In *BRAF* V600E+ pediatric low-grade glioma

TRANSFORM YOUR PATIENTS' TREATMENT

WITH TAFINLAR + MEKINIST

Hypothetical patient.

INDICATION

TAFINLAR, in combination with MEKINIST, is indicated 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.

Limitation of Use: 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 pediatric safety population of TAFINLAR administered with MEKINIST ("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.

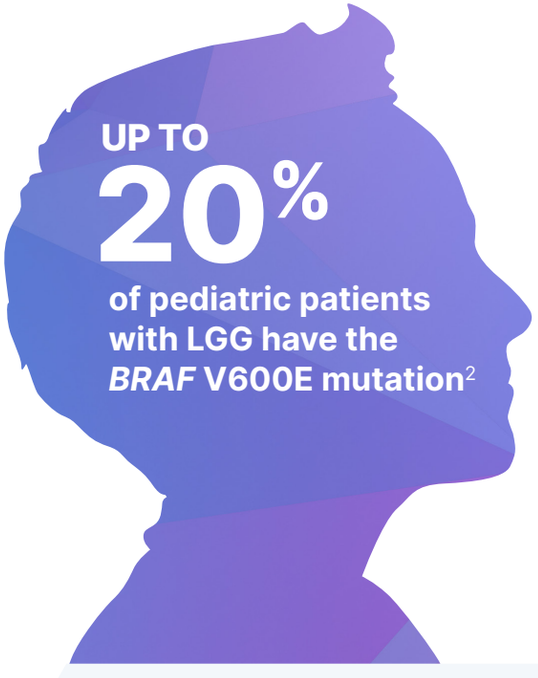
Please see additional Important Safety Information for TAFINLAR + MEKINIST throughout this brochure and here.

Please click here for full Prescribing Information for TAFINLAR, and click here for full Prescribing Information for MEKINIST.

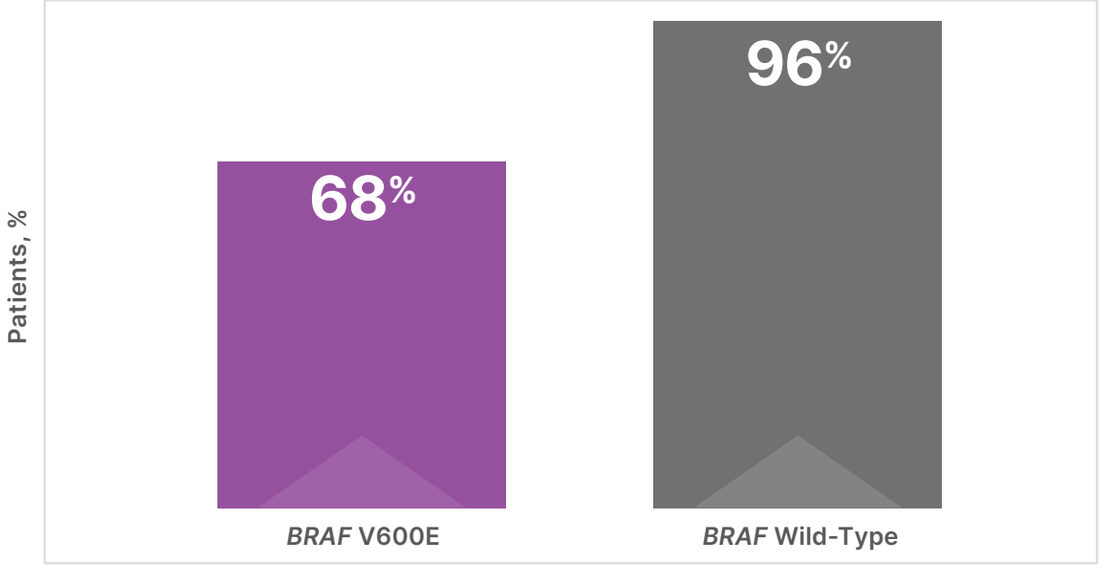
Tafinlar® (dabrafenib) 50 mg, 75 mg capsules + Mekinist® (trametinib) 0.5 mg, 2 mg tablets

BRAF V600E MUTATION IS COMMON IN PEDIATRIC LGG AND TYPICALLY HAS A POOR PROGNOSIS[1,2]

- Low-grade glioma (LGG) is the most common brain tumor diagnosed in children. *BRAF* V600E is the second most common mutation observed in pediatric LGG[2]
- *BRAF* V600E–mutated LGG has distinct and more aggressive clinical characteristics compared with wild-type, including increased risk of progression[1]



5-year progression-free survival after tumor resection[1]



Historically, pediatric patients with LGG who required treatment achieved suboptimal outcomes with standard treatment options.[1]

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.

