TAFINLAR + MEKINIST

EXPAND THE POSSIBILITIES FOR PATIENTS WITH *BRAF* V600E–MUTANT SOLID TUMORS

The first and only combination *BRAF* + *MEK* inhibitor approved for the treatment of adults and children 1 year of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options[1-7]

MEK, mitogen-activated extracellular signal-regulated kinase.

INDICATION

TAFINLAR, in combination with MEKINIST, is indicated for the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitation of Use: TAFINLAR, in combination with MEKINIST, is not indicated for the treatment of patients with colorectal cancer because of known intrinsic resistance to *BRAF* inhibition. TAFINLAR is not indicated for the treatment of patients with wild-type *BRAF* solid tumors.

IMPORTANT SAFETY INFORMATION

New Primary Malignancies

Cutaneous Malignancies

In the pooled adult safety population of TAFINLAR administered with MEKINIST ("the combination"), the incidence of cutaneous squamous cell carcinoma (cuSCC, including keratoacanthomas) occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and <1% of patients, respectively.

In the pooled pediatric safety population of the combination, new primary melanoma occurred in <1% of patients.

Perform dermatologic evaluations prior to initiation of the combination, every 2 months while on therapy, and for up to 6 months following discontinuation.

Please see additional Important Safety Information for TAFINLAR + MEKINIST throughout this brochure.
Please click here for full Prescribing Information for TAFINLAR and click here for full Prescribing Information for MEKINIST.

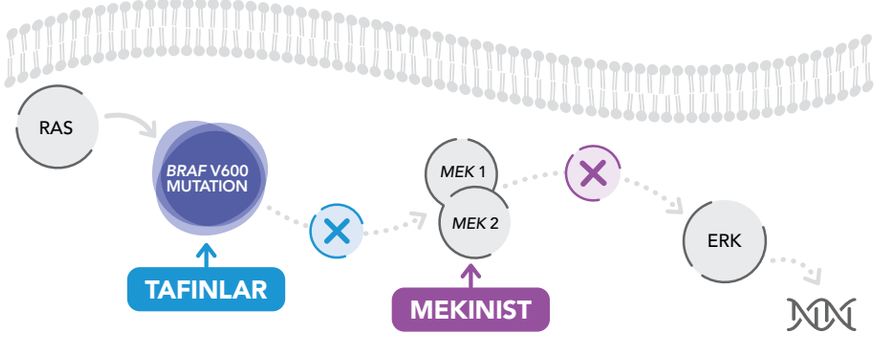
TESTING FOR *BRAF* MUTATIONS IN SOLID TUMORS CAN INFORM CRITICAL TREATMENT DECISIONS

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

BRAF V600 has been identified as a driver mutation across various solid tumors[8]

- *BRAF* mutations occur in about 8% of solid tumors, most commonly in melanoma and thyroid cancers[9]
  - *BRAF* V600E mutations may occur in various cancers.[8,10,11] Please see Section 14.6 of the Prescribing Information for both TAFINLAR and MEKINIST for more information about tumor types included in studies of *BRAF* V600E–mutant solid tumors
- V600E is the most common *BRAF* mutation in cancer, accounting for up to 90% of *BRAF*-mutant cancers[8]

TAFINLAR + MEKINIST inhibits 2 points on the *MAPK* pathway, which is constitutively active in *BRAF* V600–mutated solid tumors[1,2]



ERK, extracellular signal-related kinase; *MAPK*, mitogen-activated protein kinase; *MEK*, mitogen-activated extracellular signal-regulated kinase; RAS, monomeric G protein.

BRAF V600 mutations can result in increased _MAPK_ pathway activity, leading to heightened cellular growth and proliferation[12]

In the setting of *BRAF*-mutant colorectal cancer, induction of epidermal growth factor receptor–mediated *MAPK* pathway reactivation has been identified as a mechanism of intrinsic resistance to *BRAF* inhibitors.[1,2]

IMPORTANT SAFETY INFORMATION (continued)

New Primary Malignancies (continued)

Noncutaneous Malignancies

Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of monomeric G protein (RAS) through mutation or other mechanisms. In the pooled adult safety population of TAFINLAR monotherapy and the combination, noncutaneous malignancies occurred in 1% of patients.

Monitor patients receiving the combination for signs or symptoms of noncutaneous malignancies. Permanently discontinue TAFINLAR for RAS-mutation–positive noncutaneous malignancies. No dose modification is required for MEKINIST in patients who develop noncutaneous malignancies.

Please see additional Important Safety Information for TAFINLAR + MEKINIST throughout this brochure.
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ENSURE TESTING POLICIES SUPPORT EARLY IDENTIFICATION OF *BRAF* V600E AND OTHER ACTIONABLE ALTERATIONS

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

Testing modalities used to identify *BRAF* V600E mutations:

- **NGS** — **Next-generation sequencing (NGS):** scalable DNA sequencing that is able to simultaneously analyze multiple genes[13,14]
- **PCR** — **Mutation-specific polymerase chain reaction (PCR):** rapidly making copies of small segments of DNA[15]
- **rtPCR** — **Mutation-specific real-time PCR (rtPCR):** a more sensitive technique than traditional PCR where targeted DNA segments are amplified and quantified simultaneously[13-15]
- **IHC** — **Immunohistochemistry (IHC):** detects tumor cells harboring a specific antigen by cytoplasmic staining of cells containing a mutation-specific monoclonal antibody[16]
- **Other** — **Other testing methods:** Sanger sequencing, pyrosequencing[13,14]

In the ROAR Study, *BRAF* mutation status was determined using a range of methods, including NGS, IHC, PCR, dideoxy DNA sequencing, pyrosequencing, and mass spectrometry.[14]

Confirm the presence of *BRAF* V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and MEKINIST. An FDA-approved test for the detection of *BRAF* V600E mutation in solid tumors other than melanoma and non-small cell lung cancer is not currently available.[1,2]

Identifying *BRAF* mutation status is a critical step in giving patients new hope for a potential treatment option[1,2]

IMPORTANT SAFETY INFORMATION (continued)

Tumor Promotion in *BRAF* Wild-type Tumors. In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (*MAPK*) signaling and increased cell proliferation in *BRAF* wild-type cells that are exposed to *BRAF* inhibitors. Confirm evidence of *BRAF* V600E or V600K mutation status prior to initiation of therapy.

