HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OJEMDA safely and effectively. See full prescribing information for OJEMDA.

OJEMDA (tovorafenib) tablets, for oral use
OJEMDA (tovorafenib) for oral suspension
Initial U.S. Approval: 2024

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1) 04/2025

----------INDICATIONS AND USAGE----------

OJEMDA is a kinase inhibitor 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. (1)

This indication is approved under accelerated approval based on response rate and duration of response *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

----------DOSAGE AND ADMINISTRATION----------

- Confirm the presence of BRAF fusion or rearrangement, or BRAF V600 mutation prior to initiation of treatment with OJEMDA. (2.1)
- Recommended dosage of OJEMDA is based on body surface area (*see Tables 1 and 2*). (2.3)
- Administer OJEMDA orally, once weekly, with or without food. (2.3, 2.4).
- Tablets: Swallow tablets whole with water. Do not chew, cut, or crush. (2.4)
- For Oral Suspension: See full prescribing information for preparation and administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 100 mg (3)
For Oral Suspension: 25 mg/mL (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hemorrhage: Major hemorrhagic events can occur during treatment with OJEMDA. Withhold, resume at reduced dose, or permanently discontinue based on severity. (5.1)
- Skin Toxicity Including Photosensitivity: Advise patients to monitor for new or worsening skin reactions. Advise patients to limit direct ultraviolet exposure and use precautionary measures such as sunscreen, sunglasses and/or protective clothing during treatment with OJEMDA. Withhold, reduce the dose or permanently discontinue based on severity. (5.2)
- Hepatotoxicity: OJEMDA can cause hepatotoxicity. Monitor liver function tests prior to administration and during treatment. Withhold, reduce the dose or permanently discontinue based on severity. (5.3)
- Effect on Growth: Reductions in growth velocity have been reported. Routinely monitor growth in pediatric patients. (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of the potential risk to a fetus and to use effective nonhormonal contraception. (5.5, 8.1, 8.3)
- NF1 Associated Tumors: Increased tumor growth may occur with OJEMDA. (5.6, 13.2)

----------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. (6.1)

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

To report SUSPECTED ADVERSE REACTIONS, contact Day One Biopharmaceuticals at toll-free phone # 1-877-204-2820 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Moderate and Strong CYP2C8 Inhibitors: Avoid coadministration with OJEMDA. (7.1).
- Moderate and Strong CYP2C8 Inducers: Avoid coadministration with OJEMDA. (7.1).
- Certain CYP3A Substrates: Avoid coadministration of OJEMDA with CYP3A substrates where minimal concentration changes can cause reduced efficacy. (7.2).
- Hormonal contraceptives: Avoid coadministration with OJEMDA. (7.2).

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)
- Infertility: May impair fertility in males and females. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OJEMDA 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 *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with OJEMDA based on the presence of BRAF fusion or rearrangement, or BRAF V600 mutation in tumor specimens *[see Clinical Studies (14)]*.

Information on FDA-approved tests is available at http://www.fda.gov/companiondiagnostics.

2.2 Recommended Testing Before Initiating OJEMDA

Before initiating OJEMDA, evaluate liver function tests, including ALT, AST and bilirubin *[see Warnings and Precautions (5.3)]*.

2.3 Recommended Dosage

The recommended dosage of OJEMDA based on body surface area (BSA) is 380 mg/m^2 orally once weekly (the maximum recommended dosage is 600 mg orally once weekly) with or without food *[see Administration (2.4) and Clinical Pharmacology (12.3)]* until disease progression or intolerable toxicity. OJEMDA may be administered as an immediate release tablet (see Table 1) or as an oral suspension (see Table 2). A recommended dosage for patients with BSA less than 0.3 m^2 has not been established.