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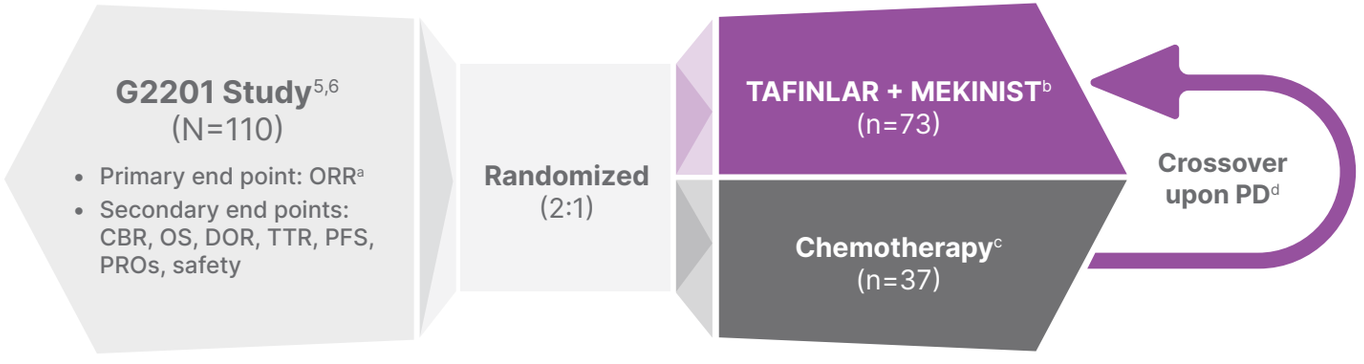
TAFINLAR + MEKINIST WAS INVESTIGATED vs CHEMOTHERAPY (VINCRISTINE AND CARBOPLATIN) IN PEDIATRIC PATIENTS WITH *BRAF*+ LGG

Study design

The efficacy and safety of TAFINLAR + MEKINIST in pediatric patients aged 1 to <18 years with *BRAF* V600E mutation–positive LGG were evaluated in the multicenter, open-label, phase 2 clinical trial G2201.[3-5]*

- Patients in the G2201 study had progressive disease following surgical resection, or had not received surgery and needed to begin systemic treatment because of risk of neurological impairment[6]



Key eligibility criteria[6]:

- Aged 1 to <18 years
- Histologically confirmed *BRAF* V600+ LGG
- Locally determined and centrally confirmed measurable disease
- No prior *BRAF*- or *MEK*-inhibitor treatment, systemic therapy, or radiotherapy
- Karnofsky/Lansky performance status ≥50%

*The efficacy and safety of TAFINLAR + MEKINIST have not been established in pediatric patients <1 year old with *BRAF* V600E+ LGG.[3,4]
CBR, clinical benefit rate; DOR, duration of response; LGG, low-grade glioma; *MEK*, mitogen-activated extracellular signal-regulated kinase; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PROs, patient-reported outcomes; RANO, Response Assessment in Neuro-Oncology; TTR, time to response.
[a]Independent review based on RANO LGG (2017) criteria after all patients had completed at least 32 weeks of therapy.[3,4]
[b]Patients received age- and weight-based dosing of TAFINLAR and MEKINIST until loss of clinical benefit or until unacceptable toxicity.[3,4]
[c]Vincristine and carboplatin were dosed based on body surface area at doses 1.5 mg/m^2 and 175 mg/m^2 (0.05 mg/kg for patients <12 kg), respectively, as one 10-week induction course followed by eight 6-week cycles of maintenance therapy.[3,4]
[d]Patients with centrally confirmed RANO-defined disease progression will be allowed to cross over to the TAFINLAR + MEKINIST arm.[6]

IMPORTANT SAFETY INFORMATION (continued)

New Primary Malignancies (continued)

Noncutaneous Malignancies (continued)

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.

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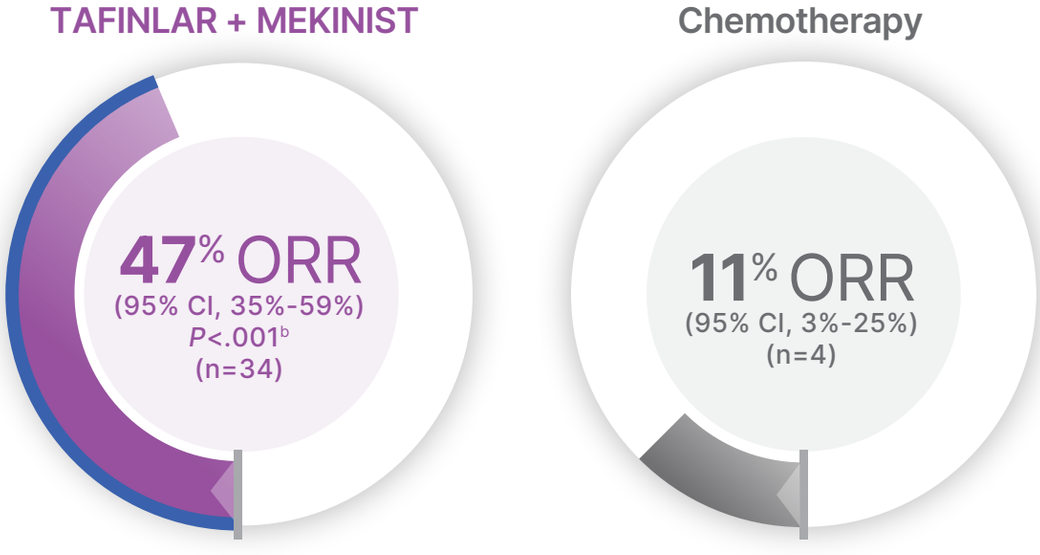
TAFINLAR + MEKINIST—RAISING THE BAR FOR THE TREATMENT OF *BRAF* V600E+ PEDIATRIC LGG[3,4]

4x improvement in overall response rate vs chemotherapy (vincristine and carboplatin)[3,4]

Nearly half of patients experienced a response with TAFINLAR + MEKINIST vs chemotherapy (47% [95% CI, 35%-59%] vs 11% [95% CI, 3%-25%], respectively) (*P*<.001).[3,4]

Overall response rate (primary end point)[3-5,a]



Hypothetical patient.

