Product Monograph

Including Patient Medication Information

PrOJEMDA™

Tovorafenib tablets

For oral use

100 mg of tovorafenib

Tovorafenib for oral suspension

For oral use

Powder, 300 mg tovorafenib per bottle (25 mg/mL after reconstitution)

Antineoplastic agent

OJEMDA, indicated for:

- monotherapy for the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harbouring a *BRAF* fusion or rearrangement, or *BRAF* V600 mutation, who have received one or more prior systemic therapies

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for OJEMDA please refer to Health Canada's Notice of Compliance with conditions - drug products web site."

Ipsen Biopharmaceuticals Canada Inc.

5050 Satellite Dr Suite 500

Mississauga, ON L4W 0G1

Date of Authorization:
2026-07-13

Control Number: 301603

OJEMDA is a registered trademark of Day One Biopharmaceuticals Inc.

What is a Notice of Compliance with Conditions (NOC/c)?

A NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

Recent Major Label Changes

Not applicable

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent Major Label Changes **2**

Table of Contents **2**

Part 1: Healthcare Professional Information **5**

1. Indications **5**

1.1. Pediatrics 5

1.2. Geriatrics 5

2. Contraindications **5**

4. Dosage and Administration **5**

4.1. Dosing Considerations 5

4.2. Recommended Dose and Dosage Adjustment 5

4.3. Reconstitution 8

4.4. Administration 9

4.5. Missed Dose 9

5. Overdose **10**

6. Dosage Forms, Strengths, Composition, and Packaging **10**

7. Warnings and Precautions **10**

General 10
Driving and Operating Machinery 11
Hematologic 11
Hepatic/Biliary/Pancreatic 11
Musculoskeletal 11
Reproductive Health 12
Skin 12
7.1. Special Populations 13
7.1.1. Pregnancy 13
7.1.2. Breastfeeding 13
8. Adverse Reactions 13
8.1. Adverse Reaction Overview 13
8.2. Clinical Trial Adverse Reactions 13
8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data 17
9. Drug Interactions 18
9.2. Drug Interactions Overview 18
9.3. Drug-Behaviour Interactions 18
9.4. Drug-Drug Interactions 19
9.5. Drug-Food Interactions 20
9.6. Drug-Herb Interactions 20
9.7. Drug-Laboratory Test Interactions 21
10. Clinical Pharmacology 21
10.1. Mechanism of Action 21
10.2. Pharmacodynamics 21
10.3. Pharmacokinetics 21
11. Storage, Stability, and Disposal 23
Part 2: Scientific Information 24
13. Pharmaceutical Information 24
14. Clinical Trials 24
14.1. Clinical Trials by Indication 24
Pediatric Low-grade Glioma 24

15. Microbiology 26

16. Non-Clinical Toxicology 26

Patient Medication Information 28

Part 1: Healthcare Professional Information

1. Indications

OJEMDA (tovorafenib tablets and tovorafenib for oral suspension) is indicated as:

- monotherapy for the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harbouring a *BRAF* fusion or rearrangement, or *BRAF* V600 mutation, who have received one or more prior systemic therapies.

A validated test is required to identify the *BRAF* fusion or rearrangement, or *BRAF* V600 mutation status to select patients appropriate for treatment with OJEMDA.

1.1. Pediatrics

Pediatrics (< 6 months of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of OJEMDA in pediatric patients below 6 months of age has not been established.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2. Contraindications

OJEMDA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4. Dosage and Administration

4.1. Dosing Considerations

Before initiating OJEMDA, liver function should be evaluated, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin (see 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

4.2. Recommended Dose and Dosage Adjustment

The recommended dose of OJEMDA based on body surface area (BSA) is 380 mg/m^2 orally once weekly (the maximum recommended dose is 600 mg orally once weekly), until disease progression or unacceptable toxicity.

OJEMDA may be administered as an immediate release tablet (see Table 1) or as an oral suspension (see Table 2).

A recommended dose for patients with BSA less than 0.3 m^2 has not been established.

Table 1 – Recommended dose based on body surface area (tablets)

Body Surface Area	Recommended dose
0.30-0.89 m^2	Administer the oral suspension once weekly (see Table 2)
0.90-1.12 m^2	400 mg once weekly

Body Surface Area	Recommended dose
1.13-1.39 m^2	500 mg once weekly
≥1.40 m^2	600 mg once weekly

Table 2 – Recommended dose based on body surface area (oral suspension)

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

*The maximum dose per bottle is 300 mg (12 ml).

Dose Modifications for Adverse Reactions

The management of adverse reactions may require dose reduction, treatment interruption or treatment discontinuation.

