Novartis receives EU approval for Tafinlar® and Mekinist®, first combination approved for patients with aggressive form of melanoma

- Approval based on two Phase III studies demonstrating statistically significant overall survival benefit with combination therapy vs BRAF inhibitor monotherapy
- Targeted combination offers BRAF V600 mutation-positive melanoma patients in the EU new first-line option with improved efficacy and manageable safety profile

Basel, September 1, 2015 – Novartis today announced that the European Commission has approved the combination of Tafinlar® (dabrafenib) and Mekinist® (trametinib) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. This is the first targeted therapy combination approved in the EU to treat patients with the most aggressive form of skin cancer, demonstrating improved overall survival versus the current standard of care with BRAF inhibitor monotherapy in two Phase III studies.

"We look forward to making the Tafinlar and Mekinist targeted combination treatment, which demonstrated a significant overall survival benefit in two robust clinical trials, available across Europe as soon as possible," said Bruno Strigini, President, Novartis Oncology. "Today’s EU approval further demonstrates our ongoing commitment to deliver medicines that can further enhance outcomes for patients with metastatic melanoma."

Metastatic melanoma is the most serious and life-threatening type of skin cancer and is associated with low survival rates; approximately one out of every five people will survive for five years following a diagnosis with late-stage disease. There are about 200,000 new cases of melanoma diagnosed worldwide each year, approximately half of which have BRAF mutations. Gene tests can determine whether a tumor has a BRAF mutation, and results can play a key role in prognosis and determining appropriate treatment.

Marketing authorization is based on results from the Phase III COMBI-d and COMBI-v studies, in which the Tafinlar/Mekinist combination demonstrated overall survival benefit compared to Tafinlar and Zelboraf monotherapies respectively in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The COMBI-d study showed that the combination of Tafinlar and Mekinist achieved a statistically significant OS benefit compared to Tafinlar monotherapy (median of 25.1 months vs 18.7 months; Hazard Ratio [HR] 0.71 [95% Confidence Interval (CI), 0.55-0.92], p=0.011). In those who received Tafinlar in combination with Mekinist, OS was 74% at 1 year and 51% at 2 years versus 68% and 42% for those who received Tafinlar only, respectively. Safety results from the COMBI-d study were consistent with the profile observed to date for the combination; no new safety concerns were observed. The most common adverse events (>=20%) in the combination arm were pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, joint pain (arthralgia), hypertension, vomiting, cough, and peripheral edema. Adverse events or toxicities were generally manageable with appropriate intervention, as described in the product labelling submitted with the
application. Updated results from COMBI-v will be presented at an upcoming medical congress.

The European Commission approval applies to all 28 EU member states, plus Iceland, Norway and Liechtenstein.

In the US, the Food and Drug Administration (FDA) granted priority review in July 2015 for regular approval of the Tafinlar and Mekinist combination in BRAF V600 mutation-positive metastatic melanoma. Since January 2014, the combination of Tafinlar and Mekinist has been approved for use in the US in patients with BRAF V600E/K mutation-positive unresectable or metastatic melanoma as detected by an FDA-approved test. The combination was approved through the FDA’s Accelerated Approval program and reviewed under a priority review designation. The approval was contingent on the results of the COMBI-d study, which was designed to evaluate the clinical benefit of the combination in patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

About the COMBI-d Study
COMBI-d is a pivotal Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, Tafinlar, and the MEK inhibitor, Mekinist, to single agent therapy with Tafinlar and placebo in patients with unresectable (Stage IIIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The study randomized 423 patients at investigative sites in Australia, Europe and North and South America. The primary endpoint of this study was investigator-assessed progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response (DoR), and safety. There was no crossover between treatment arms.

Updated results from the COMBI-d study showed that the combination of Tafinlar and Mekinist achieved a statistically significant OS benefit compared to Tafinlar monotherapy (median of 25.1 months vs 18.7 months; HR 0.71 [95% CI, 0.55-0.92], p=0.011). In those who received the Tafinlar and Mekinist combination, OS was 74% at 1 year and 51% at 2 years versus 68% and 42% for those who received Tafinlar only, respectively. The analysis for the combination also showed median PFS of 11.0 months, ORR of 69%, and median DoR of 12.9 months. The safety results were consistent with the profile observed to date for the combination and consistent with the profile observed for Tafinlar monotherapy; no new safety concerns were observed. The most common adverse events (>=20%) in the combination arm were pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, joint pain (arthritis), hypertension, vomiting, cough, and peripheral edema. More patients had AEs leading to dose modifications in the combination arm compared to Tafinlar monotherapy. Increased incidence (57% vs 33%) and severity (grade 3, 7% (n=15) vs 2% (n=4)) of pyrexia occurred with combination treatment as compared to Tafinlar monotherapy. There was a lower incidence of cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma with the combination arm (3% (n=6)) compared to the Tafinlar monotherapy arm (10% (n=22)). Discontinuation of treatment due to adverse events occurred in 11% (n=24) vs 7% (n=14) of patients in the combination group and the monotherapy group, respectively.