- Complete response (CR): 3% (n=2) for TAFINLAR + MEKINIST vs 3% (n=1) for chemotherapy[3,4]
- Partial response (PR): 44% (n=32) for TAFINLAR + MEKINIST vs 8% (n=3) for chemotherapy[3,4]

ORR, overall response rate.
[a]ORR is defined as complete response + partial response.
[b]The *P* value is computed from $\chi 2$ test (Mantel-Haenszel) at a 1-sided 2.5% level of significance.[6]

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.

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.

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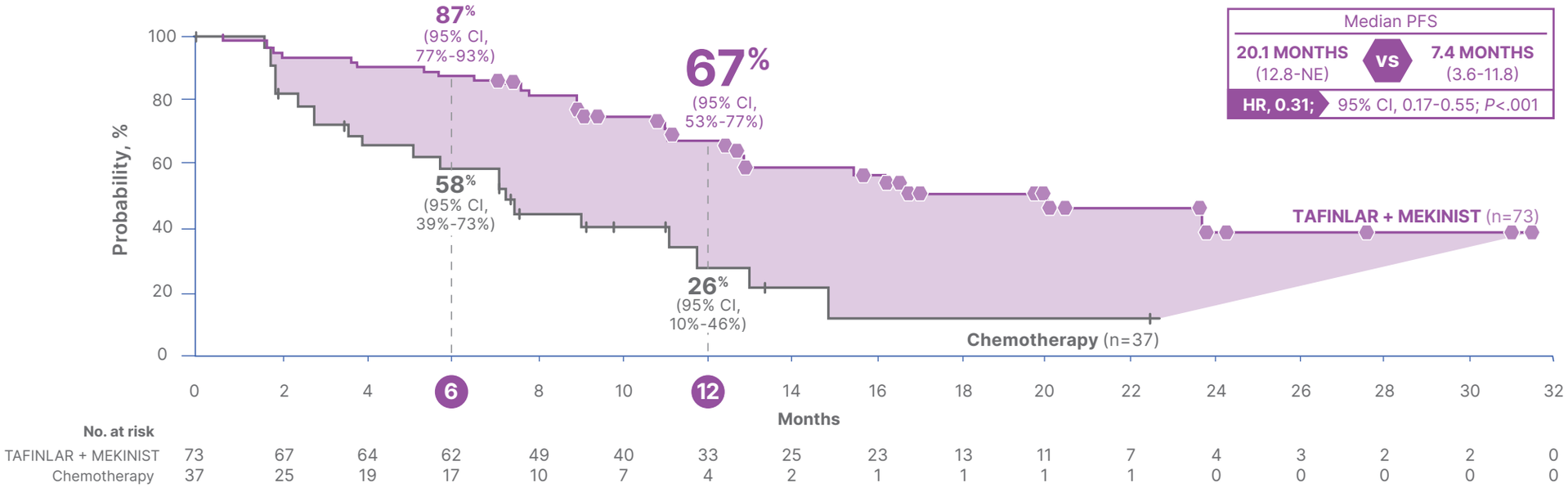
APPROXIMATELY 70% REDUCTION IN THE RISK OF PROGRESSION OR DEATH DELIVERED BY TAFINLAR + MEKINIST vs CHEMOTHERAPY[3,4]

67% of patients continued to be progression free at 1 year[6]



No. at risk																	
TAFINLAR + MEKINIST	73	67	64	62	49	40	33	25	23	13	11	7	4	3	2	2	0
Chemotherapy	37	25	19	17	10	7	4	2	1	1	1	1	0	0	0	0	0

Results at 6 and 12 months were not prespecified and are observational in nature. As such, there was no prespecified statistical procedure controlling for Type 1 error. No clinical conclusions can be made.

HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

IMPORTANT SAFETY INFORMATION (continued)