Please see additional Important Safety Information for TAFINLAR + MEKINIST throughout this brochure.
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STUDY DESIGNS

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

Across tumor types, TAFINLAR + MEKINIST was evaluated in patients with *BRAF* V600E–mutant solid tumors

TAFINLAR + MEKINIST was evaluated in *BRAF* V600E–mutant solid tumors based on collective evidence from 2 adult trials and 2 pediatric trials, and is supported by the results of COMBI-d, COMBI-v, and BRF113928 studies.[1,2]

Adult studies

ROAR (BRF117019) Study

TAFINLAR + MEKINIST was evaluated in a multicohort, multicenter, nonrandomized, open-label trial in adult patients with selected tumors with the *BRAF* V600E mutation, including high-grade glioma (HGG) (n=45), biliary tract cancer (BTC) (n=43), low-grade glioma (LGG) (n=13), adenocarcinoma of small intestine (n=3), gastrointestinal stromal tumor (n=1), and anaplastic thyroid cancer (ATC) (n=36). Patients were enrolled based on local assessments of *BRAF* V600E mutation status; a central laboratory confirmed the *BRAF* mutation in 93 of 105 patients.[1,2]

NCI-MATCH (EAY131-H) Study

TAFINLAR + MEKINIST was evaluated in Arm H (EAY131-H) of the NCI-MATCH Study, a single-arm, open-label study that enrolled patients with a *BRAF* V600E mutation. Patients with melanoma, thyroid cancer, or colorectal cancer were excluded. *BRAF* V600E mutation status for enrollment was determined either by central or local laboratory test. The study included adult patients with solid tumors including gastrointestinal tumors (n=14), lung tumors (n=7), gynecologic or peritoneal tumors (n=6), central nervous system tumors (n=4), and ameloblastoma of mandible (n=1).[1,2]

In both adult studies, patients received TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily. The major efficacy outcome measures were overall response rate (ORR) per Response Evaluation Criteria In Solid Tumors v1.1, Response Assessment in Neuro-Oncology (RANO) (HGG) or modified RANO (LGG) criteria, and duration of response (DOR).[1,2]

IMPORTANT SAFETY INFORMATION (continued)

Hemorrhage. Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with the combination. Fatal cases have been reported.

In the pooled adult safety population of the combination, hemorrhagic events occurred in 17% of patients; gastrointestinal hemorrhage occurred in 3% of patients; intracranial hemorrhage occurred in 0.6% of patients; fatal hemorrhage occurred in 0.5% of patients. The fatal events were cerebral hemorrhage and brainstem hemorrhage.

In the pooled pediatric safety population of the combination, hemorrhagic events occurred in 25% of patients; the most common type of bleeding was epistaxis (16%). Serious events of bleeding occurred in 3.6% of patients and included gastrointestinal hemorrhage (1.2%), cerebral hemorrhage (0.6%), uterine hemorrhage (0.6%), post-procedural hemorrhage (0.6%), and epistaxis (0.6%).

Permanently discontinue TAFINLAR for all grade 4 hemorrhagic events and for any grade 3 hemorrhagic events that do not improve. Withhold TAFINLAR for grade 3 hemorrhagic events; if improved, resume at the next lower dose level. Permanently discontinue MEKINIST for all grade 4 hemorrhagic events and for any grade 3 hemorrhagic events that do not improve. Withhold MEKINIST for grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

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STUDY DESIGNS (continued)

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

Pediatric studies

CTMT212X2101 (X2101) Study

Study X2101 was a multicenter, open-label, multiple-cohort study in pediatric patients with refractory or recurrent solid tumors.

- Part C was a dose-escalation phase of TAFINLAR + MEKINIST in patients with *BRAF* V600–mutant tumors
- Part D was a cohort-expansion phase of TAFINLAR + MEKINIST in patients with *BRAF* V600E–mutant LGG

The major efficacy outcome was ORR as assessed by an independent review committee per RANO criteria. The efficacy of TAFINLAR + MEKINIST was evaluated in 48 patients, including those with LGG (n=34) and HGG (n=2).[1,2]

CDRB436G2201 (G2201) Study

TAFINLAR + MEKINIST was evaluated in a multicenter, randomized, open-label, phase 2 study in chemotherapy-naive pediatric patients with *BRAF* V600E–mutant LGG and relapsed or progressive *BRAF* V600E–mutant HGG.

Patients with HGG (N=41) were enrolled in a single-arm cohort. The major efficacy outcome measure for the HGG cohort was ORR as assessed by independent review committee per RANO 2010 criteria.[1,2]

HGG, high-grade glioma; LGG, low-grade glioma; ORR, overall response rate; RANO; Response Assessment in Neuro-Oncology.

IMPORTANT SAFETY INFORMATION (continued)

Colitis and Gastrointestinal Perforation. Colitis and gastrointestinal perforation, including fatal outcomes, can occur. In the pooled adult safety population of MEKINIST administered with TAFINLAR, colitis occurred in <1% of patients and gastrointestinal perforation occurred in <1% of patients. In the pooled pediatric safety population of MEKINIST administered with TAFINLAR, colitis events occurred in <1% of patients. Monitor patients closely for colitis and gastrointestinal perforations.