Table 1 Recommended OJEMDA Tablets Dosage Based on Body Surface Area

Body Surface Area (m^2)	Recommended Dosage
0.30-0.89	Administer OJEMDA oral suspension once weekly (see Table 2)
0.90-1.12	400 mg once weekly
1.13-1.39	500 mg once weekly
≥ 1.40	600 mg once weekly

Table 2 Recommended Dosage for OJEMDA for Oral Suspension Based on Body Surface Area

Body Surface Area (m^2)	Dose Volume (mL)[1]	Dosage
0.30-0.35	5	125 mg once weekly
0.36-0.42	6	150 mg once weekly
0.43-0.48	7	175 mg once weekly
0.49-0.54	8	200 mg once weekly
0.55-0.63	9	225 mg once weekly
0.64-0.77	11	275 mg once weekly
0.78-0.83	12	300 mg once weekly
0.84-0.89	14	350 mg once weekly
0.90-1.05	15	375 mg once weekly
1.06-1.25	18	450 mg once weekly
1.26-1.39	21	525 mg once weekly
≥1.40	24	600 mg once weekly

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

Continue once weekly dosing until disease progression or intolerable toxicity.

2.4 Administration

- Take OJEMDA at a regularly scheduled time once weekly.
- OJEMDA may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

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 and Administration

- 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 (e.g., 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 the OJEMDA for oral suspension is not administered within 15 minutes after preparation, instruct the patient to discard it.

2.5 Dosage Modifications for Adverse Reactions

The recommended dosage reductions for adverse reactions for OJEMDA tablets are provided in Table 3 and OJEMDA for oral suspension in Table 4.

Table 3 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 (see Table 4)	
1.13-1.39	400 mg once weekly	Administer OJEMDA oral suspension once weekly (see Table 4)
≥1.40	500 mg once weekly	400 mg once weekly

Table 4 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 mg once weekly	3	75 mg once weekly
0.36-0.42	5	125 mg once weekly	4	100 mg once weekly
0.43-0.48	6	150 mg once weekly	5	125 mg once weekly
0.49-0.54	7	175 mg once weekly	6	150 mg once weekly
0.55-0.63	8	200 mg once weekly	6	150 mg once weekly
0.64-0.77	9	225 mg once weekly	8	200 mg once weekly
0.78-0.83	10	250 mg once weekly	8	200 mg once weekly
0.84-0.89	12	300 mg once weekly	10	250 mg once weekly
0.90-1.05	13	325 mg once weekly	11	275 mg once weekly
1.06-1.25	15	375 mg once weekly	13	325 mg once weekly
1.26-1.39	18	450 mg once weekly	15	375 mg once weekly
≥1.40	20	500 mg once weekly	16	400 mg once weekly

The recommended dosage modifications of OJEMDA for adverse reactions are in Table 5.

Table 5 Recommended Dosage Modifications for Adverse Reactions

Severity of ADR[a]	Dosage Modification[b]
Hemorrhage *[see Warnings and Precautions (5.1)]*	
• 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 *[see Warnings and Precautions (5.2)]*	
• Intolerable Grade 2 • Grade 3 or 4	Withhold OJEMDA. • If improved to Grade 0-1, resume at lower dosage. • If not improved, consider permanent discontinuation of OJEMDA.
Hepatotoxicity *[see Warnings and Precautions (5.3)]*	
• 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 Adverse Reactions *[see Adverse Reactions (6.1)]*	
• 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.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

[b] See Table 3 and Table 4 for recommended dosage reductions.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

•100 mg: orange, film-coated, oval tablets debossed with “100” on one side and “D101” on the opposite side. Each tablet contains 100 mg of tovorafenib.

For Oral Suspension:

•25 mg/mL: white to off white powder. After reconstitution, each mL of strawberry flavored tovorafenib suspension contains 25 mg of tovorafenib. Each bottle delivers 300 mg of tovorafenib in 12 mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with OJEMDA. In the pooled safety population *[see Adverse Reactions (6.1)],* 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 *[see Dosage and Administration (2.5)]*.

5.2 Skin Toxicity Including Photosensitivity

OJEMDA can cause rash, including maculopapular rash and photosensitivity. In the pooled safety population *[see Adverse Reactions (6.1)],* 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 *[see Dosage and Administration (2.5)]*.