Hemorrhage (continued)**.** 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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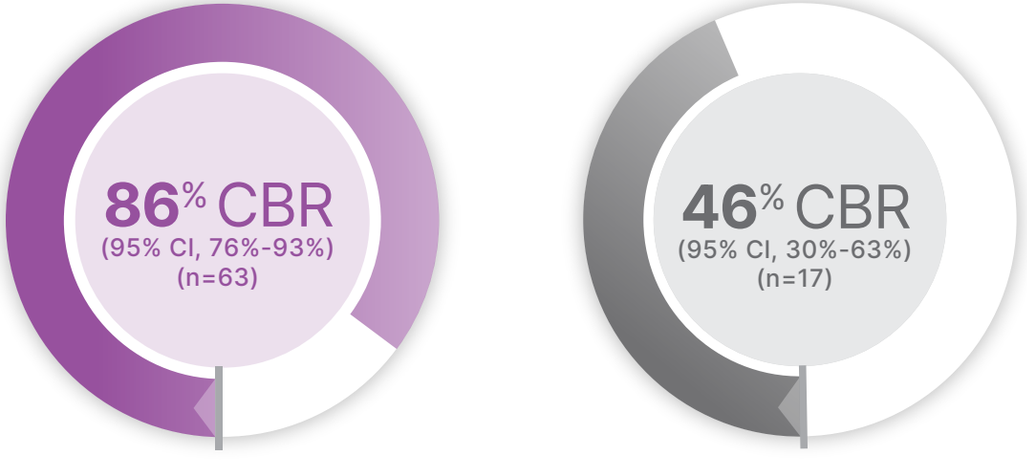
86% CLINICAL BENEFIT RATE ACHIEVED WITH TAFINLAR + MEKINIST[5]

Clinical benefit rate (secondary end point)[5]



CBR, clinical benefit rate.

Hypothetical patient.

- Clinical benefit rate is defined as CR + PR + stable disease (SD)[3-5]*
  - TAFINLAR + MEKINIST: CR, PR, and SD were 3% (n=2), 44% (n=32), and 41% (n=30), respectively
  - Chemotherapy: CR, PR, and SD were 3% (n=1), 8% (n=3), and 41% (n=15), respectively

*SD is not a component of overall response rate and can reflect the natural progression of disease rather than a direct therapeutic effect.

IMPORTANT SAFETY INFORMATION (continued)

Colitis and Gastrointestinal Perforation. Colitis and gastrointestinal perforation, including fatal outcomes, can occur. 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 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 deep vein thrombosis (DVT) or pulmonary embolism (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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BOTH AN EARLY AND SUSTAINED RESPONSE SEEN WITH TAFINLAR + MEKINIST OVER THE STUDY PERIOD[3-5]

Response seen as early as:

~6 WEEKS

Median time to response:
3.6 months; range 1.6-13.0[5,a]

Among patients who responded, response sustained over time with median DOR of:

23.7 MONTHS

Range:
14.5-NE[3,4]

No clinical or statistical conclusions can be drawn.
DOR, duration of response; NE, not estimable.
[a]Time to response evaluated using descriptive statistics among patients with confirmed complete response and partial response.[5]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend dabrafenib + trametinib for the treatment of pediatric patients with *BRAF* V600E–mutated central nervous system cancers.[7*†]

*The National Comprehensive Cancer Network® (NCCN®) makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
†Preferred regimen for recurrent/progressive disease and other recommended regimen in the adjuvant setting. Note that regimens and recommendations are for those patients who elect not to participate in clinical trials.

IMPORTANT SAFETY INFORMATION (continued)

Cardiomyopathy. Cardiomyopathy, including cardiac failure, can occur. In the pooled pediatric 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 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.

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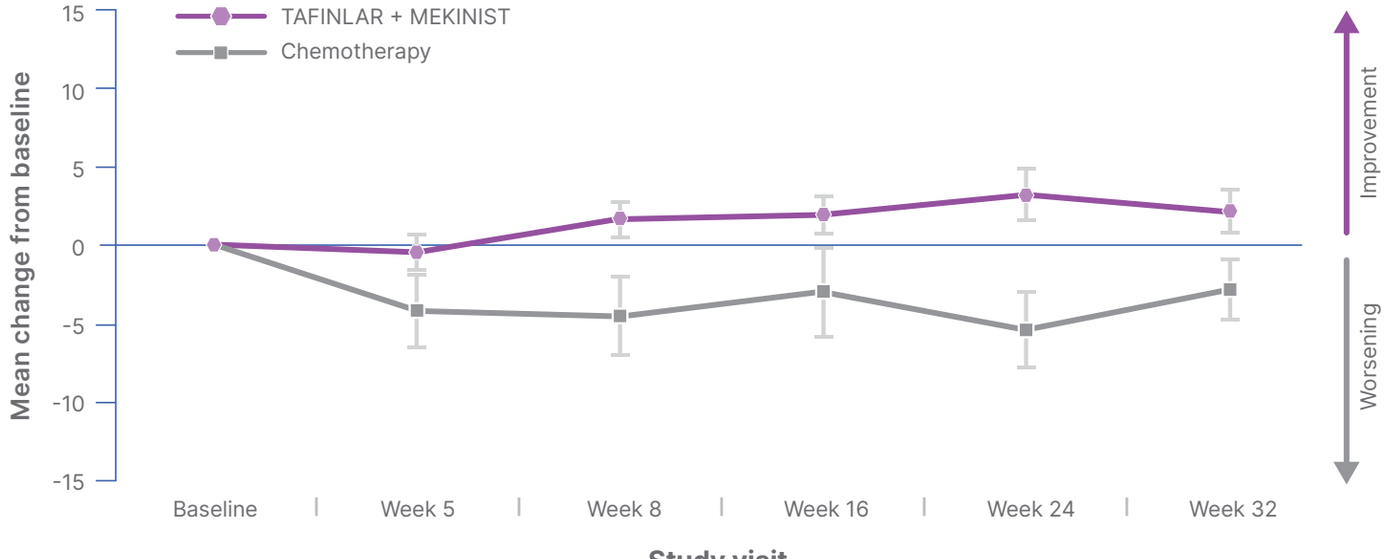
PATIENT-REPORTED OUTCOMES