Venous Thromboembolic Events. In the pooled adult safety population of MEKINIST administered with TAFINLAR, deep vein thrombosis (DVT) and pulmonary embolism (PE) occurred in 2% of patients. In the pooled pediatric safety population of MEKINIST administered with TAFINLAR, embolism events occurred in <1% of patients.

Advise patients to immediately seek medical care if they develop symptoms of DVT or PE, such as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue MEKINIST for life-threatening PE. Withhold MEKINIST for uncomplicated DVT and PE for up to 3 weeks; if improved, MEKINIST may be resumed at a lower dose.

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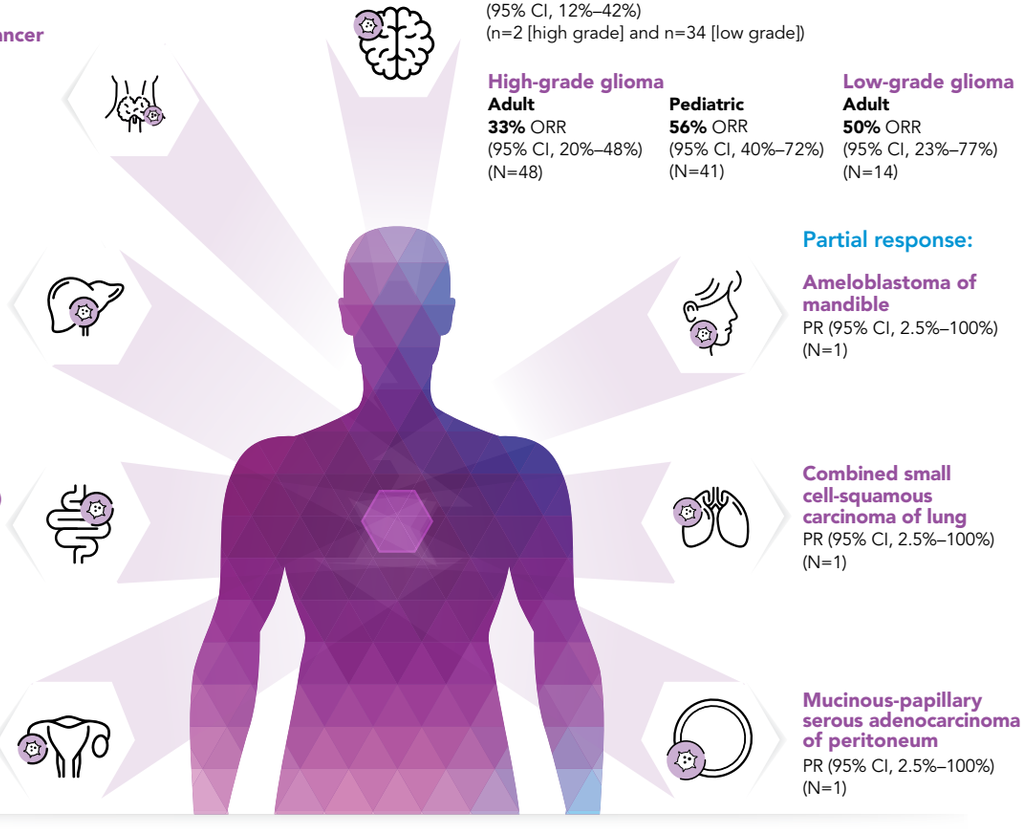
TAFINLAR + MEKINIST DEMONSTRATED EFFICACY IN A RANGE OF SOLID TUMORS

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

Broad antitumor activity across multiple studies: Up to 80%* ORR in adults with various *BRAF* V600E–mutant solid tumors[1,2]

Proven response across various *BRAF* V600E–mutant solid tumors in adults and children[1,2,a]



High- and low-grade glioma[b]
Pediatric
25% ORR
(95% CI, 12%–42%)
(n=2 [high grade] and n=34 [low grade])

High-grade glioma
Adult
33% ORR
(95% CI, 20%–48%)
(N=48)

Pediatric
56% ORR
(95% CI, 40%–72%)
(N=41)

Low-grade glioma
Adult
50% ORR
(95% CI, 23%–77%)
(N=14)

Anaplastic thyroid cancer (adult)
In a subset of patients in the ROAR Study
53% ORR
(95% CI, 35.5%–69.6%)
(N=36)

Biliary tract cancer (adult)
46% ORR
(95% CI, 31%–61%)
(N=48)

Adenocarcinoma of small intestine (adult)
50% ORR
(95% CI, 7%–93%)
(N=4)

Low-grade serous ovarian carcinoma (adult)
80% ORR
(95% CI, 28%–100%)
(N=5)

Partial response:

Ameloblastoma of mandible
PR (95% CI, 2.5%–100%)
(N=1)

Combined small cell-squamous carcinoma of lung
PR (95% CI, 2.5%–100%)
(N=1)

Mucinous-papillary serous adenocarcinoma of peritoneum
PR (95% CI, 2.5%–100%)
(N=1)

No response:

- **Adenocarcinoma pancreas** (N=3)
- **Mixed ductal/adenoneuroendocrine carcinoma** (N=2)
- **Neuroendocrine carcinoma of colon** (N=2)
- **Adenocarcinoma of anus** (N=1)
- **Gastrointestinal stromal tumors** (N=1)

Safety and efficacy were supported by results in COMBI-d, COMBI-v, and BRF113928 studies

ATC, anaplastic thyroid cancer; ORR, overall response rate; PR, partial response.

*In tumor types with N>4.
[a]Excludes non-small cell lung cancer (N=6) (previously approved tumor type for TAFINLAR + MEKINIST).[1,2]
[b]Patients with pediatric LGG evaluated in this dataset represent a previously treated population with refractory or recurrent tumors. Therefore, data differs from results seen in separately approved pediatric LGG indication, which included patients who required their first systemic treatment (ORR: 46.6%; N=73).

