NOW APPROVED

For patients with BRAF-altered relapsed or refractory pediatric low-grade glioma (R/R pLGG)

OJEMDA™ (tovorafenib)

Clinical Overview

The first and only once-weekly oral type II RAF inhibitor to target a BRAF fusion or rearrangement, or a BRAF V600 mutation

BRAF=v-Raf murine sarcoma viral oncogene homolog B1; RAF=rapidly accelerated fibrosarcoma.

INDICATION

OJEMDA™ (tovorafenib) is indicated for the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with OJEMDA. Advise patients and caregivers of the risk of hemorrhage during treatment with OJEMDA. Monitor for signs and symptoms of hemorrhage and evaluate as clinically indicated. Withhold and resume at reduced dose upon improvement, or permanently discontinue based on severity.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

ojemda™
(tovorafenib)
100 mg tablets
25 mg/mL for oral suspension

OJEMDA was studied in a multicenter, open-label, single-arm clinical trial

The efficacy and safety of OJEMDA was evaluated in patients 6 months or older with relapsed or refractory pLGG harboring a BRAF fusion or rearrangement, or a BRAF V600 mutation (FIREFLY-1; NCT04775485).

The efficacy of OJEMDA was measured by overall response rate (ORR) determined by Independent Radiology Review Committee (IRC) following treatment was evaluated in 76 patients. The safety of OJEMDA was evaluated in 137 patients.

Patients with tumors harboring additional activating molecular alteration(s) (eg, IDH1/2 mutations, FGFR mutations, etc.) or patients with known or suspected diagnosis of NF1 were excluded.

Patients received OJEMDA approximately 420 mg/m^2 orally once weekly (range: 290 to 476 mg/m^2, 0.76 to 1.25 times the approved recommended dosage) according to body surface area (BSA) with a maximum dosage of 600 mg until disease progression or unacceptable toxicity. Although the OJEMDA dosages administered in FIREFLY-1 were between 290 mg/m^2 to 476 mg/m^2, the recommended OJEMDA dosage is 380 mg/m^2 orally once weekly.

Major efficacy outcome

The major efficacy outcome measure was ORR, defined as the proportion of patients with complete response (CR), partial response (PR), or minor response (MR) by independent review based on Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria.

Additional outcomes

Additional efficacy outcome measures were time to response, duration of response, and ORR by independent review based on Response Assessment in Neuro-Oncology Low-Grade Glioma (RANO-LGG; 2011) criteria.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Skin Toxicity Including Photosensitivity

OJEMDA can cause rash, including maculopapular rash and photosensitivity. Monitor for new or worsening skin reactions. Consider dermatologic consultation and initiate supportive care as clinically indicated. Withhold, reduce the dose, or permanently discontinue OJEMDA based on severity of adverse reaction.

Photosensitivity

Advise patients to use precautionary measures against ultraviolet exposure such as use of sunscreen, sunglasses, and/or protective clothing during treatment with OJEMDA. Withhold, reduce the dose, or permanently discontinue OJEMDA based on severity of adverse reaction.

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Baseline patient characteristics in FIREFLY-1

	OJEMDA (N=76)
Age (years)	
Median (range)	8.5 (2-21)
Sex	
Male	53%
Female	47%
Race	
White	53%
Asian	7%
Black or African American	3%
Hispanic or Latino	4%
Multiple races	4%
Other race	8%
Race not reported	26%
Karnofsky/Lansky performance status	
80 to 100	93%
Most common tumor location	
Optic pathway	51%
Deep midline structures	12%
Brain stem	8%
Cerebral hemisphere	7%
Cerebellum	7%
BRAF alteration	
KIAA1549:BRAF fusion	74%
BRAF V600E	16%
Other BRAF alteration, duplication or rearrangement	11%
Lines of prior systemic regimens	
Median (range)	3 (1-9)
Prior MAPK pathway targeted therapy	
Yes	59%
No	41%

FGFR=fibroblast growth factor receptor; IDH1/2=isocitrate dehydrogenase 1/2; MAPK=mitogen-activated protein kinase; NF1=neurofibromatosis type 1.

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ORR and additional data

Efficacy results based on independent review in FIREFLY-1 (arm 1)

Efficacy parameter	RAPNO (N=76)*
Overall response rate	
ORR (95% CI)†	51% (40, 63)
Complete response (CR), n (%)	0 (0)
Partial response (PR), n (%)	28 (37)
Minor response (MR), n (%)	11 (14)
Duration of response	**N=39**
Median (95% CI)‡, months	13.8 (11.3, NE)
% with observed DOR ≥6 months	85%
% with observed DOR ≥12 months	23%

*At least one measurable lesion at baseline based on RAPNO-LGG criteria.
†Based on Clopper-Pearson exact confidence interval.
‡Based on Kaplan-Meier estimate.