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

Table 3 – Recommended dose reductions for adverse reactions (tablets)

Body Surface Area	First Dose Reduction	Second Dose Reduction
0.30-1.12 m^2	Administer the oral suspension once weekly (see Table 4)	
1.13-1.39 m^2	400 mg once weekly	Administer the oral suspension once weekly (see Table 4)
≥1.40 m^2	500 mg once weekly	400 mg once weekly

Table 4 – Recommended dose reductions for adverse reactions (oral suspension)

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

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

Table 5 – Recommended Dose Modifications for Adverse Reactions

Severity of AR[a]	Dose Modification[b]
Hemorrhage	
• Intolerable Grade 2 • Grade 3	Withhold until improvement. If improved to Grade 0-1, resume at a reduced dose. If not improved, consider permanent discontinuation.
• First occurrence of any Grade 4	Withhold until improvement. If improved to Grade 0-1, resume at a reduced dose. If not improved, permanently discontinue.
• Recurrent Grade 4	Permanently discontinue.
Skin Toxicity, including photosensitivity	
• Intolerable Grade 2 • Grade 3 or 4	Withhold until improvement. If improved to Grade 0-1, resume at a reduced dose.

Severity of AR[a]	Dose Modification[b]
	If not improved, consider permanent discontinuation.
Hepatotoxicity	
• Grade 3 AST or ALT • Grade 3 bilirubin	Withhold until improvement. If improved to Grade ≤ 2 or baseline, resume as follows: • If laboratory abnormality resolves within 8 days, resume at the same dose. • If laboratory abnormality does not resolve within 8 days, resume at a reduced dose.
• First occurrence of any Grade 4	Withhold until improvement. If improved to Grade 0-1, resume at a reduced dose. If not improved, permanently discontinue.
• Recurrent Grade 4	Permanent discontinuation.
Other Adverse Reactions	
• Intolerable Grade 2 • Grade 3	Withhold until improvement. If improved to Grade 0-1, resume at a reduced dose. If not improved, consider permanent discontinuation.
• Grade 4	Withhold until improvement. If improved to Grade 0-1, resume at a reduced dose. If not improved or recurrent, permanently discontinue.

Abbreviations: AR = adverse reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase
[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
[b] See Table 3 and Table 4 for recommended dose reductions.

Special populations

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) or severe (bilirubin > 3x ULN and any AST) hepatic impairment (see 10.3 Pharmacokinetics).

Renal impairment: No dose adjustment is recommended for patients with mild-to-moderate (eGFR ≥ 30 mL/min/1.73 m^2 calculated by Schwartz equation or MDRD equation) renal impairment. OJEMDA has not been studied in patients with severe (eGFR <30 mL/min/1.73 m^2) renal impairment (see 10.3 Pharmacokinetics).

4.3. Reconstitution

Oral Suspension:

OJEMDA powder must be reconstituted to the oral suspension prior to being administered. Prior to use of the oral suspension for the first time, instruct caregivers (and if appropriate, patients) on the proper preparation, dose, and administration of OJEMDA.

Reconstitute the powder in each supplied bottle with exactly 14 mL of room temperature water to form the oral suspension. After reconstitution, each bottle of the oral suspension delivers 300 mg of OJEMDA in 12 ml (25 mg/ml). Let the bottle sit for 60 seconds to allow the foam to settle, as product foaming after reconstitution reduces the deliverable volume.

For doses greater than 300 mg, reconstitute two bottles to achieve the recommended dose. Split the dose as equally as possible between the two bottles (e.g., 6 mL and 7 mL for a 325 mg dose). Prepare the first bottle and administer dose prior to preparing the second bottle.

OJEMDA oral suspension must be administered within 15 minutes after reconstitution. If the oral suspension is not administered within 15 minutes after preparation, instruct the patient to discard it (see 11 Storage, Stability, and Disposal).

4.4. Administration

OJEMDA is for oral use. The tablets and powder may be used interchangeably.

OJEMDA should be taken orally at a regularly scheduled time once weekly with or without food (see 10Clinical Pharmacology10.3 Pharmacokinetics).

Tablets

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

Oral Suspension

Administer the oral suspension using the supplied oral dosing syringe (co-packaged) by mouth or through a feeding tube (not included, minimum 12 French) immediately after preparation per the Instructions for Use (see Patient Medication Information, INSTRUCTIONS FOR USE).

4.5. Missed Dose

If a dose is missed by 3 days or less, the missed dose should be taken as soon as possible, and the next dose should be taken on its regularly scheduled day.

If a dose is missed by more than 3 days, the missed dose should be skipped, and the next dose should be taken on its regularly scheduled day.

A minimum of four days should occur between doses.

If vomiting occurs immediately after taking a dose, the dose should be repeated.

