Novartis receives positive CHMP opinion for Tafinlar® + Mekinist® in BRAF-positive non-small cell lung cancer (NSCLC) patients

- If approved, Tafinlar + Mekinist will be the first targeted therapy specifically for NSCLC patients with a BRAF V600 mutation
- CHMP opinion based on positive data from pivotal study of patients with BRAF V600-positive NSCLC
- With new targeted therapy, BRAF becomes fourth actionable oncogenic driver of lung cancer, similar to EGFR, ALK and ROS1

Basel, February 24, 2017 – Novartis today announced the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending approval of Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) to treat patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors express the BRAF V600 mutation. If approved, Tafinlar + Mekinist will be the first targeted treatment available for patients with BRAF V600-positive NSCLC. Of the estimated 1.8 million new cases of lung cancer diagnosed worldwide each year, 1-3%, may be driven by the BRAF mutation.

“At Novartis, we are committed to finding treatments for rare cancers with an unmet need. Today’s CHMP opinion marks a major milestone for NSCLC patients with the BRAF V600 mutation, who have very limited treatment options,” said Bruno Strigini, CEO, Novartis Oncology. “We welcome the CHMP’s opinion as a first step towards that goal, and look forward to continuing to work with European health authorities to make Tafinlar + Mekinist available for appropriate NSCLC patients.”

The positive CHMP opinion was based on safety and efficacy data from a Phase II study of Tafinlar + Mekinist in patients with BRAF V600-positive NSCLC (36 treatment-naïve and 57 previously treated with chemotherapy).

The 57 patients who had tumor progression on at least one platinum based chemotherapy, receiving 150 mg of Tafinlar twice daily and 2 mg of Mekinist once daily, demonstrated an overall response rate (ORR) of 63.2% (95% confidence interval [CI], 49.3%, 75.6%) and duration of response of 9.0 months (95% CI, 6.9, 18.3 months). The most common adverse events (incidence >20%) were pyrexia, nausea, vomiting, diarrhea, asthenia, decreased appetite, dry skin, chills, peripheral edema, cough and rash. Updated data from the previously treated and treatment-naïve cohorts were included in the overall data package for EMA review and will also be presented at upcoming medical meetings.

The European Commission (EC) typically adheres to the recommendation of the CHMP and usually delivers its final decision within two months. The decision will be applicable to all 28 European Union (EU) member states plus Iceland and Norway. In Europe, Tafinlar and Mekinist is approved for the treatment of patients with unresectable or metastatic melanoma who have a BRAF V600 mutation.
The US Food and Drug Administration (FDA) granted Tafinlar + Mekinist Breakthrough Therapy Designation for advanced or metastatic BRAF V600-positive NSCLC patients in 2015 and Priority Review in November 2016. Combination use of Tafinlar + Mekinist is also approved in the US, Australia, Canada and additional countries for patients with unresectable or metastatic melanoma whose tumors tested positive for the BRAF V600 mutation.

Worldwide, lung cancer causes more deaths than colon, breast, and prostate cancer combined\(^4\), and an estimated 1.8 million new cases of lung cancer are diagnosed each year\(^2\). Among patients with NSCLC, roughly 30% have an actionable mutation that may be targeted with available therapies\(^5, 6, 7, 8\). To determine that treatment, medical organizations recommend genetic testing for patients with lung cancer\(^9\).

**Novartis Commitment to Lung Cancer**

Novartis Oncology’s research into targeted therapies has helped transform treatment approaches for patients living with mutation-driven types of lung cancer. Patients with a mutation-driven NSCLC may be candidates for treatment with targeted therapies\(^6\).

Novartis continues its commitment to the global lung cancer community through ongoing studies, as well as the exploration of investigational compounds that target genetic biomarkers in NSCLC.

**About Tafinlar + Mekinist Combination**

Combination use of Tafinlar + Mekinist in patients with unresectable or metastatic melanoma who have a BRAF V600 mutation is approved in the US, EU, Australia, Canada and other countries.

Tafinlar and Mekinist target different kinases within the serine/threonine kinase family - BRAF and MEK1/2, respectively - in the RAS/RAF/MEK/ERK pathway, which is implicated in non-small cell lung cancer (NSCLC) and melanoma, among other cancers. When Tafinlar is used with Mekinist, the combination has been shown to slow tumor growth more than either drug alone. The combination of Tafinlar + Mekinist is currently being investigated in an ongoing clinical trial program across a range of tumor types conducted in study centers worldwide. The safety and efficacy profile of the Tafinlar + Mekinist combination has not yet been established outside of the approved indications.

Tafinlar and Mekinist are also indicated in more than 40 countries worldwide, including the US and EU, as single agents to treat patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

**Tafinlar + Mekinist Combination Important Safety Information for Metastatic Melanoma**

Tafinlar + Mekinist combination may cause serious side effects.

Tafinlar in combination with Mekinist should only be used to treat melanoma with a change (mutation) in the BRAF gene; therefore, doctors should test their patients before treatment, as patients without a BRAF mutation and with a RAS mutation can be at risk of increased cell proliferation in the presence of a BRAF inhibitor.

Doctors should also consider other treatment options for their patients if they had been previously treated with a BRAF inhibitor as single agent, as the limited data available have shown that the efficacy of Tafinlar + Mekinist is lower in these patients.

When Tafinlar is used in combination with Mekinist, or when Tafinlar is administered as monotherapy, it can cause new cancers (both skin cancer and non-skin cancer). Patients should be advised to contact their doctor immediately for any new lesions, changes to existing lesions on their skin, or signs and symptoms of other malignancies.
Tafinlar in combination with Mekinist, or Mekinist alone, can cause severe bleeding, and in some cases can lead to death. Patients should be advised to call their healthcare provider and get medical help right away if they have headaches, dizziness, or feel weak, cough up blood or blood clots, vomit blood or their vomit looks like "coffee grounds," have red or black stools that look like tar, or any unusual signs of bleeding.