- Among responders, the median time to response was 5.3 months (range 1.6, 11.2)
- In exploratory analyses of BRAF alteration status, the ORR was 52% among patients with BRAF fusion or rearrangement (n=64), and 50% among patients with BRAF V600E mutation (n=12), respectively
- In exploratory analyses of prior therapies, the ORR was 49% among patients who had received prior MAPK-targeted therapy (n=45), and 55% among patients who had not received prior MAPK-targeted therapy (n=31)

Based on RANO LGG (2011) criteria (n=76):

- The ORR was 53% (95% CI: 41, 64), including 20 patients each with PR and MR, respectively

DOR=duration of response; NE=not estimable.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Hepatotoxicity

OJEMDA can cause hepatotoxicity. Monitor liver function tests, including ALT, AST and bilirubin, before initiation of OJEMDA, one month after initiation and then every three months thereafter and as clinically indicated. Withhold and resume at the same or reduced dose upon improvement, or permanently discontinue OJEMDA based on the severity.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Warnings and precautions with OJEMDA

The safety population described in warnings and precautions reflects exposure to OJEMDA taken orally once weekly at a dose based on body surface area in 140 patients with R/R pLGG or advanced solid tumors harboring a RAF alteration and a flat dose of 600 mg in 32 adult patients with advanced solid tumors until disease progression or intolerable toxicity. Among 172 patients treated with OJEMDA, 86% were exposed for 6 months or longer and 49% were exposed for 1 year or longer.

Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with OJEMDA. In the pooled safety population, hemorrhagic events occurred in 37% of patients, including epistaxis in 26% and intratumoral hemorrhage in 9%. Serious events of bleeding occurred in 5% of patients including grade 5 tumor hemorrhage in 1 patient (0.6%). OJEMDA was permanently discontinued for hemorrhage in 2% of patients. Advise patients and caregivers of the risk of hemorrhage during treatment with OJEMDA. Monitor for signs and symptoms of hemorrhage and evaluate as clinically indicated. Withhold and resume at reduced dose upon improvement, or permanently discontinue based on severity.

Skin toxicity including photosensitivity

OJEMDA can cause rash, including maculopapular rash and photosensitivity. In the pooled safety population, rash occurred in 67% of patients treated with OJEMDA, including grade 3 rash in 12%. Rash resulted in dose interruption in 15% of patients and dose reduction in 7% of patients. OJEMDA was permanently discontinued due to rash in 1% of patients (n=2). In the pooled safety population, dermatitis acneiform occurred in 26% of patients treated with OJEMDA, including grade 3 dermatitis acneiform in 0.6% of patients (n=1). Dose reduction was required in 2% of patients (n=3) due to dermatitis acneiform. Monitor for new or worsening skin reactions. Consider dermatologic consultation and initiate supportive care as clinically indicated. Withhold, reduce the dose, or permanently discontinue OJEMDA based on severity of adverse reaction.

Photosensitivity

In the pooled safety population, photosensitivity occurred in 12% of patients treated with OJEMDA, including grade 3 events in 0.6% of patients (n=1). Advise patients to use precautionary measures against ultraviolet exposure such as use of sunscreen, sunglasses, and/or protective clothing during treatment with OJEMDA. Withhold, reduce the dose, or permanently discontinue OJEMDA based on severity of adverse reaction.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Effect on Growth

OJEMDA can cause reductions in growth velocity. Growth velocity recovered after interruption of treatment with OJEMDA. Routinely monitor patient growth during treatment with OJEMDA.

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Warnings and precautions with OJEMDA (cont'd)

Hepatotoxicity

OJEMDA can cause hepatotoxicity. In the pooled safety population, increased alanine aminotransferase (ALT) occurred in 42% and increased aspartate aminotransferase (AST) occurred in 74%, including Grade 3 ALT in 4% and increased AST in 2% of patients treated with OJEMDA. The median time to onset of increased ALT or AST was 14 days (range: 3 to 280 days). Increased ALT or AST leading to dose interruption occurred in 5% of patients and dose reductions were required in 1.2% of patients. Increased bilirubin occurred in 23% of patients, including Grade 3 increased bilirubin in 0.6% of patients (n=1) treated with OJEMDA. Hyperbilirubinemia leading to dose discontinuation occurred in a single adult patient with an advanced non-CNS solid tumor.