Photosensitivity

In the pooled safety population *[see Adverse Reactions (6.1)],* 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 *[see Dosage and Administration (2.5)]*.

5.3 Hepatotoxicity

OJEMDA can cause hepatotoxicity. In the pooled safety population *[see Adverse Reactions (6.1)]*, 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 *[see Dosage and Administration (2.5)]*.

5.4 Effect on Growth

OJEMDA can cause reductions in growth velocity. In FIREFLY-1 *[see Adverse Reactions (6.1)]*, 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 *[see Adverse Reactions (6), Use in Specific Populations (8.4)]*.

5.5 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 *[see Drug Interactions (7.2)]*. 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 *[see Use in Specific Populations (8.1, 8.3)]*.

5.6 NF1 Associated Tumors

Based on nonclinical data in NF1 models without BRAF alterations, tovorafenib may promote tumor growth in patients with NF1 tumors *[see Nonclinical Toxicology (13.2)]*. Confirm evidence of a BRAF alteration prior to initiation of treatment with OJEMDA.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Skin Toxicity Including Photosensitivity *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Effect on Growth *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population described in WARNINGS AND PRECAUTIONS reflects exposure to OJEMDA taken orally once weekly at a dose based on body surface area *[see Clinical Studies (14)]* in 140 patients with relapsed or refractory pediatric LGG 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.

Pediatric Low-grade Glioma

The safety of OJEMDA was evaluated in 137 patients with relapsed or refractory pediatric LGG harboring a BRAF alteration in FIREFLY-1 (Arms 1 and 2) *[see Clinical Studies (14)]*. Patients received OJEMDA at a dose based on body surface area *[see Dosage and Administration (2.3]* orally once weekly until disease progression or intolerable toxicity.

The median age of patients was 9 years (range 1 to 24 years); 53% male; 58% White, 7% Asian, 2% Black or African American, 6% other races, 25% race was not reported; 2.9% were Hispanic or Latino; and 90% Karnofsky/Lansky performance status of 80 to 100.

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 creatine phosphokinase, increased alanine aminotransferase, decreased albumin, decreased lymphocytes, decreased leukocytes, increased aspartate transferase, decreased potassium, and decreased sodium.

Table 6 and Table 7 present adverse reactions and laboratory abnormalities, respectively, identified in FIREFLY-1 (Arms 1 and 2).

Table 6 Adverse Reactions (≥20%) in Patients with Pediatric LGG Who Received OJEMDA in FIREFLY-1 (Arms 1 and 2)

Adverse Reaction	OJEMDA (N=137)	
	All Grades (%)	Grade 3 or 4 (%)
Skin and Subcutaneous Tissue Disorders		
Rash[a]	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[b]	26	0
Infections and Infestations		
Viral infection[c]	55	7
Upper respiratory tract infection	31	1.5
Paronychia	26	1.5
Gastrointestinal Disorders		
Vomiting[d]	50	4
Constipation	33	0
Nausea	33	0
Abdominal pain	28	0
Diarrhea[e]	22	1.5
Stomatitis[f]	20	0
Nervous system disorders		
Headache	45	1
Vascular Disorders		
Hemorrhage[g]	42	5*

[a] Includes terms erythema multiforme, eczema, rash erythematous, rash macular, rash follicular, rash pruritic, rash maculopapular, rash, rash popular, rash pustular, skin exfoliation, drug eruption, dermatitis, dermatitis bullous.

[b] Includes terms lip edema, periorbital edema, edema peripheral, localized edema, face edema, vulval edema.