ADDITIONAL INDICATION[1,2]

TAFINLAR, in combination with MEKINIST, is indicated for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with *BRAF* V600E mutation and with no satisfactory locoregional treatment options.

IMPORTANT SAFETY INFORMATION (continued)

Cardiomyopathy. Cardiomyopathy, including cardiac failure, can occur. In the pooled adult safety population of the combination, cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% from baseline and below the institutional lower limit of normal (LLN), occurred in 6% of patients. Development of cardiomyopathy resulted in dose interruption or discontinuation of TAFINLAR in 3% and <1% of patients, respectively, and in 3% and <1% of patients receiving MEKINIST, respectively. Cardiomyopathy resolved in 45 of 50 patients who received the combination. In the pooled pediatric safety population of the combination, cardiomyopathy, defined as a decrease in LVEF ≥10% from baseline and below the institutional LLN, occurred in 9% of patients.

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TAFINLAR + MEKINIST DEMONSTRATED EFFICACY IN A RANGE OF SOLID TUMORS (continued)

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

Demonstrated DOR across multiple tumor types

DOR in the ROAR (adult) and NCI-MATCH (adult) Studies[1,2]

Tumor type[a]	Patients (N)	Range (months)	Other DOR data
ATC	19	—	**Median DOR:** 13.6 months (95% CI, 3.8-NE) **DOR ≥6 months:** 68% **DOR ≥12 months:** 53%
BTC	48	1.8[b]-40[b]	**Median DOR:** 9.8 months (95% CI, 5.3-20.4)
HGG	48	3.9-44	**Median DOR:** 13.6 months (95% CI, 5.5-26.7)
LGG	14	6-29[b]	—
LGSOC	5	12-42[b]	—
Adenocarcinoma of small intestine	4	7-8	—
Ameloblastoma of mandible	1	30	—
Combined small cell-squamous carcinoma of lung	1	5	—
Mucinous-papillary serous adenocarcinoma of peritoneum	1	8	—

DOR was not applicable for tumor types that had no response.

Across tumor types, DOR ranged from 1.8 months to as long as 44 months in patients with *BRAF* V600E–mutant solid tumors who responded to treatment with TAFINLAR + MEKINIST

ATC, anaplastic thyroid cancer; BTC, biliary tract cancer; DOR, duration of response; HGG, high-grade glioma; LGG, low-grade glioma; LGSOC, low-grade serous ovarian carcinoma; NE, not estimable.
No additional DOR measures evaluated where marked "–".
[a]Excludes non-small cell lung cancer (N=6) (previously approved tumor type for TAFINLAR + MEKINIST). Data for ATC were assessed in patients with locally advanced, unresectable, or metastatic disease and no standard locoregional treatment options.
[b]Denotes a right-censored DOR.

DOR assessment in pediatric studies[1,2]

- **X2101 (HGG and LGG):** For the 9 patients who responded, DOR was ≥6 months for 78% of patients and ≥24 months for 44% of patients
- **G2201 (HGG cohort):** Median DOR was not estimable (NE) (95% CI, 9.2-NE). For the 23 patients who responded, DOR was ≥6 months for 78% of patients, ≥12 months for 48% of patients, and ≥24 months for 22% of patients

IMPORTANT SAFETY INFORMATION (continued)

Cardiomyopathy (continued). Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of the combination, 1 month after initiation, and then at 2- to 3-month intervals while on treatment. Withhold TAFINLAR for symptomatic cardiomyopathy or asymptomatic left ventricular dysfunction of >20% from baseline that is below institutional LLN. Resume TAFINLAR at the same dose level upon recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease ≤10% compared to baseline. For an asymptomatic absolute decrease in LVEF of 10% or greater from baseline that is below the LLN, withhold MEKINIST for up to 4 weeks. If improved to normal LVEF value, resume at a lower dose. If no improvement to normal LVEF value within 4 weeks, permanently discontinue MEKINIST. For symptomatic cardiomyopathy or an absolute decrease in LVEF of >20% from baseline that is below LLN, permanently discontinue MEKINIST.

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SAFETY PROFILE

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

Adverse reactions (adult)

The safety of TAFINLAR + MEKINIST in adults with *BRAF* V600E–mutant solid tumors was determined by the ROAR Study[1,2]

Adverse reactions (≥20%) of adult patients taking TAFINLAR + MEKINIST[1,2,a]

Adverse Reactions	TAFINLAR + MEKINIST (N=206)	
	All grades, %	Grade 3 or 4, %
General		
Pyrexia	55	4.9
Fatigue[b]	50	5
Chills	30	0.5
Edema peripheral[c]	22	0
Gastrointestinal		
Nausea	40	1.5
Constipation	27	0
Vomiting	27	1.5
Diarrhea	26	2.9
Skin		
Rash[d]	40	2.4
Nervous system		
Headache	30	1.5
Vascular disorders		
Hemorrhage[e]	29	4.4
Respiratory		
Cough[f]	29	0
Musculoskeletal and connective tissue		
Myalgia[g]	24	0.5
Arthralgia	23	0.5

- **Serious adverse reactions** occurred in 45% of adult patients, which included pyrexia (11%) and pneumonia (6%) in >5% of patients[1,2]
- **Fatal adverse reactions** occurred in 3.9% of adult patients, which included sepsis (1.9%) in >1% of patients[1,2]
- **Permanent treatment discontinuation** due to adverse reactions occurred in 13% of adult patients, which included nausea (1.5%) in >1% of patients[1,2]
- **Dosage interruptions** due to an adverse reaction occurred in 55% of adult patients, which included pyrexia (22%), chills (9%), fatigue (6%), neutropenia (6%), and nausea (5%) in >5% of patients[1,2]
- **Dose reductions** due to an adverse reaction occurred in 44% of patients, which included pyrexia (18%), chills (8%), and fatigue (6%) in >5% of patients[1,2]