Monitor liver function tests, including ALT, AST and bilirubin, before initiation of OJEMDA, one month after initiation and then every three months thereafter and as clinically indicated. Withhold and resume at the same or reduced dose upon improvement, or permanently discontinue OJEMDA based on the severity.

Effect on growth

OJEMDA can cause reductions in growth velocity. In FIREFLY-1 , treatment-emergent adverse effects on growth occurred in 15% of patients 18 years of age or younger, including grade 3 events in 5% of patients. OJEMDA was permanently discontinued for reduction in growth velocity in 2% of patients (n=2). Growth velocity recovered after interruption of treatment with OJEMDA. Routinely monitor patient growth during treatment with OJEMDA.

Embryo-fetal toxicity

Based on findings from animal studies and its mechanism of action, OJEMDA may cause fetal harm when administered to a pregnant woman. Tovorafenib was embryo lethal in rats at doses approximately 0.8-fold the human exposure at the recommended dose based on area under the curve (AUC). Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with OJEMDA and for 28 days after the last dose, since OJEMDA can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective nonhormonal contraception during treatment with OJEMDA and for 2 weeks after the last dose.

NF1 associated tumors

Based on nonclinical data in NF1 models without BRAF alterations, OJEMDA may promote tumor growth in patients with NF1 tumors. Confirm evidence of a BRAF alteration prior to initiation of treatment with OJEMDA.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Adverse reactions

Additional safety information in FIREFLY-1

The safety of OJEMDA was evaluated in 137 patients with R/R pLGG harboring a BRAF alteration in FIREFLY-1 (Arms 1 and 2). Patients received OJEMDA at a dose based on body surface area orally once weekly until disease progression, or intolerable toxicity.

Serious adverse reactions occurred in 45% of patients who received OJEMDA. Serious adverse reactions in >2% of patients included viral infection (9%), pneumonia (4%), and sepsis (4%). A fatal adverse reaction of tumor hemorrhage occurred in 1 patient (1%).

Permanent discontinuation of OJEMDA due to an adverse reaction occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of OJEMDA in more than one patient were tumor hemorrhage and reduction in growth velocity.

Dosage interruptions of OJEMDA due to an adverse reaction occurred in 57% of patients. Adverse reactions which required dose interruption in ≥5% of patients included rash, pyrexia, vomiting, and hemorrhage.

Dosage reductions of OJEMDA due to an adverse reaction occurred in 24% of patients. Adverse reactions which required dose reduction in ≥2% of patients included rash and fatigue.

The most common adverse reactions (≥30%) were rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, and upper respiratory tract infection.

The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased phosphate, decreased hemoglobin, increased creatinine phosphokinase, increased alanine aminotransferase, decreased albumin, decreased lymphocytes, decreased leukocytes, increased aspartate transferase, decreased potassium, and decreased sodium.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, OJEMDA may cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective nonhormonal contraception during treatment with OJEMDA and for 28 days after the last dose, since OJEMDA can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective nonhormonal contraception during treatment with OJEMDA and for 2 weeks after the last dose.

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Adverse reactions in FIREFLY-1

Adverse reactions (≥20%) in patients with pLGG who received OJEMDA in FIREFLY-1 (arms 1 and 2)

	OJEMDA (N=137)	
	All grades (%)	**Grades 3 or 4 (%)**
Skin and subcutaneous tissue disorders		
Rash	77	12
Hair color changes	76	0
Dry skin	36	0
Dermatitis acneiform	31	1
Pruritus	26	1
General disorders		
Fatigue	55	4
Pyrexia	39	4
Edema	26	0
Infections and infestations		
Viral infection	55	7
Upper respiratory tract infection	31	1.5
Paronychia	26	1.5
Gastrointestinal disorders		
Vomiting	50	4
Constipation	33	0
Nausea	33	0
Abdominal pain	28	0
Diarrhea	22	1.5
Stomatitis	20	0
Nervous system disorders		
Headache	45	1
Vascular disorders		
Hemorrhage	42	5*

*Includes one grade 5 event.