[c] Includes terms viral infection, rhinovirus infection, enterovirus infection, viral upper respiratory tract infection, enterocolitis viral, oral herpes, gastroenteritis viral, influenza, influenza like illness, respiratory syncytial virus infection, enterovirus infection, coronavirus infection, COVID-19, SARS-COV-2 test positive, herpes simplex, parainfluenza virus infection, adenoviral upper respiratory infection, viraemia, adenovirus infection, conjunctivitis viral, eye infection viral, metapneumovirus infection, parvovirus infection, respiratory syncytial virus bronchiolitis, respiratory tract infection viral, viral pharyngitis, viral rhinitis, viral tonsillitis.

[d] Includes terms retching, hematemesis.

[e] Includes terms colitis, enterocolitis.

[f] Includes terms mouth ulceration, mucosal inflammation, aphthous ulcer, cheilitis.

[g] Includes terms tumor hemorrhage, gastrointestinal hemorrhage, subdural hemorrhage, epistaxis, intracranial tumor hemorrhage, upper gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, vaginal hemorrhage, gingival bleeding, post procedural hemorrhage, hemoptysis, anal hemorrhage.

*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 *[see Warnings and Precautions (5.4)]* and photosensitivity *[see Warnings and Precautions (5.2)]*.

Table 7 Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Pediatric LGG Who Received OJEMDA in FIREFLY-1 (Arms 1 and 2)

Laboratory Abnormality[1]	OJEMDA[2]	
	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

[1] Severity as defined by National Cancer Institute CTCAE v5.0
[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 creatine phosphokinase was a clinically important laboratory abnormality that worsened from baseline in patients treated with OJEMDA.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on OJEMDA

Table 8 describes drug interactions where coadministration with another drug affects OJEMDA.

Table 8 Coadministration with Other Drugs that Affect the Use of OJEMDA	
Strong or Moderate CYP2C8 Inhibitors	
Prevention or Management	• Avoid coadministration of OJEMDA with a strong or moderate CYP2C8 inhibitor.
Mechanism and Clinical Effect(s)	• Tovorafenib is a CYP2C8 substrate. Strong or moderate CYP2C8 inhibitors are predicted to increase tovorafenib exposure based on a mechanistic understanding of its elimination *[see Clinical Pharmacology (12.3)],* 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. Strong or moderate CYP2C8 inducers are predicted to decrease tovorafenib exposure based on a mechanistic understanding of its elimination *[see Clinical Pharmacology (12.3)],* which may reduce the effectiveness of OJEMDA.

7.2 Effects of OJEMDA on Other Drugs

Table 9 describes drug interactions where coadministration with OJEMDA affects another drug.

Table 9 Coadministration with OJEMDA that Affects the Use of Other Drugs	
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 where minimal concentration changes may lead to serious therapeutic failures. 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 *[see Clinical Pharmacology (12.3)],* 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 *[see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, OJEMDA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of OJEMDA in pregnant women. Oral administration of tovorafenib to pregnant rats during the period of organogenesis resulted in embryo lethality at exposures 0.8 times the human exposure at the recommended dose based on AUC (*see Data*). Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, once daily oral administration of tovorafenib to pregnant rats during the period of organogenesis from gestation days 7 through 17 at doses of 37.5, 75, and 150 mg/kg resulted in early resorptions and total litter loss at all doses. The dose of 37.5 mg/kg/day is approximately 0.8-fold the human exposure at the recommended dose based on AUC.

8.2 Lactation

Risk Summary

There are no data on the presence of tovorafenib or its metabolites in human milk, their effects on the breastfed child, or on milk production. Due to the potential for serious adverse reactions in breastfed children from OJEMDA, advise lactating women not to breastfeed during treatment with OJEMDA and for 2 weeks following the last dose.

8.3 Females and Males of Reproductive Potential

OJEMDA can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating OJEMDA *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective nonhormonal contraception during treatment with OJEMDA and for 28 days after the last dose. OJEMDA can render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

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.

Infertility

Based on findings in animals, OJEMDA may impact fertility in males and females of reproductive potential. The effects on male fertility were reversible. The effects on female fertility were not reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of OJEMDA in pediatric patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation have been established based on data from a multicenter, open-label, single-arm clinical trial *[see Clinical Studies (14)]*.