[a]National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.
[b]Includes fatigue, asthenia, and malaise.
[c]Includes edema peripheral and peripheral swelling.
[d]Includes rash, rash maculo-papular, rash erythematous, rash pustular, and rash papular.
[e]Includes epistaxis, hematuria, contusion, hematoma, hemoptysis, conjunctival hemorrhage, hematochezia, rectal hemorrhage, hemorrhoidal hemorrhage, melena, purpura, eye contusion, eye hemorrhage, gastric hemorrhage, gingival bleeding, hematemesis, hemorrhage intracranial, hemorrhagic stroke, hemothorax, increased tendency to bruise, large intestinal hemorrhage, mouth hemorrhage, petechiae, pharyngeal hemorrhage, prothrombin time prolonged, pulmonary hematoma, retinal hemorrhage, vaginal hemorrhage, and vitreous hemorrhage.
[f]Includes cough and productive cough.
[g]Includes myalgia, musculoskeletal chest pain, and musculoskeletal pain.

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SAFETY PROFILE (continued)

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Adverse reactions (pediatric)

The safety of TAFINLAR + MEKINIST in pediatric patients with *BRAF* V600E–mutant solid tumors was determined by the X2101 Study[1,2]

Adverse reactions (≥20%) of pediatric patients taking TAFINLAR + MEKINIST[1,2,a]

	TAFINLAR + MEKINIST (N=48)	
Adverse Reactions	**All grades, %**	**Grade 3 or 4, %**
General		
Pyrexia	75	17
Fatigue[b]	48	0
Skin		
Rash[c]	73	2.1
Dry skin	48	0
Dermatitis acneiform[d]	40	0
Gastrointestinal		
Vomiting	52	4.2
Diarrhea	42	2.1
Abdominal pain[e]	33	4.2
Nausea	33	2.1
Constipation	23	0
Respiratory		
Cough	44	0
Nervous system		
Headache	35	0
Vascular disorders		
Hemorrhage[f]	33	0
Infections		
Paronychia	23	0

- **Serious adverse reactions** occurred in 46% of pediatric patients, which included pyrexia (25%) and ejection fraction decreased (6%) in >5% of patients[1,2]
- **Permanent treatment discontinuation** due to an adverse reaction occurred in 21% of patients, which included alanine aminotransferase increased (6%), aspartate aminotransferase increased (4.2%), and ejection fraction decreased (4.2%) in >3% of patients[1,2]
- **Dosage interruptions** due to an adverse reaction occurred in 73% of patients, which included pyrexia (56%), vomiting (19%), neutropenia (13%), rash (13%), ejection fraction decreased (6%), and uveitis (6%) in >5% of patients[1,2]
- **Dose reductions** due to an adverse reaction occurred in 25% of patients, which included pyrexia (13%) in >5% of patients[1,2]

[a]National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.
[b]Includes fatigue, asthenia, and malaise.
[c]Includes rash, rash maculo-papular, rash erythematous, rash papular, rash pustular, and rash macular.
[d]Includes dermatitis acneiform and acne.
[e]Includes abdominal pain and abdominal pain upper.
[f]Includes epistaxis, hematuria, contusion, hematoma, petechiae, rectal hemorrhage, and red blood cell count decreased.

Please see additional Important Safety Information for TAFINLAR + MEKINIST throughout this brochure.
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RECOMMENDED DOSING FOR ADULTS

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

Adult dosing*:

- The recommended dosage for TAFINLAR in adult patients is 150 mg (two 75-mg capsules) taken orally twice daily[1]
- The recommended dosage for MEKINIST in adult patients is 2 mg taken orally once daily[2]

Dose reductions for adult patients[1,2]

	TAFINLAR STARTING DOSE	MEKINIST STARTING DOSE
	TAFINLAR 150 mg (2 × 75 mg) orally twice daily	**MEKINIST 2 mg orally once daily**
First dose reduction	100 mg (two 50-mg capsules)	1.5 mg (three 0.5-mg tablets)
Second dose reduction	75 mg	1 mg (two 0.5-mg tablets)
Third dose reduction	50 mg	Permanently discontinue MEKINIST if unable to tolerate 1 mg orally once daily
Subsequent modification	Permanently discontinue TAFINLAR if unable to tolerate 50 mg orally twice daily	

*Treatment is recommended until disease progression or unacceptable toxicity.[1,2]

IMPORTANT SAFETY INFORMATION (continued)

Ocular Toxicities

Retinal Vein Occlusion (RVO): There were no cases of RVO across clinical trials of the combination. RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Urgently (within 24 hours) perform ophthalmologic evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue MEKINIST in patients with documented RVO.

Retinal Pigment Epithelial Detachment (RPED): RPED can occur. Retinal detachments may be bilateral and multifocal, occurring in the central macular region of the retina or elsewhere in the retina. In clinical trials, routine monitoring of patients to detect asymptomatic RPED was not conducted; therefore, the true incidence of this finding is unknown. In the pooled pediatric safety population of MEKINIST administered with TAFINLAR, RPED events occurred in <1% of patients.

Perform ophthalmologic evaluation periodically, and at any time a patient reports visual disturbances. Withhold MEKINIST if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmologic evaluation within 3 weeks, resume MEKINIST at the same or a reduced dose. If no improvement after 3 weeks, resume at a reduced dose or permanently discontinue MEKINIST.