Results from the PROMIS Parent Proxy Global Health 7+2 Questionnaire[5,6]



No. with data					
TAFINLAR + MEKINIST	48	50	46	45	45
CHEMOTHERAPY	16	17	10	10	11

A questionnaire of parents of children receiving TAFINLAR + MEKINIST revealed that the global health score increased from baseline.[6]

The PROMIS Parent Proxy Global Health 7+2 Questionnaire was used to evaluate the quality of life of patients between the 2 treatment arms. The 7+2 parent proxy pediatric global health measure includes a global health score plus a single score from pain and a score from fatigue interference item, which were scored independently. A higher score for global health indicates better overall well-being.[5] **Results were not powered to show clinical significance**; no clinical or statistical conclusions can be made.

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.

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SAFETY IN PEDIATRIC PATIENTS CONSISTENT WITH PREVIOUSLY ESTABLISHED SAFETY PROFILE

The safety of TAFINLAR + MEKINIST in pediatric patients aged 1 to <18 years with *BRAF* V600E mutation–positive LGG was evaluated in the multicenter, open-label, phase 2 clinical trial G2201. **The safety profile of TAFINLAR + MEKINIST in pediatric patients was consistent with the established safety profile, with no new safety signals identified.**[3-6]

Adverse reactions (≥15%) in pediatric patients in the G2201 study[3,4,a]

Adverse Reactions	TAFINLAR + MEKINIST (n=73)		Chemotherapy (n=33)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Gastrointestinal				
Vomiting	34	1	48	3
Diarrhea[b]	29	0	18	6
Nausea	25	0	45	0
Abdominal Pain[c]	25	0	24	0
Constipation	12	0	36	0
Stomatitis[d]	10	0	18	0
General				
Pyrexia[e]	68	8	18	3
Fatigue[f]	33	0	39	0
Nervous System				
Headache[g]	47	1	33	3
Dizziness[h]	15	0	9	3
Peripheral Neuropathy[i]	7	0	45	6
Vascular Disorders				
Hemorrhage[j]	25	0	12	0
Skin				
Rash[k]	51	2.7	18	3
Dry Skin	26	0	3	0
Dermatitis Acneiform[l]	22	0	0	0
Alopecia	3	0	24	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[m]	34	0	30	0
Pain in Jaw	1.4	0	18	0
Metabolism and Nutrition Disorders				
Decreased Appetite	5	0	24	0

Adverse Reactions	TAFINLAR + MEKINIST (n=73)		Chemotherapy (n=33)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Respiratory, Thoracic, and Mediastinal Disorders				
Oropharyngeal Pain	11	0	18	0
Psychiatric Disorders				
Anxiety	1.4	0	15	3
Immune System Disorders				
Hypersensitivity	0	0	15	3
Infections and Infestations				
Upper Respiratory Tract Infection	15	0	6	0
Injury, Poisoning, and Procedural Complications				
Infusion-Related Reaction	0	0	15	3
Investigations				
Weight Increased	15	7	0	0

[a]National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
[b]Includes diarrhea, colitis, enterocolitis, and enteritis.
[c]Includes abdominal pain and upper abdominal pain.
[d]Includes stomatitis, cheilitis, mouth ulceration, aphthous ulcer, and glossitis.
[e]Includes pyrexia and body temperature increased.
[f]Includes fatigue and asthenia.
[g]Includes headache and migraine with aura.
[h]Includes dizziness and vertigo.
[i]Includes peripheral neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia, neuralgia, hypoaesthesia, and peripheral sensory neuropathy.
[j]Includes epistaxis, post procedural hemorrhage, hematuria, upper gastrointestinal hemorrhage, and hemorrhage intracranial.
[k]Includes rash, rash macular, rash maculo-papular, rash pustular, rash papular, rash erythematous, eczema, erythema multiforme, dermatitis, dermatitis exfoliative, skin exfoliation, palmar-plantar erythrodysesthesia syndrome, and dermatitis bullous.
[l]Includes dermatitis acneiform, acne, and acne pustular.
[m]Includes back pain, myalgia, pain in extremity, arthralgia, bone pain, non-cardiac chest pain, neck pain, and musculoskeletal stiffness.