The efficacy of OJEMDA was evaluated in 76 patients with relapsed or refractory pediatric LGG. The safety of OJEMDA was evaluated in 137 patients with relapsed or refractory pediatric LGG in FIREFLY-1 (Arms 1 and 2). Of these 137 patients, 2% (n=3) were 6 month to < 2 years of age, 67% (n=92) were 2 years to < 12 years of age, and 31% (n=42) were >12 years of age *[see Adverse Reactions (6.1)]*. C_{max} and AUC in pediatric patients aged 11 months to 17 years were within the range of values observed in adults given the same dose per body surface area.

The safety and effectiveness of OJEMDA in patients younger than 6 months of age have not been established.

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 *[see Warnings and Precautions (5.4)]*.

8.6 Hepatic Impairment

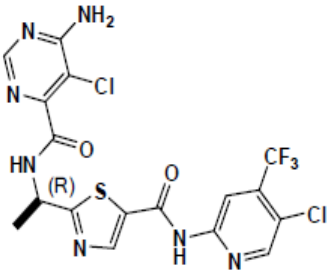
No dose adjustment is recommended for patients with mild (bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or bilirubin > 1x to 1.5x ULN and any AST) hepatic impairment. OJEMDA has not been studied in patients with moderate (bilirubin > 1.5x to 3x ULN and any AST) to severe (bilirubin > 3x ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild-to-moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 calculated by Schwartz equation or MDRD equation). OJEMDA has not been studied in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

OJEMDA contains tovorafenib, a kinase inhibitor. Tovorafenib has the molecular formula $C_{17}H_{12}Cl_2F_3N_7O_2S$ and a molecular weight of 506.29. The chemical name for tovorafenib is 6-amino-5-chloro-N-[(1R)-1-[5-[[[5-chloro-4-(trifluoromethyl)-2-pyridinyl]amino]carbonyl]-2-thiazolyl]ethyl]-4-pyrimidinecarboxamide. Tovorafenib has the following chemical structure:



It is a white to off-white powder. The solubility of tovorafenib at 37ºC is ≤ 3 micrograms/mL from pH 1.2 to 8 in aqueous media.

OJEMDA (tovorafenib) tablets are supplied as 100 mg strength tablets for oral administration. Each tablet contains 100 mg tovorafenib and the following inactive ingredients: copovidone, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and orange film coating (hypromellose, polyethylene glycol 8000, titanium dioxide, ferric oxide yellow, ferric oxide red).

OJEMDA (tovorafenib) for oral suspension is a white to off white powder which produces a white suspension when reconstituted with water. Each mL of reconstituted tovorafenib suspension contains 25 mg of tovorafenib and the following inactive ingredients: artificial strawberry flavor, colloidal silicon dioxide, copovidone, maltodextrin, mannitol, microcrystalline cellulose, simethicone, sodium lauryl sulfate, and sucralose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tovorafenib is a Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases.

Tovorafenib exhibited antitumor activity in cultured cells and xenograft tumor models harboring BRAF V600E and V600D mutations, and in a xenograft model harboring a BRAF fusion.

12.2 Pharmacodynamics

Exposure Response Relationships

Tovorafenib exposure is associated with reduction in height-for-age z-scores in pediatric patients. Reduced height-for-age risk persists during treatment with tovorafenib.

Higher tovorafenib exposure is associated with increased risk of skin rash, elevated liver enzymes (AST and ALT), and elevated creatine phosphokinase.

The exposure-response relationship for overall response rate based on RAPNO-LGG (Response Assessment in Pediatric Neuro-Oncology), and RANO-LGG (Response Assessment in Neuro-Oncology) were not clinically significant over the dosage range of 290 to 476 mg/m^2 (0.76-1.25 times the approved recommended dosage) *[see Dosage and Administration (2.3)* and *Clinical Studies (14)]*.

Cardiac Electrophysiology

At the recommended OJEMDA dosage of 380 mg/m^2 orally once weekly (not to exceed 600 mg), a mean increase in the QT interval >20 milliseconds was not observed.