5. Overdose

There is no information on overdose with OJEMDA. If overdose occurs, OJEMDA should be withheld and the patient should be treated supportively with appropriate monitoring as necessary. Since tovorafenib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with OJEMDA.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 6 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 100 mg tovorafenib	Colloidal silicon dioxide, Copovidone, Croscarmellose sodium, Magnesium stearate, Microcrystalline cellulose, Orange film coating (hypromellose, polyethylene glycol 8000, titanium dioxide, ferric oxide yellow, ferric oxide red).
Oral	Powder 25mg/ml tovorafenib	Artificial strawberry flavor, Colloidal silicon dioxide, Copovidone, Maltodextrin, Mannitol, Microcrystalline cellulose, Simethicone, Sodium lauryl sulfate, Sucralose

Tablets

- Orange, film-coated, oval tablets debossed with "100" on one side and "D101" on the opposite side.
- Packaged in boxes of:
  - 16 film-coated tablets: 4 blister cards (4 tablets each) per box.
  - 20 film-coated tablets: 5 blister cards (4 tablets each) per box or 4 blister cards (5 tablets each) per box.
  - 24 film-coated tablets: 4 blister cards (6 tablets each) per box.

Powder

- White to off white powder.
- Packaged in a 30 mL clear glass bottle with a white child-resistant screw cap, co-packaged with a press-in bottle adaptor and a 20 mL oral dosing syringe.

7. Warnings and Precautions

General

Neurofibromatosis Type 1 (NF1) Associated Tumours

Based on nonclinical data in NF1 models without *BRAF* alterations, OJEMDA may promote tumour growth in patients with NF1 tumours. In FIREFLY-1, patients with a known or suspected NF1 tumour were excluded. A *BRAF* alteration should be confirmed prior to initiation of OJEMDA treatment (see 1 Indications).

Driving and Operating Machinery

OJEMDA can cause fatigue (see 8.2 Clinical Trial Adverse Reactions). While taking OJEMDA, patients should be cautioned not to drive, operate dangerous machinery or engage in activities that require alertness or physical coordination if they are experiencing this effect.

Hematologic

Hemorrhage

In FIREFLY-1 (Arm 1 and Arm 2; N=137), hemorrhage events were observed in 40% of patients, with Grade 3 events occurring in 2% of patients (see 8.2 Clinical Trial Adverse Reactions). Tumour hemorrhage and intracranial tumour hemorrhage occurred in 19 (14%) patients, including one Grade 5 tumour hemorrhage event. OJEMDA was permanently discontinued due to intra-tumoral or tumour hemorrhage in 4 (3%) patients.

Advise patients and caregivers of the risk of hemorrhage during treatment with OJEMDA. Monitor for signs and symptoms of hemorrhage, including tumour hemorrhage, and evaluate as clinically indicated. If hemorrhage occurs, patients should be treated as clinically indicated. Withhold and resume OJEMDA at a reduced dose upon improvement, or permanently discontinue based on the severity of adverse reactions (see 4.2 Recommended Dose and Dosage Adjustment).

Hepatic/Biliary/Pancreatic

Hepatotoxicity

In FIREFLY-1, adverse events of increased alanine aminotransferase (ALT) were reported in 25% of patients, and increased aspartate aminotransferase (AST) occurred in 38% of patients, including Grade ≥3 increased ALT and AST in 6% and 3% of patients, respectively. Adverse events of increased blood bilirubin were reported in 15% of patients, including 1 (1%) patient with a Grade 3 event (see 8.2 Clinical Trial Adverse Reactions). Increased ALT or AST resulted in dose interruption in 5% and 3% of patients, respectively, and dose reduction in 2% and 1% of patients, respectively.

Monitor liver function tests, including ALT, AST and bilirubin, before initiating OJEMDA, one month after initiation, routinely during treatment, and as clinically indicated. OJEMDA should be withheld and resumed at the same or a reduced dose upon improvement, or permanently discontinued based on the severity of adverse reactions (see 4.2 Recommended Dose and Dosage Adjustment).

Musculoskeletal

Effect on Growth

OJEMDA can cause decreased growth velocity. In FIREFLY-1, treatment-emergent decreased growth velocity occurred in 61 (45%) patients aged 1 to 14 years, including Grade 3 events in 33% of patients (see 8.2 Clinical Trial Adverse Reactions). OJEMDA was interrupted in 7 patients (5%) and permanently discontinued in 4 patients (3%) due to decreased growth velocity. The median change from baseline in height percentile was -14 (z-score change -0.6) for evaluable patients on study for 12 months (N=107) and -20.3 (z-score change -0.9) for evaluable patients on study for 18 months (N=95).

Improvement in growth velocity was observed following permanent discontinuation or prolonged interruption of OJEMDA. Among 34 evaluable patients, the median annualized growth velocity (AGV) was 1.8 cm/year during the 2-year active treatment period. Of those, patients off-treatment for 3 months (N = 17), 6 months (N = 9), and 9 months (N = 7) had median AGVs of 4.2 cm/year, 10.9 cm/year, and 5.8 cm/year, respectively.

