifesting with flushing, diarrhea, bronchospasm and hypotension, occurred in 1% of patients and typically occurred during or within 24 hours following the initial Lutathera dose. Monitor patients for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms of tumor-related hormonal release.



Administer intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes as indicated.

**Embryo-Fetal**

**Toxicity:** Lutathera

can cause fetal harm. Advise females and males of reproductive potential of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and after.

Verify pregnancy status of females of reproductive potential prior to initiating Lutathera.

**Temporary**

**Infertility:**

Radiation absorbed by testis and ovaries from the recommended

cumulative Lutathera dose falls within the range in which temporary or permanent infertility can be expected following external beam radiotherapy.

**ADVERSE REACTIONS**

The most common Grade 3-4 adverse reactions observed in Lutathera clinical trials were lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea (5%), elevated AST (5%), increased ALT (4%), hyperglycemia (4%), and hypokalemia (4%).

The following serious adverse reactions are rare but have been observed with a median follow-up time of more than 4 years after treatment with Lutathera: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%).

Patients should be counseled and monitored in accordance with the Lutathera prescribing information.

## **DRUG INTERACTIONS**

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of Lutathera. Discontinue long-acting somatostatin analogs at least 4 weeks and short-acting octreotide at least 24 hours prior to each Lutathera dose. Administer short- and long-acting octreotide during Lutathera treatment as recommended.

### **Please see full Prescribing Information**

**at:** [http://www.adacap.com/wp-content/uploads/2018/01/Lutathera\\_lutetium\\_Lu\\_-177\\_dotatate\\_PI\\_2018\\_01.pdf](http://www.adacap.com/wp-content/uploads/2018/01/Lutathera_lutetium_Lu_-177_dotatate_PI_2018_01.pdf)

To report SUSPECTED ADVERSE REACTIONS, contact Advanced Accelerator Applications USA, Inc. at 1-844-863-1930, or [us-pharmacovigilance@adacap.com](mailto:us-pharmacovigilance@adacap.com), or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## **Disclaimer**

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "potential," "can," "will," "plan," "expect," "anticipate," "look forward," "believe," "committed," "investigational," "pipeline," "launch," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; general economic and industry conditions, including the effects of the persistently weak economic and financial environment in many countries; safety, quality or manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. 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.

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### **About Novartis**

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 122,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit <http://www.novartis.com>.

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For questions about the site or required registration, please contact [media.relations@novartis.com](mailto:media.relations@novartis.com)

### **References**

- [1] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol.* 2017; 3(10):1335-1342.
- [2] Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26:3063-3072.
- [3] LUTATHERA® [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA, Inc.; January 2018. [http://www.adacap.com/wp-content/uploads/2018/01/Lutathera\\_lutetium\\_Lu\\_-177\\_dotatate\\_PI\\_2018\\_01.pdf](http://www.adacap.com/wp-content/uploads/2018/01/Lutathera_lutetium_Lu_-177_dotatate_PI_2018_01.pdf)

\* USAN: lutetium Lu 177 dotatate/INN: lutetium (177Lu) oxodotreotide

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Novartis Media Relations  
Central media line: +41 61 324 2200  
E-mail: [media.relations@novartis.com](mailto:media.relations@novartis.com)

Eric Althoff  
Novartis Global Media Relations  
+41 61 324 7999 (direct)  
+41 79 593 4202 (mobile)  
[eric.althoff@novartis.com](mailto:eric.althoff@novartis.com)

Kristen Klasey  
Novartis Division Communications  
+862 778 4763 (direct)  
+862 754 1732 (mobile)  
[kristen.klasey@novartis.com](mailto:kristen.klasey@novartis.com)

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**Novartis Investor Relations**

Central investor relations line: +41 61 324 7944

E-mail: [investor.relations@novartis.com](mailto:investor.relations@novartis.com)

Central

Samir Shah

+41 61 324 7944

Pierre-Michel Bringer

+41 61 324 1065

Thomas Hungerbuehler +41 61 324 8425

Isabella Zinck

+41 61 324 7188

North America

Richard Pulik +1 212 830 2448

Cory Twining +1 212 830 2417

**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: January 26, 2018 By: /s/ PAUL PENEPEPENT  
Name: Paul Penepent  
Head Group Financial  
Title: Reporting and  
Accounting