Tafinlar in combination with Mekinist, or either drug alone, can cause severe eye problems that can lead to blindness. Patients should be advised to call their healthcare provider right away if they get these symptoms of eye problems: blurred vision, loss of vision, or other vision changes, seeing color dots, halo (seeing blurred outline around objects), eye pain, swelling, or redness.

Tafinlar in combination with Mekinist, or Tafinlar alone, can cause fever which may be serious. When taking Tafinlar in combination with Mekinist, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever. Patients should be advised to call their healthcare provider right away if they get a fever above 38.5°C (101.3°F) while taking Tafinlar.

Tafinlar in combination with Mekinist, or Mekinist alone, can affect how well the heart pumps blood. A patient's heart function should be checked before and during treatment. Patients should be advised to call their healthcare provider right away if they have any of the following signs and symptoms of a heart problem: feeling like their heart is pounding or racing, shortness of breath, swelling of their ankles and feet, or feeling lightheaded.

Tafinlar in combination with Mekinist, or Tafinlar alone, can cause abnormal kidney function or inflammation of the kidney. Abnormal kidney function may happen more often for patients with fever or too much fluid loss. Patients should be advised to call their healthcare provider right away if they have a fever above 38.5°C (101.3°F), decreased urine, fatigue, loss of appetite or discomfort in lower abdomen or back. Tafinlar has not been studied in patients with renal insufficiency (defined as creatinine > 1.5 x ULN) therefore caution should be used in this setting.

Elevations in blood pressure have been reported in association with Mekinist in combination with Tafinlar, or with Mekinist alone, in patients with or without pre-existing hypertension. Patients should be advised to monitor blood pressure during treatment with Mekinist and control potential hypertension by standard therapy, as appropriate.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause inflammation of the lung tissue. Patients should notify their doctor if they experience any new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Rash is a common side effect of Tafinlar in combination with Mekinist, or with Mekinist alone. Tafinlar in combination with Mekinist, or Mekinist alone, can also cause other skin reactions which can be severe, and may need to be treated in a hospital. Patients should be advised to call their healthcare provider if they get any of the following symptoms: skin rash that bothers them or does not go away, acne, redness, swelling, peeling, or tenderness of hands or feet, skin redness.
Tafinlar in combination with Mekinist, or Mekinist alone, can cause muscle breakdown, a condition called Rhabdomyolysis. Patients experiencing muscle pain, tenderness, weakness or a swelling of their muscles should contact their healthcare provider immediately.

Tafinlar in combination with Mekinist, or Tafinlar alone, can uncommonly cause an inflammation of the pancreas (pancreatitis). Patients should be promptly investigated if they experience unexplained abdominal pain and closely monitored if they re-start Tafinlar after a prior episode of pancreatitis.

Tafinlar in combination with Mekinist, or Mekinist alone, can cause blood clots in the arms or legs, which can travel to the lungs and can lead to death. Patients should be advised to get medical help right away if they have the following symptoms: chest pain, sudden shortness of breath or trouble breathing, pain in their legs with or without swelling, swelling in their arms or legs, or a cool or pale arm or leg.

Mekinist, alone or in combination with Tafinlar, may increase the risk of developing holes in the stomach or intestine (gastrointestinal perforation). Treatment with Mekinist alone or in combination with Tafinlar should be used with caution in patients with risk factors for gastrointestinal perforation, including concomitant use of medications with a recognised risk of gastrointestinal perforation.

Tafinlar and Mekinist both can cause harm to an unborn baby when taken by a pregnant woman. Tafinlar can also render hormonal contraceptives ineffective.

The most common side effects of Tafinlar + Mekinist combination include fever, tiredness, nausea, headache, chills, diarrhea, rash, joint pain, high blood pressure, vomiting and cough. The incidence and severity of fever is increased when Mekinist is used in combination with Tafinlar. Patients should tell their doctor of any side effect that bothers them or does not go away. These are not all of the possible side effects of Tafinlar + Mekinist combination. For more information, patients should ask their doctor or pharmacist.

Patients should take Tafinlar + Mekinist combination exactly as their health care provider tells them. Patients should not change their dose or stop taking Tafinlar + Mekinist combination unless their health care provider advises them to. Mekinist should be taken only once daily (either in the morning or evening, at the same time as Tafinlar). The first and second doses of Tafinlar should be taken approximately 12 hours apart. Patients should take Tafinlar + Mekinist at least 1 hour before or 2 hours after a meal. Do not take a missed dose of Tafinlar within 6 hours of the next dose of Tafinlar. Do not open, crush, or break Tafinlar capsules. Do not take a missed dose of Mekinist within 12 hours of the next dose of Mekinist.

Please see full Prescribing Information for Tafinlar and Mekinist.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as “positive CHMP opinion,” “will,” “recommending,” “committed,” “first step,” “goal,” “look forward,” “upcoming,” “recommendation,” “usually,” “Breakthrough Therapy designation,” “Priority Review,” “commitment,” “may,” “ongoing,” “investigational,” “being investigated,” “yet,” or similar terms, or by express or implied discussions regarding potential new indications or labeling for Tafinlar + Mekinist, or regarding potential future revenues from Tafinlar and Mekinist, both as single agents and in combination with the other. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management 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 Tafinlar + Mekinist will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Tafinlar and Mekinist, either as single agents or in combination with the other will be
commercially successful in the future. In particular, management’s expectations regarding Tafinlar and Mekinist, both as single agents and in combination with the other 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; the company’s ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; 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.

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 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 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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