Other clinically important adverse reactions observed in less than 20% of patients treated with OJEMDA were reductions in growth velocity and photosensitivity.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Adverse reactions in FIREFLY-1 (cont'd)

Additional information on effect on growth

Patients with pediatric LGG treated with OJEMDA for up to 24 months showed reductions from baseline in Z-scores for height compared to age and sex-matched normative data. Among 19 patients who experienced reductions in growth velocity who had hand radiographs taken to assess bone age, there was no evidence of premature closure of the epiphyseal growth plates or advancement of bone age. Patients followed after interruption of treatment with OJEMDA showed recovery of growth and increase in Z-scores. Monitor growth routinely during treatment.

Laboratory abnormalities

Select laboratory abnormalities (≥20%) that worsened from baseline in patients with pLGG who received OJEMDA in FIREFLY-1 (arms 1 and 2)

	OJEMDA*	
Laboratory abnormality	**All grades (%)**	**Grade 3 or 4 (%)**
Hematology		
Decreased hemoglobin	90	15
Decreased lymphocytes	50	2
Decreased leukocytes	31	2
Increased lymphocytes	23	0
Chemistry		
Decreased phosphate	87	25
Increased AST	83	2
Increased creatine phosphokinase	83	11
Increased LDH	73	0
Decreased potassium	51	2
Increased ALT	50	5
Increased bilirubin	22	1
Decreased albumin	24	5
Decreased sodium	20	2

*The denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 67 to 137 patients.

Increased creatinine phosphokinase was a clinically important laboratory abnormality that worsened from baseline in patients treated with OJEMDA.

ALT=alanine transaminase; AST=aspartate aminotransferase; LDH=lactate dehydrogenase; LGG=low-grade glioma.

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OJEMDA dosage and administration

Patient selection for OJEMDA

Confirm the presence of BRAF fusion or rearrangement, or BRAF V600 mutation prior to initiation of treatment with OJEMDA. An FDA-approved test for the detection of BRAF fusion or rearrangement, or BRAF V600 mutation in relapsed or refractory pediatric LGG is not currently available.

Recommended testing before initiating OJEMDA

Before initiating OJEMDA, evaluate liver function tests, including ALT, AST and bilirubin.

Recommended dosage for OJEMDA

The recommended dosage of OJEMDA based on BSA is 380 mg/m^2 orally once weekly (the maximum recommended dosage is 600 mg orally once weekly) with or without food, until disease progression or intolerable toxicity. OJEMDA may be administered as an immediate release tablet or as an oral suspension. A recommended dosage for patients with BSA less than 0.3 m^2 has not been established.

Recommended OJEMDA tablets dosage based on body surface area

BSA (m^2)	Recommended dosage
0.30-0.89	Administer OJEMDA for oral suspension once weekly
0.90-1.12	400 mg once weekly
1.13-1.39	500 mg once weekly
≥1.40	600 mg once weekly

Recommended dosage for OJEMDA for oral suspension based on body surface area

BSA (m^2)	Dose volume (mL)*	Dosage (once weekly)
0.30-0.35	5	125 mg
0.36-0.42	6	150 mg
0.43-0.48	7	175 mg
0.49-0.54	8	200 mg
0.55-0.63	9	225 mg
0.64-0.77	11	275 mg
0.78-0.83	12	300 mg
0.84-0.89	14	350 mg
0.90-1.05	15	375 mg
1.06-1.25	18	450 mg
1.26-1.39	21	525 mg
≥1.40	24	600 mg

Continue once weekly dosing until disease progression or intolerable toxicity.

*OJEMDA for oral suspension has a concentration of 25 mg/mL. Each bottle of OJEMDA for oral suspension delivers 300 mg/12 mL.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Additional dosing information for OJEMDA

General administration with OJEMDA

- Take OJEMDA at a regularly scheduled time once weekly
- OJEMDA may be taken with or without food

Missed doses with OJEMDA

If a dose is missed by

- 3 days or less, take the missed dose as soon as possible, and take the next dose on its regularly scheduled day
- More than 3 days, skip the missed dose and take the next dose on its regularly scheduled day

If vomiting occurs immediately after taking a dose, repeat that dose

OJEMDA tablets

- Swallow tablets whole with water
- Do not chew, cut, or crush

OJEMDA for oral suspension

- Prior to first-time use of OJEMDA for oral suspension, ensure that caregivers (and if appropriate, patients) read and understand the "Instructions for Use" before preparing, measuring, and administering OJEMDA

Preparation of oral suspension:

- Reconstitute the powder in each supplied bottle with exactly 14 mL of room temperature water to form the OJEMDA for oral suspension. After reconstitution each mL contains 25 mg of tovorafenib. Product foaming after reconstitution reduces the deliverable volume
- Each bottle delivers 300 mg of tovorafenib in 12 mL. For doses greater than 300 mg, reconstitute two bottles to achieve the dose. Split the dose as equally as possible between the two bottles (eg, 6 mL and 7 mL for a 325-mg dose)
- Administer OJEMDA for oral suspension using the supplied oral dosing syringe or feeding tube (minimum 12 French) immediately after preparation
- If OJEMDA for oral suspension is not administered within 15 minutes after preparation, instruct the patient to discard it

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

NF1 Associated Tumors

Based on nonclinical data in NF1 models without BRAF alterations, tovorafenib may promote tumor growth in patients with NF1 tumors. Confirm evidence of a BRAF alteration prior to initiation of treatment with OJEMDA.

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Dosage reductions

OJEMDA tablets: Recommended dosage reductions for adverse reactions

BSA (m^2)	First dosage reduction	Second dosage reduction
0.30-1.12	Administer the oral suspension once weekly	
1.13-1.39	400 mg once weekly	Administer OJEMDA for oral suspension once weekly
≥1.40	500 mg once weekly	400 mg once weekly

OJEMDA for oral suspension: Recommended dosage reductions for adverse reactions

BSA (m^2)	First dosage reduction		Second dosage reduction	
	Volume (mL)	Dose (mg)	Volume (mL)	Dose (mg)
0.30-0.35	4	100	3	75
0.36-0.42	5	125	4	100
0.43-0.48	6	150	5	125
0.49-0.54	7	175	6	150
0.55-0.63	8	200	6	150
0.64-0.77	9	225	8	200
0.78-0.83	10	250	8	200
0.84-0.89	12	300	10	250
0.90-1.05	13	325	11	275
1.06-1.25	15	375	13	325
1.26-1.39	18	450	15	375
≥1.40	20	500	16	400

IMPORTANT SAFETY INFORMATION (cont'd)

Adverse Reactions

The most common adverse reactions (≥30%) were rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, and upper respiratory tract infection.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Dosage modifications

Recommended dosage modifications for adverse reactions

Severity of adverse drug reaction (ADR)	Dosage modification
Hemorrhage	
Intolerable grade 2 Any grade 3	Withhold OJEMDA. • If improved to grade 0-1, resume at lower dosage • If not improved, consider permanent discontinuation of OJEMDA
First occurrence of any grade 4	Withhold OJEMDA. • If improved to grade 0-1, resume at lower dosage, OR • Permanently discontinue OJEMDA
Recurrent grade 4	Permanently discontinue OJEMDA.
Skin toxicity including photosensitivity	
Intolerable grade 2 Grade 3 or 4	Withhold OJEMDA. • If improved to grade 0-1, resume OJEMDA at a lower dosage • If not improved, consider permanent discontinuation of OJEMDA
Hepatotoxicity	
Grade 3 AST or ALT Grade 3 bilirubin	Withhold OJEMDA. If improved to grade ≤ 2 or baseline, resume as follows: • If laboratory abnormality resolves within 8 days, resume OJEMDA at the same dose. • If laboratory abnormality does not resolve within 8 days, resume OJEMDA at lower dosage.
First occurrence of any grade 4	Withhold OJEMDA. • If improved to grade 0-1, resume at lower dosage, OR • Permanently discontinue OJEMDA
Recurrent grade 4	• Permanently discontinue OJEMDA
Other ADRs	
Intolerable grade 2 Any grade 3	Withhold OJEMDA. • If improved to grade 0-1, resume at a lower dosage • If not improved, consider permanent discontinuation of OJEMDA
First occurrence of any grade 4	Withhold OJEMDA. • If improved to grade 0-1, resume at lower dosage • If not improved, consider permanent discontinuation of OJEMDA
Recurrent grade 4	Permanently discontinue OJEMDA.

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Drug interactions with OJEMDA

Coadministration with other drugs that affect the use of OJEMDA[1]

Strong or moderate CYP2C8 inhibitors	
Prevention or management	• Avoid coadministration with a strong or moderate CYP2C8 inhibitor
Mechanism and clinical effect(s)	• Tovorafenib is a CYP2C8 substrate, which may increase the risk of adverse reactions with OJEMDA
Strong or moderate CYP2C8 inducers	
Prevention or management	• Avoid coadministration of OJEMDA with a strong or moderate CYP2C8 inducer
Mechanism and clinical effect(s)	• Tovorafenib is a CYP2C8 substrate, which may reduce the effectiveness of OJEMDA