- **Serious treatment-related adverse reactions (ARs)** occurred in 14% of patients who received TAFINLAR + MEKINIST and in 24% who received chemotherapy[5]
- **Permanent treatment discontinuation** due to ARs occurred in 4% of patients who received TAFINLAR + MEKINIST and in 18% who received chemotherapy[3-5]

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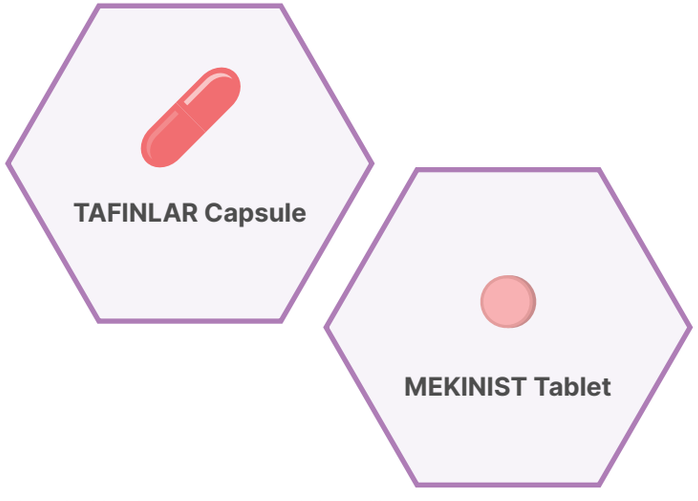
THE FIRST AND ONLY ORAL TREATMENT FOR PEDIATRIC PATIENTS WITH *BRAF* V600E+ LGG WHO REQUIRE SYSTEMIC THERAPY[3,4,8]

TAFINLAR + MEKINIST is available in 2 forms for oral dosing[3,4]



Capsule and tablet shown are not actual size or likeness.

TAFINLAR and MEKINIST should be taken at the same time each day, 1 hour prior or 2 hours after a meal. TAFINLAR doses should be taken 12 hours apart. Missed doses of TAFINLAR should not be taken within 6 hours of the next dose. MEKINIST doses should be taken 24 hours apart. Missed doses of MEKINIST should not be taken within 12 hours of the next dose.[3,4]

TAFINLAR and MEKINIST can be administered in capsule and tablet form, respectively. 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.) The recommended dosage for capsules and tablets has not been established in patients who weigh less than 26 kg.[3,4]

IMPORTANT SAFETY INFORMATION (continued)

Ocular Toxicities (continued)

Retinal Pigment Epithelial Detachment (RPED) (continued)*:* 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 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.

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WEIGHT-BASED ORAL DOSING FOR TAFINLAR + MEKINIST[3,4]

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.

Information about dose reductions and recommended dose modifications for both formulations can be found

HERE

- Treatment is recommended until disease progression or unacceptable toxicity[3,4]
- 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[3,4]

IMPORTANT SAFETY INFORMATION (continued)

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

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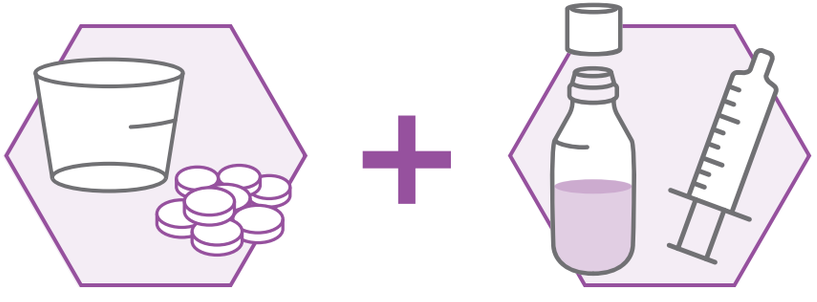
LIQUID FORMULATION DOSING

TAFINLAR + MEKINIST can be administered as a liquid formulation for patients who may have difficulty swallowing or are unable to swallow.[5] Ensure caregivers are properly trained to administer TAFINLAR + MEKINIST in liquid form with the Caregiver Brochure.[6]

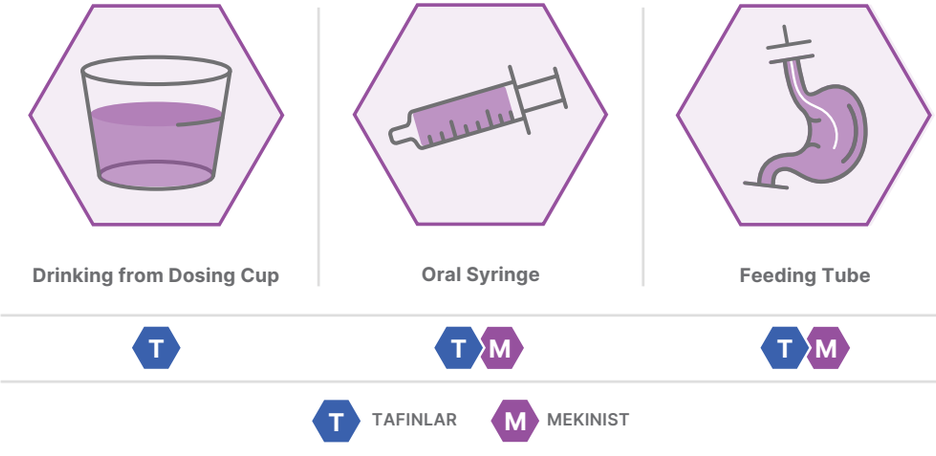
TAFINLAR oral suspension is prepared by dissolving TAFINLAR tablets in 5 to 10 mL of water. MEKINIST is provided as an oral solution by your patient's pharmacy.[3,4]

TAFINLAR Oral Suspension (prepared by dissolving the tablets)

MEKINIST Oral Solution (pre-mixed solution)



TAFINLAR + MEKINIST liquid formulation can be administered in multiple ways[3,4]:



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

IMPORTANT SAFETY INFORMATION (continued)

Serious Febrile Reactions (continued)**.** Withhold TAFINLAR and MEKINIST for temperature of ≥100.4 ºF. 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 and here.