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In pediatric patients aged 1 year and older with *BRAF* V600E–mutant solid tumors

FOR THE FIRST TIME, TAFINLAR + MEKINIST IS AVAILABLE IN 2 FORMS FOR ORAL DOSING[1,2]

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

Pediatric dosing:

- TAFINLAR + MEKINIST is available as capsules and tablets and as a liquid formulation[1,2]
- The recommended dosage for TAFINLAR (capsules) and MEKINIST (tablets) in pediatric patients is based on body weight, beginning at 26 kg. (Note: This applies to capsule and tablet dosing only.) A recommended dose for TAFINLAR + MEKINIST has not been established in patients who weigh less than 26 kg[1,2]

Weight-based oral dosing for TAFINLAR capsules and MEKINIST tablets[1,2]

TAFINLAR		MEKINIST	
Body Weight	**Recommended Pediatric Dose (Capsules)**	**Body Weight**	**Recommended Pediatric Dose (Tablets)**
26 to 37 kg	75 mg (one 75-mg capsule) orally BID	26 to 37 kg	1 mg (two 0.5-mg tablets) orally QD
38 to 50 kg	100 mg (two 50-mg capsules) orally BID	38 to 50 kg	1.5 mg (three 0.5-mg tablets) orally QD
≥51 kg	150 mg (two 75-mg capsules) orally BID	≥51 kg	2 mg (one 2-mg tablet) orally QD

BID, twice daily; QD, once daily.

For information about recommended liquid formulation dosing and dose modifications for both formulations, please click here

- Treatment is recommended until disease progression or unacceptable toxicity[1,2]
- The number of TAFINLAR capsules and MEKINIST tablets included in the chart above are an example. TAFINLAR and MEKINIST are also available in other strengths. TAFINLAR is available as 50-mg and 75-mg capsules, and MEKINIST is available as 0.5-mg and 2-mg tablets[1,2]
- TAFINLAR and MEKINIST should be taken at the same time each day, 1 hour prior or 2 hours after a meal[1,2]
- TAFINLAR doses should be taken 12 hours apart. Missed doses of TAFINLAR should not be taken within 6 hours of the next dose[1]
- MEKINIST doses should be taken 24 hours apart. Missed doses of MEKINIST should not be taken within 12 hours of the next dose[2]
- TAFINLAR and MEKINIST can be administered in capsule and tablet form, respectively[1,2]

For complete administration instructions, please see the full Prescribing Information for the appropriate medications. Please share the Instructions for Use with your patients and caregivers.

IMPORTANT SAFETY INFORMATION (continued)

Ocular Toxicities (continued)

Uveitis: In the pooled adult safety population of the combination, uveitis occurred in 2% of patients. In the pooled pediatric safety population of the combination, uveitis occurred in 1.2% of patients.

Please see additional Important Safety Information for TAFINLAR + MEKINIST throughout this brochure.
Please click here for full Prescribing Information for TAFINLAR and click here for full Prescribing Information for MEKINIST.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

TAFINLAR, in combination with MEKINIST, is indicated for the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitation of Use: TAFINLAR, in combination with MEKINIST, is not indicated for the treatment of patients with colorectal cancer because of known intrinsic resistance to *BRAF* inhibition. TAFINLAR is not indicated for the treatment of patients with wild-type *BRAF* solid tumors.

IMPORTANT SAFETY INFORMATION

New Primary Malignancies

Cutaneous Malignancies

In the pooled adult safety population of TAFINLAR administered with MEKINIST ("the combination"), the incidence of cutaneous squamous cell carcinoma (cuSCC, including keratoacanthomas) occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and <1% of patients, respectively.

In the pooled pediatric safety population of the combination, new primary melanoma occurred in <1% of patients.

Perform dermatologic evaluations prior to initiation of the combination, every 2 months while on therapy, and for up to 6 months following discontinuation.

Noncutaneous Malignancies

Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of monomeric G protein (RAS) through mutation or other mechanisms. In the pooled adult safety population of TAFINLAR monotherapy and the combination, noncutaneous malignancies occurred in 1% of patients.

Monitor patients receiving the combination for signs or symptoms of noncutaneous malignancies. Permanently discontinue TAFINLAR for RAS-mutation–positive noncutaneous malignancies. No dose modification is required for MEKINIST in patients who develop noncutaneous malignancies.

Tumor Promotion in *BRAF* Wild-type Tumors. In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (*MAPK*) signaling and increased cell proliferation in *BRAF* wild-type cells that are exposed to *BRAF* inhibitors. Confirm evidence of *BRAF* V600E or V600K mutation status prior to initiation of therapy.

Hemorrhage. Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with the combination. Fatal cases have been reported.

In the pooled adult safety population of the combination, hemorrhagic events occurred in 17% of patients; gastrointestinal hemorrhage occurred in 3% of patients; intracranial hemorrhage occurred in 0.6% of patients; fatal hemorrhage occurred in 0.5% of patients. The fatal events were cerebral hemorrhage and brainstem hemorrhage.

In the pooled pediatric safety population of the combination, hemorrhagic events occurred in 25% of patients; the most common type of bleeding was epistaxis (16%). Serious events of bleeding occurred in 3.6% of patients and included gastrointestinal hemorrhage (1.2%), cerebral hemorrhage (0.6%), uterine hemorrhage (0.6%), postprocedural hemorrhage (0.6%), and epistaxis (0.6%).

Permanently discontinue TAFINLAR for all grade 4 hemorrhagic events and for any grade 3 hemorrhagic events that do not improve. Withhold TAFINLAR for grade 3 hemorrhagic events; if improved, resume at the next lower dose level. Permanently discontinue MEKINIST for all grade 4 hemorrhagic events and for any grade 3 hemorrhagic events that do not improve. Withhold MEKINIST for grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

Colitis and Gastrointestinal Perforation. Colitis and gastrointestinal perforation, including fatal outcomes, can occur. In the pooled adult safety population of MEKINIST administered with TAFINLAR, colitis occurred in <1% of patients and gastrointestinal perforation occurred in <1% of patients. In the pooled pediatric safety population of MEKINIST administered with TAFINLAR, colitis events occurred in <1% of patients. Monitor patients closely for colitis and gastrointestinal perforations.