12.3 Pharmacokinetics

Tovorafenib pharmacokinetic parameters are presented as mean (CV%) unless otherwise indicated. Tovorafenib steady state maximum concentration (C_{max}) is 6.9 µg/mL (23%) and the area under the concentration-time curve (AUC) is 508 µg*h/mL (31%). Time to reach steady state of tovorafenib is 12 days (33%). Tovorafenib exposure increases in a dose-proportional manner. No clinically significant tovorafenib accumulation occurs.

Absorption

Tovorafenib median (minimum, maximum) time to achieve peak plasma concentration (T_{max}) is 3 hours (1.5, 4 hours), following a single dose with tablets or oral suspension.

Effect of Food

No clinically significant differences in tovorafenib C_{max} and AUC were observed following administration of tablets with a high-fat meal (approximately 859 total calories, 54% fat) compared to fasted conditions, but the T_{max} was delayed to 6.5 hours.

Distribution

Tovorafenib apparent volume of distribution is 60 L/m^2 (23%). Tovorafenib is 97.5% bound to human plasma proteins in vitro.

Elimination

Tovorafenib terminal half-life is approximately 56 hours (33%) and the apparent clearance is 0.7 L/h/m^2 (31%).

Metabolism

Tovorafenib is primarily metabolized by aldehyde oxidase and CYP2C8 in vitro. CYP3A, CYP2C9, and CYP2C19 metabolize tovorafenib to a minor extent.

Excretion

Following a single oral dose of radiolabeled tovorafenib, 65% of the total radiolabeled dose was recovered in the feces (8.6% unchanged) and 27% of the dose was recovered in the urine (0.2% unchanged).

Specific Populations

No clinically significant differences of tovorafenib were observed based on age (range: 1 to 94 years), sex, race (White, Black, Asian), mild hepatic impairment [bilirubin ≤ upper limit of normal (ULN) and AST > ULN or bilirubin > 1 to 1.5x ULN and any AST], and mild-to-moderate renal impairment (eGFR) ≥ 30 mL/min/1.73 m^2 calculated by Schwartz equation or MDRD equation.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

CYP3A Substrates: Midazolam (CYP3A4 substrate) steady-state C_{max} and AUC are predicted to decrease by at least 20% following coadministration with tovorafenib.

In Vitro Studies

CYP450 Enzymes: Tovorafenib inhibits CYP2C8, CYP2C9, CYP2C19 and CYP3A, but does not inhibit CYP1A2, CYP2B6, and CYP2D6 at clinically relevant concentrations.

Tovorafenib induces CYP3A, CYP2C8, CYP1A2, CYP2B6, CYP2C9 and CYP2C19 at clinically relevant concentrations.

Transporter Systems: Tovorafenib is not a substrate of BCRP, P-glycoprotein (P-gp), OATP1B1 and OATP1B3. Tovorafenib has not been evaluated as a substrate of OAT1, OAT3, MATE1, MATE2-K and OCT2. Tovorafenib inhibits BCRP at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tovorafenib have not been conducted.

Tovorafenib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Tovorafenib was not genotoxic in cultured human lymphocytes without metabolic activation. Tovorafenib induced chromosomal aberrations in cultured human lymphocytes with metabolic activation at a single concentration in vitro. Tovorafenib was not genotoxic in an in vivo rat bone marrow micronucleus assay.

In a fertility and early embryonic development study in rats, animals were administered tovorafenib doses of 37.5, 75, or 150 mg/kg/day orally. Female animals, paired with untreated males, were dose for 14 days prior to pairing, during the mating period, and up to Gestation Day 6. Tovorafenib decreased the number of pregnancies, corpora lutea, and live embryos, as well as increased post-implantation losses at all doses. The dose of 37.5 mg/kg/day is approximately 0.8-fold the human exposure at the recommended dose based on AUC.