Routinely monitor patient growth during treatment with OJEMDA.

Reproductive Health

- **Contraception**

Women of childbearing potential should have a pregnancy test prior to starting treatment with tovorafenib. Before initiating treatment in women of childbearing potential, appropriate advice on effective methods of contraception should be provided. Women of childbearing potential must use effective nonhormonal contraception during therapy and for 28 days after the last dose of tovorafenib. Tovorafenib may decrease the efficacy of hormonal contraceptives, and effective nonhormonal contraception should be used (see 9.4 Drug-Drug Interactions). Male patients with female partners of reproductive potential must use condoms and effective contraception during treatment with tovorafenib and for 2 weeks after the last dose.

- **Fertility**

There are no data on the effects of tovorafenib on fertility in humans. Based on findings in animals, tovorafenib may impact fertility in males and females of reproductive potential (see 16 Non-Clinical Toxicology). The impact on fertility may not be reversible based on non-clinical data.

Skin

Rash

OJEMDA can cause rash. In FIREFLY-1, rash occurred in 83% of patients, including Grade 3 rash in 12% of patients. Rash resulted in dose interruption in 16% of patients, dose reduction in 9% of patients, and permanent treatment discontinuation in 1 patient (1%). Dermatitis acneiform occurred in 38% of patients treated with OJEMDA, including Grade 3 dermatitis acneiform in 1 (1%) patient (see 8.2 Clinical Trial Adverse Reactions). Dose reduction was required in 2 patients (2%) 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 the severity of adverse reactions (see 4.2 Recommended Dose and Dosage Adjustment).

Photosensitivity

In FIREFLY-1, photosensitivity occurred in 20 (15%) patients, including one Grade 3 event in a single patient (1%). Photosensitivity resulted in dose interruption and permanent discontinuation in 1 (1%) patient each (see 8.2 Clinical Trial Adverse Reactions).

Patients should be advised to use precautionary measures against ultraviolet exposure such as use of sunscreen (SPF ≥50), sunglasses, and/or protective clothing during treatment with OJEMDA. Withhold, reduce the dose, or permanently discontinue OJEMDA based on the severity of adverse reactions (see 4.2 Recommended Dose and Dosage Adjustment).

7.1. Special Populations

7.1.1. Pregnancy

There are no data on the use of OJEMDA in pregnant women. Animal studies showed that tovorafenib caused embryo-fetal lethality in rats at exposures below those achieved in humans at the recommended dose (see 16 Non-Clinical Toxicology). Advise pregnant women of the potential risk to a fetus. If a patient becomes pregnant while taking tovorafenib, the patient should be informed of the potential hazard to the fetus (see 7 Warnings and Precautions).

7.1.2. Breastfeeding

It is unknown whether tovorafenib or its metabolites are excreted in human milk. Due to the potential risk to the breastfed child, breastfeeding should be discontinued during treatment with OJEMDA and for 2 weeks after the last dose.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Among the 137 patients with pediatric LGG and treated in FIREFLY-1 study (Arm 1 and Arm 2), the most common adverse reactions (≥20% of patients) were rash, hair colour changes, viral infection, blood creatine phosphokinase increased, anemia, fatigue, vomiting, hypophosphatemia, headache, dry skin, pyrexia, decreased growth velocity, hemorrhage, aspartate aminotransferase increased, blood lactate dehydrogenase increased, dermatitis acneiform, nausea, constipation, upper respiratory tract infection, edema, decreased appetite, paronychia, abdominal pain, hypokalemia, stomatitis, pruritus, diarrhea, weight decreased, alanine aminotransferase increased, skin discolouration, alopecia, and pain in extremity.

Serious adverse events occurred in 56% of patients. Serious adverse events in ≥5% of patients included pyrexia (11%), decreased growth velocity (7%), vomiting (7%), and tumour hemorrhage (5%). A fatal event of tumour hemorrhage occurred in 1 patient (1%).

Ninety (66%) patients had adverse events leading to OJEMDA dose interruption. Adverse reactions leading to dose interruption in ≥5% of patients were pyrexia (14%), rash maculopapular (10%), vomiting (10%), fatigue (6%), nausea (5%), headache (5%), and alanine aminotransferase increased (5%).

Forty-four (32%) patients experienced adverse events that led to OJEMDA dose reduction. Adverse reaction leading to dose reduction in ≥5% of patients was rash maculopapular (5%).

