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MEDIA & INVESTOR RELEASE

Novartis Tafinlar + Mekinist approved by FDA for pediatric patients with BRAF V600E low-grade glioma, the most common pediatric brain cancer

- *New approval based on TADPOLE trial showing overall response rate (ORR) of 47% and median progression-free survival (mPFS) of 20.1 months for Tafinlar + Mekinist compared to 11% ORR and 7.4 months mPFS for standard of care*[1,2]
- *Approval also received for liquid formulation options for ease of administration across multiple approved indications*
- *Tafinlar + Mekinist is now approved in six indications across multiple BRAF V600E solid tumors, including melanoma, thyroid cancer and lung cancer*[1,2]

Basel, March 16, 2023 — Novartis today announced the U.S. Food and Drug Administration (FDA) granted approval for Tafinlar® (dabrafenib) + Mekinist® (trametinib) for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. The FDA also approved liquid formulations of Tafinlar and Mekinist, marking the first time a BRAF/MEK inhibitor has been developed in a formulation suitable for patients as young as one year of age. These approvals make Tafinlar + Mekinist the first and only approved combination targeted therapy to treat pediatric patients with BRAF V600E LGG.

“Pediatric cancer research is vital to uncover new treatment methods for a population,” said Dr. Eric Bouffet, MD, FRCPC, Principal Investigator of the TADPOLE clinical trial and Associate Scientist Emeritus at The Hospital for Sick Children (SickKids). “Developing targeted therapies based on the unique genetic features of a patient’s tumor is the future of pediatric cancer care.”

This FDA approval of Tafinlar + Mekinist is based on results from the Phase II/III TADPOLE trial (NCT02684058) that showed patients randomized to receive Tafinlar + Mekinist experienced a statistically significant improvement in overall response rate (ORR) of 47% (CI: 35-59%) compared to 11% (CI: 3-25%) for those randomized to receive chemotherapy. At a median follow-up of 18.9 months, median progression-free survival (PFS) was 20.1 months with Tafinlar + Mekinist (CI: 12.8 months-not estimable) compared to 7.4 months with chemotherapy (CI: 3.6-11.8 months, hazard ratio=0.31 [CI: 0.17-0.55] [p<0.001]).

“It is more important than ever to test for genetic mutations in patients living with low-grade glioma. This FDA approval may offer new hope to pediatric patients living with BRAF V600E low-grade glioma,” said Dr. Roger Packer, senior vice president of the Center for Neurosciences and Behavioral Medicine at Children’s National Hospital. “This has the

potential to change the way healthcare providers treat these pediatric patients, offering a significant advancement compared to chemotherapy."

The safety profile of Tafinlar + Mekinist observed in this study was consistent with the known safety profile in other approved indications. The most common adverse reactions (>=15%) were pyrexia (68%), rash (51%), headache (47%), vomiting (34%), musculoskeletal pain (34%), fatigue (33%), diarrhea (29%), dry skin (26%), nausea (25%), hemorrhage (25%), abdominal pain (25%), dermatitis acneiform (22%), dizziness (15%), upper respiratory tract infection (15%) and weight increased (15%). These data were highlighted as part of an official press briefing and oral presentation at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting.

"This new indication for Tafinlar + Mekinist is a potential new standard of care treatment option for young patients with this form of brain cancer with a BRAF V600E mutation, in formulations specifically designed for them," said Reshema Kemps-Polanco, Executive Vice President, US Oncology at Novartis. "We are thankful for the families, including children and adolescents, that participated in the clinical trial that led to this approval and whose bravery has led to a new hope for children living with this serious brain cancer."

LGG is the most common pediatric brain cancer. BRAF V600 mutations are present in 15-20% of pediatric LGGs and are associated with poor survival outcomes and less favorable response to chemotherapy[4]. BRAF mutations have been identified as drivers of cancer growth across a wide range of solid tumors, and often have limited treatment options[4,5].

Full prescribing information for Tafinlar + Mekinist can be found at https://www.novartis.us/sites/www.novartis.us/files/tafinlar.pdf and https://www.novartis.us/sites/www.novartis.us/files/mekinist.pdf.