Please click here for full Prescribing Information for TAFINLAR, and click here for full Prescribing Information for MEKINIST.

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

WEIGHT-BASED DOSING FOR TAFINLAR TABLETS FOR ORAL SUSPENSION AND MEKINIST FOR ORAL SOLUTION[3,4]

TAFINLAR Total Daily Dose		MEKINIST Total Daily Dose	
Body Weight	**Recommended Dosage (# of 10-mg Tablets of Oral Suspension BID)**	**Body Weight**	**Recommended Dosage (Total Volume of Oral Solution QD)**
8 to 9 kg	20 mg (2 tablets)	**8 kg**	6 mL (0.3 mg)
		9 kg	7 mL (0.35 mg)
10 to 13 kg	30 mg (3 tablets)	**10 kg**	7 mL (0.35 mg)
		11 kg	8 mL (0.4 mg)
		12 to 13 kg	9 mL (0.45 mg)
14 to 17 kg	40 mg (4 tablets)	**14 to 17 kg**	11 mL (0.55 mg)
18 to 21 kg	50 mg (5 tablets)	**18 to 21 kg**	14 mL (0.7 mg)
22 to 25 kg	60 mg (6 tablets)	**22 to 25 kg**	17 mL (0.85 mg)
26 to 29 kg	70 mg (7 tablets)	**26 to 29 kg**	18 mL (0.9 mg)
30 to 33 kg	80 mg (8 tablets)	**30 to 33 kg**	20 mL (1 mg)
34 to 37 kg	90 mg (9 tablets)	**34 to 37 kg**	23 mL (1.15 mg)
38 to 41 kg	100 mg (10 tablets)	**38 to 41 kg**	25 mL (1.25 mg)
42 to 45 kg	110 mg (11 tablets)	**42 to 45 kg**	28 mL (1.4 mg)
46 to 50 kg	130 mg (13 tablets)	**46 to 50 kg**	32 mL (1.6 mg)
≥51 kg	150 mg (15 tablets)	**≥51 kg**	40 mL (2 mg)

BID, twice daily; QD, once daily.

Information about dose reductions and recommended dose modifications for both formulations can be found

HERE

- Treatment is recommended until disease progression or unacceptable toxicity[3,4]
- The overall management of certain adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation, depending on severity[3,4]

IMPORTANT SAFETY INFORMATION (continued)

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 pediatric safety population of the combination, serious adverse events of skin and subcutaneous tissue disorders occurred in 1.8% of patients.

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

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IDENTIFYING THE *BRAF* MUTATION STATUS IS CRUCIAL TO TREATMENT PLANNING

NGS

Next-generation sequencing (NGS):

scalable DNA sequencing that is able to simultaneously analyze multiple genes[9,10]

PCR

Mutation-specific polymerase chain reaction (PCR):

rapidly making copies of small segments of DNA[11]

rtPCR

Mutation-specific real-time PCR (rtPCR):

a more sensitive technique than traditional PCR where targeted DNA segments are amplified and quantified simultaneously[9-11]

IHC

Immunohistochemistry (IHC):

detects tumor cells harboring a specific antigen by cytoplasmic staining of cells containing a mutation-specific monoclonal antibody[12]

Other

Other testing methods:

Sanger sequencing, pyrosequencing[9,10]

Test early for the *BRAF* V600E mutation to give patients and their caregivers new hope for pediatric LGG treatment.

Hypothetical patient.

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PATIENT SUPPORT IS AVAILABLE

Novartis Oncology Universal Co-pay Program

Patients may be eligible for immediate co-pay savings on their next prescription of TAFINLAR + MEKINIST.

- Eligible patients with private insurance may pay $0 per month ($0 per month for a 30-day supply of TAFINLAR and $0 for a 30-day supply of MEKINIST). Co-pay of $0 is only for TAFINLAR + MEKINIST combination therapy
- Novartis will pay the remaining co-pay, up to $15,000 per calendar year, per product*

*Limitations apply. This offer is only available to patients with private insurance. The program is not available for patients who are enrolled in Medicare, Medicaid, or any other federal or state health care program. Novartis reserves the right to rescind, revoke, or amend this program without notice. For full Terms and Conditions, visit Copay.NovartisOncology.com or call 1-877-577-7756.

Encourage your patients to find out if they are eligible to enroll in the Novartis Oncology Universal Co-pay Program by visiting **Copay.NovartisOncology.com** or calling **1-877-577-7756**.

NOVARTIS

Universal Co-pay Card

Eligible patients save on out-of-pocket costs

Tell your patients to visit **Copay.NovartisOncology.com** or call **1-877-577-7756.**

Hypothetical patient.

Patient Assistance Now Oncology

Patient Assistance Now Oncology (PANO) is a support center consisting of insurance specialists and case managers who provide access to information regarding an array of services. Consider PANO your first stop for information about Novartis Oncology Patient Support services. Dedicated support specialists help direct callers to the services that best fit their needs.