Fifteen (11%) patients permanently discontinued OJEMDA treatment due to adverse events. Adverse reactions which resulted in permanent treatment discontinuation in more than one patient were decreased growth velocity (3%) and tumour hemorrhage (3%).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The safety profile of OJEMDA is based on data from 137 patients 11 months of age and older with relapsed or refractory pediatric LGG harbouring an activating *BRAF* alteration who received OJEMDA

treatment in Arm 1 and Arm 2 of FIREFLY-1 (see 14.1 Clinical Trials by Indication), including 119 patients (87%) treated for at least 6 months and 108 patients (79%) treated for at least 1 year, 91 patients (66%) treated for at least 18 months, and 27 patients (20%) treated for at least 24 months. The median duration of treatment was 21 months (range 0.7 to 32.1 months).

The safety population characteristics were comprised of patients with a median age of 9 years (range 11 months to 24 years); 3 (2%) patients were 11 months to < 2 years of age, 92 (68%) patients were 2 years to < 12 years of age, and 41 (30%) patients were >12 years of age.

Adverse reactions reported in patients treated with OJEMDA monotherapy in FIREFLY-1 (n=137) are listed in Table 7.

Table 7 – Adverse Reactions Occurring in ≥ 1% of Patients with Pediatric LGG Treated with OJEMDA in FIREFLY-1 (Arm 1 and Arm 2)

Adverse Reaction	**OJEMDA N = 137**	
	All grades n (%)	**Grade 3 and Grade 4 n (%)**
Blood and lymphatic system disorders		
Anemia[a]	84 (61)	18 (13)
Eosinophilia	11 (8)	0
Gastrointestinal disorders		
Vomiting	77 (56)	9 (7)
Nausea	51 (37)	0
Constipation	50 (36)	1 (1)
Abdominal pain[b]	40 (29)	1 (1)
Stomatitis[c]	39 (28)	0
Diarrhea[d]	36 (26)	2 (1)
General disorders and administration site conditions		
Fatigue	83 (61)	6 (4)
Pyrexia	64 (47)	9 (7)
Edema[e]	46 (34)	0

Adverse Reaction	OJEMDA N = 137	
	All grades n (%)	Grade 3 and Grade 4 n (%)
Infections and Infestations		
Viral Infection[f]	86 (63)	14 (10)
Upper respiratory tract infection	49 (36)	2 (1)
Paronychia	41 (30)	2 (1)
Investigations		
Blood creatine phosphokinase increased	85 (62)	17 (12)
Hypophosphatemia[g]	76 (55)	2 (1)
Aspartate aminotransferase increased	52 (38)	4 (3)
Blood lactate dehydrogenase increased	52 (38)	0
Weight decreased	35 (26)	2 (1)
Alanine aminotransferase increased	34 (25)	8 (6)
Lymphocyte count decreased	23 (17)	1 (1)
Blood bilirubin increased	20 (15)	1 (1)
White blood cell count decreased	16 (12)	2 (1)
Metabolism and nutrition disorders		
Decreased appetite	41 (30)	5 (4)
Hypokalemia	39 (28)	6 (4)
Hypoalbuminemia	20 (15)	1 (1)
Hyponatremia	19 (14)	3 (2)
Musculoskeletal and connective tissue disorders		
Decreased growth velocity[h]	61 (45)	46 (34)
Pain in extremity	28 (20)	1 (1)
Myalgia	22 (16)	0

Adverse Reaction	OJEMDA N = 137	
	All grades n (%)	Grade 3 and Grade 4 n (%)
Arthralgia	19 (14)	0
Nervous system disorders		
Headache	72 (53)	3 (2)
Skin and subcutaneous tissue disorders		
Rash[i]	114 (83)	17 (12)
Hair colour changes	106 (77)	0
Dry skin[j]	65 (47)	0
Dermatitis acneiform[j]	52 (38)	1 (1)
Pruritus	38 (28)	2 (1)
Skin discolouration[l]	30 (22)	0
Alopecia	28 (20)	0
Photosensitivity reaction	20 (15)	1 (1)
Vascular disorders		
Hemorrhage[m]	55 (40)	3 (2)
Intratumoural hemorrhage[n]	19 (14)	5* (4)
Flushing	14 (10)	0

MedDRA 23.1, CTCAE v5.0
a Includes term hemoglobin decreased.
b Includes term abdominal pain upper.
c Includes terms cheilitis, angular cheilitis, aphthous ulcer, mouth ulceration, lip ulceration.
d Includes term enterocolitis.
e Includes terms face edema, periorbital edema, edema peripheral, peripheral swelling, lip edema, swelling face, eye swelling, vulval edema.
f 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, 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.
g Includes term blood phosphorus decreased
h Includes terms growth retardation, growth failure.

i Includes terms rash maculo-papular, eczema, rash erythematous, rash papular, rash pustular, dermatitis, drug eruption, skin exfoliation, dermatitis bullous, rash follicular, rash macular, rash pruritic, erythema multiforme, rash vesicular.
j Includes terms chapped lips, lip dry, xeroderma.
k Includes term acne.
l Includes terms skin depigmentation, skin hyperpigmentation, skin hypopigmentation, melanocytic nevus, ephelides.
m Includes terms epistaxis, contusion, gingival bleeding, hematoma, petechiae, gastrointestinal hemorrhage, hematemesis, hematochezia, lower gastrointestinal hemorrhage, purpura, subdural hemorrhage, vaginal hemorrhage.
n Includes terms tumour hemorrhage, intracranial tumour hemorrhage.
*Includes a Grade 5 event.