About Tafinlar + Mekinist
The combination of Tafinlar + Mekinist, the worldwide targeted therapy leader in BRAF/MEK-inhibition research and patients reached, may help to slow tumor growth by blocking signals associated with the BRAF and MEK kinases that are implicated in the growth of various types of cancer[1,2,4,5]. Tafinlar + Mekinist has been studied in more than 6,000 BRAF-positive patients in more than 20 ongoing and completed trials, including in pediatric patients 1 year of age and older, and has been prescribed to more than 200,000 patients worldwide[6].

This FDA approval is the sixth for Tafinlar + Mekinist, which is indicated across multiple BRAF V600 solid tumors, including melanoma, thyroid cancer and lung cancer[1,2].

Indication and Important Safety Information
TAFINLAR and MEKINIST are prescription medicines that can be used in combination to treat people with a type of skin cancer called melanoma:

- that has spread to other parts of the body (metastatic) or cannot be removed by surgery (unresectable), and
- that has a certain type of abnormal "*BRAF*" (V600E or V600K mutation-positive) gene

TAFINLAR and MEKINIST are prescription medicines that can be used in combination to help prevent melanoma that has a certain type of abnormal "*BRAF*" gene from coming back after the cancer has been removed by surgery.

TAFINLAR and MEKINIST are prescription medicines that can be used in combination to treat a type of lung cancer called non-small cell lung cancer (NSCLC) that has spread to other parts of the body (metastatic NSCLC), and that has a certain type of abnormal "*BRAF* V600E" gene.

TAFINLAR and MEKINIST are prescription medicines that can be used in combination to treat a type of thyroid cancer called anaplastic thyroid cancer (ATC):

- that has spread to other parts of the body and you have no satisfactory treatment options **and**
- that has a certain type of abnormal "*BRAF*" gene

TAFINLAR and MEKINIST are prescription medicines that can be used in combination to treat solid tumors in adults and children 6 years of age and older:

- that cannot be removed by surgery or have spread to other parts of the body, and that have gotten worse (progressed) and you have no satisfactory treatment options **and**
- that have a certain type of abnormal "*BRAF*" gene

The effectiveness of TAFINLAR and MEKINIST in these patients is based on 2 adult studies and 1 pediatric study that measured 2 types of response to treatment (response rate and duration of response). No clinical information is available to show if these patients treated with TAFINLAR and MEKINIST live longer or if their symptoms improve. Ongoing studies exist to determine how TAFINLAR and MEKINIST works over a longer period.

TAFINLAR and MEKINIST are prescription medicines that can be used in combination to treat a type of brain tumor called glioma in children 1 year of age and older

- that is low-grade glioma (LGG), **and**
- that have a certain type of abnormal "*BRAF*" gene, **and**
- who require a medicine by mouth or injection (systemic therapy)

TAFINLAR, in combination with MEKINIST, is not for use in treating people with colorectal cancer or wild-type *BRAF* solid tumors. MEKINIST should not be used to treat people who already have received a *BRAF* inhibitor for treatment of their melanoma and it did not work or is no longer working.

Your health care provider will perform a test to make sure that TAFINLAR and MEKINIST, in combination, are right for you.

It is not known if TAFINLAR used in combination with MEKINIST is safe and effective in children younger than 6 years of age.

TAFINLAR and MEKINIST, in combination, may cause serious side effects such as the risk of new cancers, including both skin cancer and nonskin cancer. Patients should be advised to contact their health care provider immediately for any skin changes, including a new wart, skin sore, or bump that bleeds or does not heal, or a change in the size or color of a mole.

When TAFINLAR is used in combination with MEKINIST, it can cause serious bleeding problems, especially in the brain or stomach, that can lead to death. Patients should be advised to call their health care provider and get medical help right away if they have any signs of bleeding, including headaches, dizziness, or feeling weak, coughing up blood or blood clots, vomiting blood or their vomit looks like "coffee grounds," or red or black stools that look like tar.