Coadministration with OJEMDA that affects the use of other drugs[1]

CYP3A substrates	
Prevention or management	• *Hormonal contraceptives*: Avoid coadministration of hormonal contraceptives with OJEMDA. If coadministration is unavoidable, use an additional effective nonhormonal contraceptive method during coadministration and for 28 days after discontinuation of OJEMDA • *Other CYP3A substrates*: Avoid coadministration of OJEMDA with certain CYP3A substrates. If coadministration is unavoidable, monitor patients for loss of efficacy unless otherwise recommended in the Prescribing Information for CYP3A substrates
Mechanism and clinical effect(s)	• Tovorafenib is a CYP3A inducer • Tovorafenib is predicted to decrease exposure of certain CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures, which may reduce the effectiveness of these substrates • Coadministration with hormonal contraceptives (CYP3A substrate) may decrease progestin-x and ethinyl estradiol exposure, which may lead to contraceptive failure and/or an increase in breakthrough bleeding

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

INDICATION

OJEMDA™ (tovorafenib) is indicated for the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with OJEMDA. Advise patients and caregivers of the risk of hemorrhage during treatment with OJEMDA. Monitor for signs and symptoms of hemorrhage and evaluate as clinically indicated. Withhold and resume at reduced dose upon improvement, or permanently discontinue based on severity.

Skin Toxicity Including Photosensitivity

OJEMDA can cause rash, including maculopapular rash and photosensitivity. Monitor for new or worsening skin reactions. Consider dermatologic consultation and initiate supportive care as clinically indicated. Withhold, reduce the dose, or permanently discontinue OJEMDA based on severity of adverse reaction.

Photosensitivity

Advise patients to use precautionary measures against ultraviolet exposure such as use of sunscreen, sunglasses, and/or protective clothing during treatment with OJEMDA. Withhold, reduce the dose, or permanently discontinue OJEMDA based on severity of adverse reaction.

Hepatotoxicity

OJEMDA can cause hepatotoxicity. Monitor liver function tests, including ALT, AST and bilirubin, before initiation of OJEMDA, one month after initiation and then every three months thereafter and as clinically indicated. Withhold and resume at the same or reduced dose upon improvement, or permanently discontinue OJEMDA based on the severity.

Effect on Growth

OJEMDA can cause reductions in growth velocity. Growth velocity recovered after interruption of treatment with OJEMDA. Routinely monitor patient growth during treatment with OJEMDA.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, OJEMDA may cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective nonhormonal contraception during treatment with OJEMDA and for 28 days after the last dose, since OJEMDA can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective nonhormonal contraception during treatment with OJEMDA and for 2 weeks after the last dose.

NF1 Associated Tumors

Based on nonclinical data in NF1 models without BRAF alterations, tovorafenib may promote tumor growth in patients with NF1 tumors. Confirm evidence of a BRAF alteration prior to initiation of treatment with OJEMDA.

Adverse Reactions

The most common adverse reactions (≥30%) were rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, and upper respiratory tract infection.

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NOW APPROVED

For patients with BRAF-altered relapsed or refractory pediatric low-grade glioma (R/R pLGG)

The first and only once-weekly oral type II RAF inhibitor of both BRAF fusions or rearrangements and BRAF V600 mutations in R/R pLGG

Efficacy results from FIREFLY-1

- Based on RAPNO-LGG criteria (N=76)
  - ORR was **51%** (n=39; 95% CI: 40, 63)
  - CR: 0% (n=0); PR: **37%** (n=28), MR: **14%** (n=11)
- Among the 39 patients with a response:
  - Median time to response was **5.3 months** (range: 1.6, 11.2 months)
  - Median duration of response was **13.8 months** (95% CI: 11.3, NE months)

Safety assessed in FIREFLY-1

- Warnings and precautions include hemorrhage, skin toxicity including photosensitivity, hepatotoxicity, effect on growth, embryo-fetal toxicity, and NF1 associated tumors
- The most common adverse reactions (≥30%) were rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, and upper respiratory tract infection

Once-weekly oral dosing with or without food

- Can be administered via **tablet or oral suspension**

Consider OJEMDA for appropriate patients with relapsed or refractory pLGG with a BRAF fusion or rearrangement, or BRAF V600 mutation

Please see accompanying full Prescribing Information.

Reference: OJEMDA™ [Package Insert]. Brisbane, CA: Day One Biopharmaceuticals, Inc.; 2024.

Day One BIOPHARMACEUTICALS

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25 mg/mL for oral suspension