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

Table 8 – Abnormal Laboratory Findings Changed from Baseline in ≥ 20% of Patients with Pediatric LGG Treated with OJEMDA in FIREFLY-1 (Arm 1 and Arm 2)

	OJEMDA (N=137)	
Laboratory Abnormality[a]	**All Grades n/N[b] evaluable (%)**	**Grade 3-4 n/N[b] evaluable (%)**
Hematology		
Decreased Hemoglobin	127/137 (93)	21/137 (15)
Decreased Lymphocytes	70/133 (53)	4/133 (3)
Decreased Leukocytes	47/137 (34)	2/137 (1)
Increased Hemoglobin	45/137 (33)	0/137 (0)
Increased Lymphocytes	43/133 (32)	0/133 (0)
Decreased Neutrophils	38/137 (28)	9/137 (7)
Decreased Platelets	29/137 (21)	1/137 (1)
Clinical Chemistry		
Decreased Phosphate	59/67 (88)	18/67 (27)
Increased Creatine Kinase	114/132 (86)	17/132 (13)
Increased Aspartate Aminotransferase	117/136 (86)	3/136 (2)
Increased Lactate Dehydrogenase	100/135 (74)	0/135 (0)
Decreased Potassium	75/137 (55)	4/137 (3)
Increased Alanine Aminotransferase	70/137 (51)	8/137 (6)
Decreased Bicarbonate/Total CO2	50/135 (37)	0/135 (0)
Decreased Albumin	43/137 (31)	0/137 (0)

	OJEMDA (N=137)	
Laboratory Abnormality[a]	**All Grades n/N[b] evaluable (%)**	**Grade 3-4 n/N[b] evaluable (%)**
Decreased Glucose	42/137 (31)	0/137 (0)
Increased Bilirubin	31/137 (23)	1/137 (1)
Increased Creatinine	30/137 (22)	1/137 (1)
Increased Sodium	29/137 (21)	3/137 (2)
Decreased Sodium	28/137 (20)	2/137 (1)
Increased Prothrombin Intl. Normalized Ratio	10/49 (20)	0/49 (0)

a Laboratory parameters were graded using CTCAE v5.0 where applicable; decreased phosphate was graded using CTCAE v4.03
b 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 49 to 137 patients.

9. Drug Interactions

9.2. Drug Interactions Overview

Tovorafenib is a substrate for the metabolic enzyme CYP2C8. Coadministration with strong or moderate inhibitors or inducers of CYP2C8 may alter the systemic exposure of tovorafenib (see 9.4 Drug-Drug Interactions). In vitro, tovorafenib inhibits CYP2C8, CYP2C9, CYP2C19, and CYP3A, and induces CYP3A, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19 at clinically relevant concentrations. Coadministration may alter exposure of drugs metabolized by these enzymes. Model-informed data predict a ≥20% decrease in midazolam (CYP3A4 substrate) exposure (see 9.4 Drug-Drug Interactions). In vitro studies indicate that tovorafenib inhibits BCRP, MATE1, OAPT1B1, and OATP1B3 at clinically relevant concentrations.

9.3. Drug-Behaviour Interactions

The interaction of OJEMDA with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 9 – Established or Potential Drug-Drug Interactions

Name of the Drug Product	Source of evidence	Effect	Clinical comment
Strong or Moderate CYP2C8 Inhibitors	In vitro	Tovorafenib is a CYP2C8 substrate. Strong or moderate CYP2C8 inhibitors are predicted to increase tovorafenib exposure based on a mechanistic understanding of its elimination which may increase the risk of adverse reactions with tovorafenib.	Avoid coadministration of tovorafenib with a strong or moderate CYP2C8 inhibitor.
Strong or Moderate CYP2C8 Inducers	In vitro	Tovorafenib is a CYP2C8 substrate. Strong or moderate CYP2C8 inducers are predicted to decrease tovorafenib exposure based on a mechanistic understanding of its elimination, which may reduce tovorafenib efficacy.	Avoid coadministration of tovorafenib with a strong or moderate CYP2C8 inducer.