Support for patients includes:

- Insurance benefits verification, including information on prior authorizations and denial appeals
- Information about financial assistance that may be available
- Patient Support Counselors who are able to provide information in more than 160 languages
- Free trial or access program for select Novartis Oncology medications
- Dedicated case managers with private extensions whom you can contact directly for updates on your patient
- A combination of PANO case managers and/or field reimbursement managers are available to help, depending on the complexity of a patient's case

Patient Assistance Now Oncology

Assistance. Access. Answers.

To learn more, call **1-800-282-7630** or visit **HCP.Novartis.com/Access**

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

Please click here for full Prescribing Information for TAFINLAR, and click here for full Prescribing Information for MEKINIST.

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

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

TAFINLAR, in combination with MEKINIST, is indicated 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.

Limitation of Use: 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 pediatric safety population of TAFINLAR administered with MEKINIST ("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 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.

Colitis and Gastrointestinal Perforation. Colitis and gastrointestinal perforation, including fatal outcomes, can occur. 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 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 deep vein thrombosis (DVT) or pulmonary embolism (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.

Cardiomyopathy. Cardiomyopathy, including cardiac failure, can occur. In the pooled pediatric 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 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. (continued)

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

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IMPORTANT SAFETY INFORMATION (CONTINUED)

Cardiomyopathy (continued)**.** 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 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 pediatric safety population of the combination, pyrexia occurred in 66% of patients.

Withhold TAFINLAR and MEKINIST for temperature of ≥100.4 ºF. 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 and here.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

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 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 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 post-marketing 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 the G2201 study, the most common (≥20%) adverse reactions 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%), and dermatitis acneiform (22%).

Laboratory Abnormalities. 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%)

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

Please click here for full Prescribing Information for TAFINLAR, and click here for full Prescribing Information for MEKINIST.

References: 1. Lassaletta A, Zapotocky M, Mistry M, et al. Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. *J Clin Oncol*. 2017;35(25):2934-2941. doi:10.1200/JCO.2016.71.8726 **2.** Nobre L, Zapotocky M, Ramaswamy V, et al. Outcomes of BRAF V600E pediatric gliomas treated with targeted BRAF inhibition. *JCO Precis Oncol*. 2020;4:PO.19.00298. doi:10.1200/PO.19.00298 **3.** Tafinlar. Prescribing information. Novartis Pharmaceuticals Corp. **4.** Mekinist. Prescribing information. Novartis Pharmaceuticals Corp. **5.** Data on file. Clinical study report. CDRB436G2201. Novartis Pharmaceuticals Corp; 2022. **6.** Data on file. Primary analysis of a phase II trial of dabrafenib + trametinib in BRAF V600–mutant pediatric low-grade glioma. Novartis Pharmaceuticals Corp; 2022. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Central Nervous System Cancers V.2.2023. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed October 31, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org **8.** Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. *J Neurosurg*. 1997;86(5):747-754. doi:10.3171/jns.1997.86.5.0747 **9.** Vanni I, Tanda ET, Spagnolo F, Andreotti V, Bruno W, Ghiorzo P. The current state of molecular testing in the BRAF-mutated melanoma landscape. *Front Mol Biosci*. 2020;30(7):113. doi:10.3389/fmolb.2020.00113 **10.** Supplement to: Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutant low-grade and high-grade glioma (ROAR): a multicenter, open-label, single-arm, phase 2, basket trial. *Lancet Oncol*. 2022;23(1):53-64. **11.** National Center for Biotechnology Information. Polymerase chain reaction (PCR). Updated November 11, 2017. Accessed November 12, 2022. https://www.ncbi.nlm.nih.gov/probe/docs/techpcr **12.** Ihle M, Fassunke J, König K, et al. Comparison of high resolution melting analysis, pyrosequencing, next generation sequencing and immunohistochemistry to conventional Sanger sequencing for the detection of p.V600E and non-p.V600E BRAF mutations. *BMC Cancer*. 2014;14(1):1-13. doi:10.1186/1471-2407-14-13

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TAFINLAR + MEKINIST—
TRANSFORM YOUR PATIENTS' TREATMENT

In a clinical trial,

4X

IMPROVEMENT IN OVERALL RESPONSE RATE WITH TAFINLAR + MEKINIST vs CHEMOTHERAPY*

(47% [95% CI, 35%-59%] vs 11% [95% CI, 3%-25%], respectively) (*P*<.001)[3,4]

Approximately

70%

REDUCTION IN THE RISK OF PROGRESSION OR DEATH vs CHEMOTHERAPY*

Hazard ratio (95% CI) for TAFINLAR + MEKINIST vs chemotherapy: 0.31 (0.17-0.55); *P*<.001[3,4]

ESTABLISHED SAFETY PROFILE AND AT-HOME DOSING[3,4]

Hypothetical patients.

*Vincristine and carboplatin.

For more information about TAFINLAR + MEKINIST, visit https://www.hcp.novartis.com/products/tafinlar-mekinist/ped-glioma/

INDICATION

TAFINLAR, in combination with MEKINIST, is indicated 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.

Limitation of Use: TAFINLAR is not indicated for the treatment of patients with wild-type *BRAF* solid tumors.

IMPORTANT SAFETY INFORMATION (continued)

Serious Skin Toxicities (continued)**.** 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.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080