About the COMBI-v Study
COMBI-v was a two-arm, open-label, Phase III study comparing the combination of Tafinlar and Mekinist combination therapy with vemurafenib monotherapy in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of this study was OS. Updated results from COMBI-v will be presented at an upcoming medical congress.

About Tafinlar and Mekinist Combination
Combination use of Tafinlar and Mekinist in patients with unresectable or metastatic
melanoma who have BRAF V600E/K mutation is approved in the US, Australia, Canada and additional 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 NSCLC and melanoma, among other cancers. When Tafinlar is used with Mekinist, the combination has been shown to slow tumor growth more effectively compared with either drug alone. The combination of Tafinlar and Mekinist is currently being investigated in an ongoing clinical trial program across a range of tumor types conducted in study centers worldwide.

In 2015, as part of its purchase of oncology products from GlaxoSmithKline, Novartis obtained the worldwide exclusive rights granted by Japan Tobacco Inc. (JT) to develop, manufacture, and commercialize trametinib. JT retains co-promotion rights in Japan.

The safety and efficacy profile of the Tafinlar and Mekinist combination has not yet been established outside the approved indication.

Tafinlar and Mekinist are also indicated as single agents to treat patients with unresectable or metastatic melanoma with a BRAF V600 mutation in more than 35 countries worldwide, including the US and EU.

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

Tafinlar and Mekinist combination may cause serious side effects, such as:

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.

Before taking Tafinlar in combination with Mekinist, doctors should test their patients for BRAF wild-type melanoma, as patients without BRAF mutation and with RAS mutation can be at risk of increased cell proliferation in the presence of a BRAF inhibitor.

When Tafinlar is used in combination with Mekinist, it can increase the incidence and severity of 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, 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.

Tafinlar in combination with Mekinist can cause heart problems, including heart failure. 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 alone, or in combination with Mekinist, 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.

Patients should notify their doctor if they experience any new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Tafinlar alone or in combination with Mekinist 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.

Rash is a common side effect of Tafinlar alone, or when used in combination with Mekinist. Tafinlar alone, or in combination with Mekinist, can also cause other skin reactions. In some cases these rashes and other skin reactions 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.

Some people may develop high blood sugar or worsening diabetes during treatment with Tafinlar, alone or in combination with Mekinist. For patients who are diabetic, their healthcare provider should check their blood sugar levels closely during treatment. Their diabetes medicine may need to be changed. Patients should be advised to tell their healthcare provider if they have any of the following symptoms of severe high blood sugar: increased thirst or urinating more often than normal, or urinating an increased amount of urine.

Tafinlar may cause healthy red blood cells to break down too early in people with G6PD deficiency. This may lead to a type of anemia called hemolytic anemia where the body does not have enough healthy red blood cells. Patients should be advised to tell their healthcare provider if they have any of the following signs or symptoms of anemia or breakdown of red blood cells: yellow skin (jaundice), weakness or dizziness, or shortness of breath.

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 and Mekinist combination include fever, nausea, tiredness, rash, chills, diarrhea, headache, vomiting, hypertension, joint pain, peripheral edema 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 and Mekinist combination. For more information, patients should ask their doctor or pharmacist.

Patients should take Tafinlar and Mekinist combination exactly as their health care provider tells them. Patients should not change their dose or stop taking Tafinlar and 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 dose of Tafinlar should be taken approximately 12 hours apart. Patients should take Tafinlar and 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 “look forward,” “ongoing,” “commitment,” “can,” “will,” “upcoming,” “priority review,” “being investigated,” “yet,” or similar terms, or by express or implied discussions regarding potential marketing approvals or new indications or labeling for Tafinlar and Mekinist, either in combination or as single agents, or regarding potential future revenues from Tafinlar and Mekinist, either in combination or as single agents. 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 and Mekinist, either in combination or as single agents, will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that Tafinlar and Mekinist, either in combination or as single agents, will be submitted or approved for sale in any additional markets, or at any particular time. Nor can there be any guarantee that Tafinlar and Mekinist, either in combination or as single agents, will be commercially successful in the future. In particular, management’s expectations regarding Tafinlar and Mekinist, in combination and as single agents, could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected 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; unexpected safety issues; unexpected manufacturing or quality 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, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2014, the Group achieved net sales of USD 58.0 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 120,000 full-time-equivalent associates. Novartis products are available in more than 180 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.

References

---

Novartis Media Relations
Central media line : +41 61 324 2200
Eric Althoff Nicole Riley
Novartis Global Media Relations
+41 61 324 7999 (direct)
+41 79 593 4202 (mobile)
eric.althoff@novartis.com

Novartis Oncology
+1 862 778 3110 (direct)
+1 862 926 9040 (mobile)
nicole.riley@novartis.com

e-mail: media.relations@novartis.com

For Novartis multimedia content, please visit www.thenewsmarket.com/Novartis
For questions about the site or required registration, please contact:
journalisthelp@thenewsmarket.com.

Novartis Investor Relations

Central phone: +41 61 324 7944
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
Sloan Pavsner +1 212 830 2417

e-mail: investor.relations@novartis.com

e-mail: investor.relations@novartis.com