Name of the Drug Product	Source of evidence	Effect	Clinical comment
CYP3A Substrates	In vitro	Tovorafenib is a CYP3A inducer. Coadministration of tovorafenib is predicted to decrease exposure of certain CYP3A substrates, which may reduce the effectiveness of these substrates. Coadministration of tovorafenib with hormonal contraceptives (CYP3A substrates) may render hormonal contraceptives ineffective.	Avoid coadministration of tovorafenib 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 product labeling for CYP3A substrates. Avoid coadministration of hormonal contraceptives with tovorafenib. If coadministration is unavoidable, use an additional effective nonhormonal contraceptive method during coadministration and for 28 days following discontinuation of tovorafenib.

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, MATE1, OAPT1B1, and OATP1B3 at clinically relevant concentrations.

9.5. Drug-Food Interactions

Administration of tablets with a high-fat meal (approximately 859 total calories, 54% fat) delayed the time to peak plasma concentration of tovorafenib by approximately 3 hours compared to fasted conditions but did not result in clinically significant changes in tovorafenib exposure (see 10.3 Pharmacokinetics).

OJEMDA may be taken with or without food.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Tovorafenib is a Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases (with in vitro half maximal inhibitory concentration [IC_{50}] values of 7.1, 10.1, and 0.7 nM, respectively), and BRAF Fusion proteins.

Tovorafenib exhibited antitumor activity in cultured cells and xenograft tumor models harboring *BRAF* V600E and V600D mutations. Tovorafenib also exhibited antitumor activity in cultured cells and in xenograft tumor models harboring a *BRAF* fusion, suppressing activation of the mitogen -activated protein kinase (MAPK) pathway.

10.2. 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 dose range of 290 to 476 mg/m^2 (0.76-1.25 times the recommended dose).

Cardiac Electrophysiology

At the recommended tovorafenib dose 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.

10.3. Pharmacokinetics

Tovorafenib pharmacokinetic parameters are presented as mean (CV%) unless otherwise indicated. Tovorafenib steady state maximum concentration (C_{max}) is 6.8 µg/mL (23%) and the area under the concentration-time curve (AUC) is 500 µg*h/mL (32%). 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 with once-weekly administration.

Table 10 – Summary of tovorafenib pharmacokinetic parameters in patients with pediatric LGG

	$C_{max,SS}$ (µg/mL) (N=142)	AUC_{SS} (µg × h/mL)	CL/F (L/h/m^2)	Vc/F (L/m^2)
Multiple Dose Geometric Mean	6.8	500	0.75	60.6

$C_{max,SS}$: Maximum observed plasma concentration at steady state; AUC_{SS}: Area under the plasma concentration–time curve over one dosing interval at steady state; CL/F: Apparent oral clearance normalized by body surface area; Vc/F: Apparent central volume of distribution normalized by body surface area

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

Food effect

No clinically significant differences in tovorafenib C_{max} and AUC were observed following administration of tablets with a high-fat meal compared to fasted conditions, but the Tmax was delayed by approximately 3 hours.

Distribution: Tovorafenib apparent volume of distribution is 60.6 L/m^2 (23%). Tovorafenib is 97.5% bound to human plasma proteins in vitro.

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

Elimination: Tovorafenib terminal half-life is approximately 56 hours (33%) and the apparent clearance is 0.75 L/h/m^2 (32%). 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).

Special Populations and Conditions

- **Pediatrics:** No clinically significant differences of tovorafenib were observed based on age (range: 1 to 94 years). 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.
- **Sex:** No clinically significant differences in the pharmacokinetics of tovorafenib were observed based on sex.
- **Ethnic Origin:** No clinically significant differences of tovorafenib were observed based on race. A population PK analysis did not identify clinically relevant differences in PK of tovorafenib based on race (White, Black, Asian).
- **Hepatic Insufficiency:** No clinically significant differences of tovorafenib were observed in patients with mild hepatic impairment [bilirubin ≤ upper limit of normal (ULN) and Aspartate Aminotransferase (AST) > ULN or bilirubin > 1 to 1.5x ULN and any AST)]. Tovorafenib has not been studied in patients with moderate (bilirubin > 1.5x to 3x ULN and any AST) or severe hepatic impairment (total bilirubin >3 x ULN and any AST)4.2Recommended Dose and Dosage Adjustment.
- **Renal Insufficiency:** No clinically significant differences of tovorafenib were observed in patients with mild-to-moderate renal impairment (eGFR) ≥ 30 mL/min/1.73 m^2 calculated by Schwartz

equation or MDRD equation), no clinically significant differences of tovorafenib were observed. Tovorafenib has not been studied in patients with severe (eGFR <30 mL/min/1.73 m^2) renal impairment.

11. Storage, Stability, and Disposal

Keep out of reach of children. Store at room temperature (15°C to 30°C). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

Powder: Suspension must be used within 15 minutes after reconstitution.