Venous Thromboembolic Events. In the pooled adult safety population of MEKINIST administered with TAFINLAR, deep vein thrombosis (DVT) and pulmonary embolism (PE) occurred in 2% of patients. In the pooled pediatric safety population of MEKINIST administered with TAFINLAR, embolism events occurred in <1% of patients.

Advise patients to immediately seek medical care if they develop symptoms of DVT or PE, such as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue MEKINIST for life-threatening PE. Withhold MEKINIST for uncomplicated DVT and PE for up to 3 weeks; if improved, MEKINIST may be resumed at a lower dose.

Please see additional Important Safety Information for TAFINLAR + MEKINIST throughout this brochure.
Please click here for full Prescribing Information for TAFINLAR and click here for full Prescribing Information for MEKINIST.

IMPORTANT SAFETY INFORMATION
(continued)

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

Cardiomyopathy. Cardiomyopathy, including cardiac failure, can occur. In the pooled adult safety population of the combination, cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% from baseline and below the institutional lower limit of normal (LLN), occurred in 6% of patients. Development of cardiomyopathy resulted in dose interruption or discontinuation of TAFINLAR in 3% and <1% of patients, respectively, and in 3% and <1% of patients receiving MEKINIST, respectively. Cardiomyopathy resolved in 45 of 50 patients who received the combination. In the pooled pediatric safety population of the combination, cardiomyopathy, defined as a decrease in LVEF ≥10% from baseline and below the institutional LLN, occurred in 9% of patients.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of the combination, 1 month after initiation, and then at 2- to 3-month intervals while on treatment. Withhold TAFINLAR for symptomatic cardiomyopathy or asymptomatic left ventricular dysfunction of >20% from baseline that is below institutional LLN. Resume TAFINLAR at the same dose level upon recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease ≤10% compared to baseline. For an asymptomatic absolute decrease in LVEF of 10% or greater from baseline that is below the LLN, withhold MEKINIST for up to 4 weeks. If improved to normal LVEF value, resume at a lower dose. If no improvement to normal LVEF value within 4 weeks, permanently discontinue MEKINIST. For symptomatic cardiomyopathy or an absolute decrease in LVEF of >20% from baseline that is below LLN, permanently discontinue MEKINIST.

Ocular Toxicities

Retinal Vein Occlusion (RVO): There were no cases of RVO across clinical trials of the combination. RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Urgently (within 24 hours) perform ophthalmologic evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue MEKINIST in patients with documented RVO.

Retinal Pigment Epithelial Detachment (RPED): RPED can occur. Retinal detachments may be bilateral and multifocal, occurring in the central macular region of the retina or elsewhere in the retina. In clinical trials, routine monitoring of patients to detect asymptomatic RPED was not conducted; therefore, the true incidence of this finding is unknown. In the pooled pediatric safety population of MEKINIST administered with TAFINLAR, RPED events occurred in <1% of patients.

Perform ophthalmologic evaluation periodically, and at any time a patient reports visual disturbances. Withhold MEKINIST if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmologic evaluation within 3 weeks, resume MEKINIST at the same or a reduced dose. If no improvement after 3 weeks, resume at a reduced dose or permanently discontinue MEKINIST.

Uveitis: In the pooled adult safety population of the combination, uveitis occurred in 2% of patients. In the pooled pediatric safety population of the combination, uveitis occurred in 1.2% of patients.

Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (eg, change in vision, photophobia, and eye pain). If iritis is diagnosed, administer ocular therapy and continue TAFINLAR without dose modification. If severe uveitis (ie, iridocyclitis) or if mild or moderate uveitis does not respond to ocular therapy, withhold TAFINLAR and treat as clinically indicated. Resume TAFINLAR at the same or lower dose if uveitis improves to grade 0 or 1. Permanently discontinue TAFINLAR for persistent grade 2 or greater uveitis of >6 weeks.

Interstitial Lung Disease (ILD)/Pneumonitis. In the pooled safety population of MEKINIST administered with TAFINLAR, ILD or pneumonitis occurred in 1% of patients.

Withhold MEKINIST in patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue MEKINIST for patients diagnosed with treatment-related ILD or pneumonitis.

Serious Febrile Reactions. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur. The incidence and severity of pyrexia are increased when TAFINLAR is administered with MEKINIST.

In the pooled adult safety population of the combination, fever occurred in 58% of patients. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration or renal failure occurred in 5% of patients. Fever was complicated by hypotension in 4%, dehydration in 3%, syncope in 2%, renal failure in 1%, and severe chills/rigors in <1% of patients.

In the pooled pediatric safety population of the combination, pyrexia occurred in 66% of patients.

Withhold TAFINLAR and MEKINIST for temperature of ≥100.4 °F. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Fever may be complicated by hypotension, rigors or chills, dehydration, or renal failure. Evaluate for signs and symptoms of infection and monitor serum creatinine and other evidence of renal function during and following severe pyrexia. Upon 24 hours after resolution, if appropriate, resume both TAFINLAR and MEKINIST at the same or a lower dose. Administer antipyretics as secondary prophylaxis when resuming TAFINLAR and/or MEKINIST if the patient had a prior episode of severe febrile reaction or fever associated with complications. Administer corticosteroids (eg, prednisone 10 mg daily) for at least 5 days for second or subsequent pyrexia if temperature does not return to baseline within 3 days of onset of pyrexia, or for pyrexia associated with complications such as hypotension, severe rigors or chills, dehydration, or renal failure, and there is no evidence of active infection.

Please see additional Important Safety Information for TAFINLAR + MEKINIST throughout this brochure.
Please click here for full Prescribing Information for TAFINLAR and click here for full Prescribing Information for MEKINIST.