In repeat- dose toxicology studies in rats of up to 3 months duration, tovorafenib-related findings in female rats included reversible increased thickness of the vaginal mucosa, increased size and/or numbers of corpora hemorrhagicum and hemorrhage, and non-reversible cystic follicles, decreased corpora lutea, and interstitial cell hyperplasia were observed in ovaries at doses ≥ 50 mg/kg once every other day (approximately 0.4-fold the human exposure at the recommended dose based on AUC). In male rats, tovorafenib reduced weights of epididymis and testes, which correlated with reversible tubular degeneration/atrophy of the testes and reduced epididymal sperm at doses ≥ 50 mg/kg once every other day (approximately 0.3-fold the human exposure at the recommended dose based on AUC).

13.2 Animal Toxicology and/or Pharmacology

In vitro, tovorafenib increased phosphorylation of ERK at clinically relevant concentrations in cells with neurofibromatosis Type 1-loss of function (NF1-LOF) suggesting activation, rather than inhibition, of the MAP kinase pathway. In an NF1 genetically engineered mouse model of plexiform neurofibroma without BRAF alteration, tovorafenib did not have antitumor activity, and while not statistically significant, an increase in tumor volume was noted in 2/12 mice (approximately 17%).

14 CLINICAL STUDIES

The efficacy of OJEMDA was evaluated in a multicenter, open-label, single-arm clinical trial (FIREFLY-1; NCT04775485). Eligible patients (N=76) were required to have a relapsed or refractory pediatric low-grade glioma (LGG) harboring an activating BRAF alteration based on local laboratory testing. Patients were also required to have at least one measurable lesion as defined by RANO 2010 criteria. All patients had received at least one line of prior systemic therapy and had documented evidence of radiographic progression. Patients with tumors harboring additional activating molecular alteration(s) (e.g., IDH1/2 mutations, FGFR mutations, etc.) or patients with known or suspected diagnosis of neurofibromatosis type 1 (NF1) were excluded.

Patients received OJEMDA approximately 420 mg/m^2 orally once weekly (range: 290 to 476 mg/m^2, 0.76-1.25 times the approved recommended dosage) according to body surface area with a maximum dose 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 because this dosage was determined to be safe and effective for the treatment of patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation *[see Dosage and Administration (2.3)]*.

Tumor assessments were performed every 12 weeks.

The major efficacy outcome measure was overall response rate (ORR), defined as the proportion of patients with complete response (CR), partial response (PR), or minor response (MR) by independent review based on RAPNO-LGG (Response Assessment in Pediatric Neuro-Oncology) criteria. Additional efficacy outcome measures were duration of response, time to response, and ORR by independent review based on RANO-LGG (2011) criteria.

The efficacy population included 76 patients who had measurable disease at baseline and who received OJEMDA. The median age was 8.5 years (range 2 to 21 years); 53% were male; 53% White, 7% Asian, 2.6% Black or African American, 3.9% multiple races, 8% other race, 26% where race was not reported; 3.9% were Hispanic or Latino, and 93% had Karnofsky/Lansky performance status of 80 to 100. Patients received a median of 3 prior systemic regimens (range: 1 to 9). Forty-five patients (59%) received prior treatment with a MAP kinase pathway inhibitor. The most common tumor locations were the optic pathway (51%), deep midline structures (12%), brain stem (8%), cerebral hemisphere and cerebellum (7% each). Fifty-six patients (74%) had a KIAA1549:BRAF fusion, twelve patients (16%) had a V600E mutation, and eight patients (11%) had a BRAF alteration classified as “other” including BRAF duplication or BRAF rearrangement. Efficacy results are shown in Table 10.

