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Tafinlar® (dabrafenib) 50 mg, 75 mg capsules + Mekinist® (trametinib) 0.5 mg, 1 mg, 2 mg tablets

FOR US MEDIA ONLY

About the Tafinlar® (dabrafenib) + Mekinist® (trametinib) Combination Treatment for BRAF V600E/K Mutation–Positive Metastatic Melanoma

WHAT IS METASTATIC MELANOMA?

Melanoma is the most serious and life-threatening type of skin cancer[1] and develops when unrepaired DNA damage to skin cells triggers genetic changes that cause them to form malignant tumors[2]. Melanoma is almost always treatable when caught early, but if it metastasizes, or spreads to other parts of the body, it becomes difficult to treat and is associated with low survival rates[2].

While the average age of a newly diagnosed melanoma patient is 62[2], it is one of the most common cancers in young adults, ages 25-29[3]. In some parts of the world, melanoma is becoming more common every year[2]. Caucasian populations have a much higher risk of getting melanoma than dark-skinned populations, due to their having relatively less skin pigmentation[2]. However, excessive exposure to intense sunlight can damage any skin type[2].

Melanoma causes the majority of skin cancer deaths[2]. According to the American Cancer Society, there will be an estimated 73,870 new cases of melanoma and an estimated 9,940 melanoma-related deaths in the United States in 2015[2]. In the US, the percent of people who develop melanoma has more than doubled in the past 30 years[4].

WHAT ROLE DO GENES PLAY IN MELANOMA?

Melanoma is a complex disease and multiple gene alterations have been reported to play a role in the disease's progression. In metastatic melanoma, approximately half of all patients have a mutation in the BRAF gene[2]. Of those, more than 70 percent have a BRAF V600E mutation and approximately 20 percent have a BRAF V600K mutation[5,6].

Gene tests should be performed on patients with metastatic melanoma to determine whether their tumor demonstrates a gene mutation[2]. Results can play a key role in prognosis and determining which treatment is the most appropriate therapy for the genetic makeup of the tumor[2]. New targeted therapy combinations are changing the treatment landscape for patients with BRAF V600E/K mutation–positive metastatic melanoma.

ABOUT TAFINLAR + MEKINIST COMBINATION THERAPY IN BRAF V600E/K MUTATION–POSITIVE METASTATIC MELANOMA

Combination use of Tafinlar + Mekinist in patients with unresectable or metastatic melanoma who have a BRAF V600E/K mutation is approved in the US. In addition, combination use of Tafinlar + Mekinist in patients with unresectable or metastatic melanoma who have a BRAF V600 mutation is approved in the EU, 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 melanoma and other cancers. When Tafinlar is used with Mekinist, the combination has been shown to slow tumor growth in metastatic melanoma patients more than Tafinlar 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.

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 + Mekinist combination has not yet been established outside of the approved indication.

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

Please see full Prescribing Information for Tafinlar + Mekinist.

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CLINICAL EVIDENCE SUPPORTING USE OF TAFINLAR + MEKINIST COMBINATION IN METASTATIC MELANOMA

Two Phase III studies—COMBI-d and COMBI-v—of patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma demonstrated the following results.

PHASE III STUDY RESULTS[7]

	COMBI-d		COMBI-v	
	Tafinlar (150mg) + Mekinist (2mg) (n=211)	**Tafinlar (150mg) + placebo (n=212)**	**Tafinlar (150mg) + Mekinist (2mg) (n=352)**	**Vemurafenib (960mg) (n=352)**
Median Overall Survival (OS)*	**25.1 months**	**18.7 months**	**NR**	**17.2 months**
	HR=0.71 (95% CI, 0.55 to 0.92); p=0.01		HR=0.69 (95% CI, 0.53 to 0.89); p=0.005	
Median Progression-Free Survival (PFS)**	**9.3 months**	**8.8 months**	**11.4 months**	**7.3 months**
	HR 0.75 (95% CI, 0.57 to 0.99, p=0.035)		HR=0.56 (95% CI, 0.46 to 0.69); p<0.001	
Overall Response Rate (ORR)	**66%** (95% CI, 60 to 73)	**51%** (95% CI, 44 to 58)	**64%** (95% CI, 59 to 69)	**51%** (95% CI, 46 to 56)
Median Duration of Response (DoR)	**9.2 months** (95% CI, 7.4 to NR)	**10.2 months** (95% CI, 7.5 to NR)	**13.8 months** (95% CI, 11.0 to NR)	**7.5 months** (95% CI, 7.3 to 9.3)

*COMBI-v primary endpoint[7]
**COMBI-d primary endpoint[7]
NR = Not Reached
HR = Hazard Ratio

The safety results from these studies were consistent with the profile observed to date for the combination; no new safety concerns were observed.[7]

TAFINLAR + MEKINIST COMBINATION IMPORTANT SAFETY INFORMATION FOR METASTATIC MELANOMA

Tafinlar + Mekinist combination may cause serious side effects, such as the risk of new cancers including both skin cancer and non-skin cancer. Patients should be advised to contact their doctor immediately for 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, and 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," or have red or black stools that look like tar.

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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 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 can cause severe eye problems that can lead to blindness. Patients should be advised to call their healthcare 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 healthcare 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 more 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 healthcare provider right away if they get a fever.

Rash is a common side effect of Tafinlar in combination with Mekinist. Tafinlar 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 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 increased thirst, urinating more often than normal, or urinating an increased amount of urine.

Tafinlar in combination with Mekinist 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 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 healthcare provider if they develop high blood pressure, their blood pressure worsens, or if they have severe headache, lightheadedness, or dizziness.

The most common side effects of Tafinlar in combination with Mekinist include nausea, chills, diarrhea, vomiting, high blood pressure (hypertension), swelling of the face, arms, or legs, thickening of the outer layers of skin, headache, joint aches, cough, warts, hair loss, or redness, swelling, peeling, or tenderness of hands or feet.

Please see full prescribing information for Tafinlar and Mekinist at http://www.pharma.us.novartis.com/product/pi/pdf/tafinlar.pdf and http://www.pharma.us.novartis.com/product/pi/pdf/mekinist.pdf.

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7. Tafinlar and Mekinist Full Prescribing Information.

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