IMPORTANT SAFETY INFORMATION
(continued)

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

Serious Skin Toxicities. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with the combination.

In the pooled adult safety population of the combination, other serious skin toxicity occurred in <1% of patients. In the pooled pediatric safety population of the combination, serious adverse events of skin and subcutaneous tissue disorders occurred in 1.8% of patients.

Monitor for new or worsening serious skin reactions. Permanently discontinue the combination for SCARs. For other skin toxicities, withhold TAFINLAR and/or MEKINIST for intolerable or severe skin toxicity. Resume TAFINLAR and/or MEKINIST at a lower dose in patients with improvement or recovery from skin toxicity within 3 weeks. Permanently discontinue TAFINLAR and/or MEKINIST if skin toxicity has not improved within 3 weeks.

Hyperglycemia. In the pooled adult safety population of the combination, 15% of patients with a history of diabetes required more intensive hypoglycemic therapy. Grade 3 and grade 4 hyperglycemia occurred in 2% of patients. In the pooled pediatric safety population of the combination, grade 3 and grade 4 hyperglycemia events occurred in <1% of patients.

Monitor serum glucose levels upon initiation and as clinically appropriate in patients with preexisting diabetes or hyperglycemia. Initiate or optimize antihyperglycemic medications as clinically indicated.

Glucose-6-Phosphate Dehydrogenase Deficiency. TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR.

Embryo-fetal Toxicity. TAFINLAR and MEKINIST can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use effective nonhormonal contraception during treatment, and for 4 months after treatment.

Hemophagocytic Lymphohistiocytosis (HLH). HLH has been observed in the postmarketing setting when TAFINLAR was administered with MEKINIST. If HLH is suspected, interrupt treatment. If HLH is confirmed, discontinue treatment and initiate appropriate management of HLH.

Most Common Adverse Reactions. In Study BRF117019, the most commonly occurring adverse reactions (≥20%) in patients receiving the combination were pyrexia (55%), fatigue (50%), chills (30%), peripheral edema (22%), nausea (40%), constipation (27%), vomiting (27%), diarrhea (26%), rash (40%), headache (30%), hemorrhage (29%), cough (29%), myalgia (24%), and arthralgia (23%).

In Study X2101, the most commonly occurring adverse reactions (≥20%) in patients receiving the combination were pyrexia (75%), fatigue (48%), rash (73%), dry skin (48%), dermatitis acneiform (40%), vomiting (52%), diarrhea (42%), abdominal pain (33%), nausea (33%), constipation (23%), cough (44%), headache (35%), hemorrhage (33%), and paronychia (23%).

In the pediatric pooled safety population of Studies G2201 and X2101, the most common adverse reactions (>20%) in patients receiving the combination were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%) and dermatitis acneiform (23%). The most common (>2%) grade 3 or 4 laboratory abnormalities were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and aspartate aminotransferase increased (3.1%).

Other Clinically Important Adverse Reactions. In Study BRF117019, other clinically important adverse reactions observed in <20% of adult patients receiving the combination were peripheral neuropathy (9%), decreased ejection fraction (8%), atrioventricular block (2.9%), uveitis (1.9%), and hypersensitivity (1.9%). In Study X2101, other clinically important adverse reactions observed in <20% of patients receiving the combination were atrioventricular block (2.1%).

Laboratory Abnormalities. In Study BRF117019, the most common treatment-emergent laboratory abnormalities occurring at ≥20% of patients receiving the combination were hyperglycemia (61%), decreased sodium (35%), decreased magnesium (24%), increased creatinine (21%), increased alkaline phosphatase (51%), increased aspartate aminotransferase (AST) (51%), increased alanine aminotransferase (ALT) (39%), and decreased hemoglobin (44%).

In Study X2101, the most common treatment-emergent laboratory abnormalities occurring at ≥20% of patients receiving the combination were hyperglycemia (65%), hypoalbuminemia (48%), hypocalcemia (40%), decreased phosphate (38%), decreased magnesium (33%), hypernatremia (27%), hypokalemia (21%), increased AST (55%), increased ALT (40%), increased alkaline phosphatase (28%), increased total bilirubin (21%), decreased hemoglobin (60%), and decreased neutrophils (49%).

In Study G2201, the most common treatment-emergent laboratory abnormalities occurring at ≥20% of patients receiving the combination were decreased leukocytes (59%), increased alkaline phosphatase (55%), decreased hemoglobin (46%), decreased neutrophils (44%), increased AST (37%), decreased magnesium (34%), increased magnesium (32%), decreased platelets (30%), increased ALT (29%), and increased lymphocytes (24%).

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THE MOST PRESCRIBED TARGETED THERAPY IN *BRAF/MEK* INHIBITION IS APPROVED TO TREAT *BRAF* V600E–MUTANT SOLID TUMORS[1-7*]

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

TAFINLAR + MEKINIST is the first and only combination treatment for patients 1 year of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have no satisfactory alternative options and who have progressed following prior treatment[1-7]

Based on IQVIA prescription data collected from December 2011 to December 2021.

*Excludes colorectal cancer because of known intrinsic resistance to *BRAF* inhibition.

INDICATION

TAFINLAR, in combination with MEKINIST, is indicated for the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

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IMPORTANT SAFETY INFORMATION (continued)

Ocular Toxicities (continued)

Uveitis (continued): Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (eg, change in vision, photophobia, and eye pain). If iritis is diagnosed, administer ocular therapy and continue TAFINLAR without dose modification. If severe uveitis (ie, iridocyclitis) or if mild or moderate uveitis does not respond to ocular therapy, withhold TAFINLAR and treat as clinically indicated. Resume TAFINLAR at the same or lower dose if uveitis improves to grade 0 or 1. Permanently discontinue TAFINLAR for persistent grade 2 or greater uveitis of >6 weeks.

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