Table 10 Efficacy Results Based on Independent Review in FIREFLY-1 (Arm-1)

Efficacy Parameter	**RAPNO-LGG N=76***
Overall Response Rate	
ORR (95% CI)[a]	51% (40, 63)
Complete Response (CR), n (%)	0 (0)
Partial Response (PR), n (%)	28 (37)
Minor Response (MR), n (%)	11 (14)
Duration of Response (DoR)	**N=39**
Median (95% CI)[b], Months	13.8 (11.3, NE)
% with observed DoR ≥ 6 months	85%
% with observed DoR ≥ 12 months	23%

Abbreviations: LGG = low-grade glioma; RAPNO = Response Assessment in Pediatric Neuro-Oncology; CI = confidence interval; NE = not estimable.
*At least one measurable lesion at baseline based on RAPNO-LGG criteria.
[a]Based on Clopper-Pearson exact confidence interval.
[b]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.

16 HOW SUPPLIED/STORAGE AND HANDLING

OJEMDA tablets:

100 mg: orange, film-coated, oval tablets debossed with “100” on one side and “D101” on the opposite side and supplied as follows:

4 blister cards (4 tablets each) per box, NDC 82950-001-16.

4 blister cards (5 tablets each) per box, NDC 82950-001-20.

4 blister cards (6 tablets each) per box, NDC 82950-001-24.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Dispense product in the original package. Tablets should not be removed from blisters until immediately before use.

OJEMDA for oral suspension:

25 mg/mL: white to off white powder in a clear glass bottle, co-packaged with a press-in bottle adaptor and a 20 mL oral dosing syringe (NDC# 82950-012-01).

Each mL of reconstituted, strawberry flavored tovorafenib suspension contains 25 mg of tovorafenib. Each bottle delivers 300 mg of tovorafenib in 12 mL.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Do not use if safety seal under cap is broken or missing.

Suspension must be used immediately after reconstitution.

Discard the bottle (including any unused portion) and syringe after dosing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Hemorrhage

Advise patients that OJEMDA can cause bleeding and to contact their healthcare provider for signs or symptoms of bleeding *[see Warnings and Precautions (5.1)]*.

Skin Toxicities

Advise patients that OJEMDA can cause skin toxicities and to contact their healthcare provider for worsening or intolerable rash *[see Warnings and Precautions (5.2)]*.

Photosensitivity

Advise patients that OJEMDA can cause photosensitivity. Advise patients to limit direct ultraviolet exposure during treatment with OJEMDA. Recommend that patients use precautionary measures such as use of sunscreen, sunglasses, and/or protective clothing during treatment with OJEMDA *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Advise patients that OJEMDA can cause liver toxicity and to contact their healthcare provider for signs or symptoms of liver dysfunction. Advise patients that serial testing of serum liver tests (ALT, AST, bilirubin) is recommended during treatment with OJEMDA *[see Warnings and Precautions (5.3)]*.

Effect on Growth

Advise patients and caregivers that treatment with OJEMDA may cause a reduction in growth velocity, and that growth will be monitored during treatment with OJEMDA *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.
- Advise females to inform their healthcare provider of a known or suspected pregnancy during treatment with OJEMDA.
- Advise females of reproductive potential to use effective nonhormonal contraception during treatment and for 28 days after discontinuation of treatment with OJEMDA.
- 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.

Lactation

Advise women not to breastfeed during treatment with OJEMDA and for 2 weeks after the last dose of OJEMDA *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential of the potential risk for impaired fertility with OJEMDA *[see Nonclinical Toxicology (13.1)]*.

Dosing and Administration

Inform patients and caregivers on how to take OJEMDA and what to do for missed or vomited doses *[see Dosage and Administration (2.4)]*.

Prior to use of the oral suspension, ensure patients or caregivers receive training on proper dosing, preparation, and administration *[see Dosage and Administration (2.4) and Instructions for Use]*.

Storage

Advise patients not to take the OJEMDA tablets out of the blister pack until ready to use.

Discard the bottle (including any unused portion) and syringe after dosing.

Manufactured for:

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Brisbane CA 94005

Manufactured by (tablets):
Quotient Sciences – Philadelphia LLC
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Manufactured by (oral suspension):
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Garnet Valley, PA 19060

DAY101-USPI-042025v03