MEKINIST, alone or in combination with TAFINLAR, can cause inflammation of the intestines or tears in the stomach or intestines that can lead to death. Patients should report to their health care provider right away if they have any of the following symptoms: bleeding, diarrhea (loose stools) or more bowel movements than usual, stomach-area (abdomen) pain or tenderness, fever, or nausea.

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.

The combination of TAFINLAR and 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 health care 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, can cause severe eye problems that can lead to blindness. Patients should be advised to call their health care provider right away if they get: 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, can cause lung or breathing problems. Patients should be advised to tell their health care provider if they have new or worsening symptoms of lung or breathing problems, including shortness of breath or cough.

Fever is common during treatment with TAFINLAR in combination with MEKINIST but may also be serious. 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 health care provider right away if they get a fever.

Rash and other skin reactions are common side effects of TAFINLAR in combination with MEKINIST. In some cases, these rashes and other skin reactions can be severe or serious, may need to be treated in a hospital, or lead to death. Patients should be advised to call their health care provider if they get any of the following symptoms: blisters or peeling of skin, mouth sores, blisters on the lips or around the mouth or eyes, high fever or flu-like symptoms, and/or enlarged lymph nodes.

Some people may develop high blood sugar or worsening diabetes during treatment with TAFINLAR in combination with MEKINIST. For patients who are diabetic, their health care 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 health care provider if they have increased thirst, urinate more often than normal, or produce an increased amount of urine.

TAFINLAR may cause healthy red blood cells to break down too early in people with glucose-6-phosphate dehydrogenase 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 health care provider if they have yellow skin (jaundice), weakness or dizziness, or shortness of breath.

TAFINLAR, in combination with MEKINIST, can cause new or worsening high blood pressure (hypertension). A patient’s blood pressure should be checked during treatment. Patients should be advised to tell their health care provider if they develop high blood pressure, their blood pressure worsens, or if they have severe headache, lightheadedness, blurry vision, or dizziness.

For women of reproductive potential, TAFINLAR and MEKINIST, in combination, can harm your unborn baby. Your health care provider will do a test to see if you are pregnant before starting treatment with TAFINLAR and MEKINIST in combination. Use effective birth control (contraception) during treatment with TAFINLAR and MEKINIST in combination, and for 4 months after stopping treatment with TAFINLAR and MEKINIST.

Men (including those who have had a vasectomy) should use condoms during sexual intercourse during treatment with TAFINLAR and MEKINIST and for at least 4 months after the last dose of TAFINLAR and MEKINIST.

The most common side effects for patients with metastatic melanoma receiving the combination are pyrexia, nausea, rash, chills, diarrhea, headache, vomiting, hypertension, arthralgia, peripheral edema, and cough. The most common side effects for patients with stage III melanoma as adjuvant therapy receiving the combination are pyrexia, tiredness, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia. The most common

side effects for patients with NSCLC receiving the combination are pyrexia, tiredness, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea. The most common side effects for adults with solid tumors that cannot be removed by surgery or have spread to other parts of the body who are receiving the combination are fever, tiredness, nausea, rash, chills, headache, bleeding, cough, vomiting, constipation, diarrhea, muscle and or joint aches, and swelling of arms and legs. The most common side effects for children with solid tumors that cannot be removed by surgery or have spread to other parts of the body who are receiving the combination are fever, rash, vomiting, tiredness, dry skin, cough, diarrhea, acne, headache, stomach-area (abdomen) pain, nausea, bleeding, constipation, and skin infection around fingernails or toenails. The most common side effects of in children 1 year of age and older with low-grade glioma receiving the combination include fever, rash, headache, vomiting, muscle and bone pain, tiredness, dry skin, diarrhea, nausea, bleeding, stomach area (abdomen) pain, and acne.

Please see full Prescribing Information for TAFINLAR and MEKINIST at https://www.novartis.us/sites/www.novartis.us/files/tafinlar.pdf and https://www.novartis.us/sites/www.novartis.us/files/mekinist.pdf.

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Disclosure: Dr. Bouffet has provided consulting services to Novartis.

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