Part 2: Scientific Information

13. Pharmaceutical Information

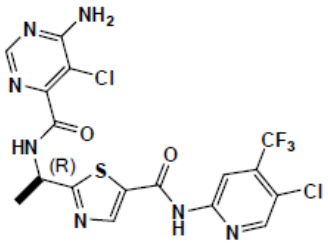
Drug Substance

Non-proprietary name of the drug substance(s): tovorafenib

Chemical name: 6-amino-5-chloro-N-[(1R)-1-[5-[[[5chloro-4-(trifluoromethyl)-2 pyridinyl]amino]carbonyl]-2-thiazolyl]ethyl]-4-pyrimidinecarboxamide

Molecular formula and molecular mass: $C_{17}H_{12}C_{l2}F_3N_7O_2S$, 506.29 g/mol

Structural formula:



Physicochemical properties: Tovorafenib is a kinase inhibitor. It is a white to off-white powder. The solubility of tovorafenib at 37°C is ≤ 3 micrograms/mL from pH 1.2 to 8 in aqueous media.

14. Clinical Trials

14.1. Clinical Trials by Indication

Pediatric Low-grade Glioma

Table 11 – Summary of Patient Demographics for the Pivotal Clinical Trial in Patients with Relapsed or Progressive Pediatric LGG after One or More Prior Systemic Therapies

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
FIREFLY-1	Phase II, multicenter, open-label, multi-arm, uncontrolled study in patients with relapsed or progressive pediatric LGG harbouring an activating *BRAF* alteration who had	420 mg/m^2 orally once weekly (range*: 290 to 476 mg/m^2) according to body surface area, with a maximum dose of 600 mg until disease progression or unacceptable	Arm 1: 77 Arm 2: 60	Arm 1: median 8 years (2-21) Arm 2: median 9.5 years (11 months-24 years)	Arm 1: male 52%; female 48% Arm 2: male 55%; female 45%

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
	received at least one prior systemic therapy	toxicity			

Abbreviation: LGG = low-grade glioma
*Actual dose range resulting from maximum dose, BSA bands, and dose rounding.

The efficacy of OJEMDA was evaluated in Arm 1 of FIREFLY-1. The presence of an eligible *BRAF* alteration was based on local laboratory testing. Patients were also required to have at least one measurable lesion as defined by the RANO-HGG (Response Assessment in Neuro-Oncology for High-Grade Glioma) criteria. All patients had received at least one line of prior systemic therapy and had documented evidence of radiographic progression. Patients with tumours harbouring additional activating molecular alteration(s) (e.g., *IDH1/2* mutations, *FGFR* mutations) or patients with known or suspected diagnosis of neurofibromatosis type 1 (NF1) were excluded.

Patients received OJEMDA at approximately 420 mg/m^2 orally once weekly (range: 290 to 476 mg/m^2) according to body surface area, with a maximum dose of 600 mg, until disease progression or unacceptable toxicity. Although the OJEMDA doses administered in FIREFLY-1 (Arm 1) were between 290 and 476 mg/m^2, the recommended OJEMDA dose is 380 mg/m^2 orally once weekly because this dose was determined to be safe and effective for the treatment of patients 6 months of age and older with relapsed or refractory pediatric LGG harbouring a *BRAF* fusion or rearrangement, or *BRAF* V600 mutation (see 4.2 Recommended Dose and Dosage Adjustment).

Tumour 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 included duration of response, time to response, and ORR by independent review based on RANO-LGG and RANO-HGG criteria.

The efficacy population comprised 76 patients in Arm 1 who had measurable disease at baseline and received OJEMDA treatment. Sixty-one percent of the patients were White, and 93% had Karnofsky/Lansky performance status of 80 to 100. Patients received a median of 3 prior systemic regimens (range: 1 to 9), with 22%, 26%, 21%, and 30% receiving 1, 2, 3, and >3 prior systemic regimens, respectively. Forty-six patients (60%) received prior treatment with a MAP kinase pathway inhibitor. The most common tumour locations were the optic pathway (51%), deep midline structures (12%), brain stem (8%), cerebellum (7%), and cerebral hemisphere (5%). Fifty-six patients (73%) had a *KIAA1549:BRAF* fusion, 13 patients (17%) had a V600E mutation, and 8 patients (10%) had a *BRAF* alteration classified as “other”, including *BRAF* duplication or *BRAF* rearrangement.

The median duration of treatment was 23.7 months (range 0.7 to 32.1 months).

Efficacy results are shown in Table 12.

Table 12 – Efficacy Results Based on Independent Review Using RAPNO-LGG Criteria in FIREFLY-1 (Arm-1)

Efficacy Parameter	OJEMDA N=76*
Overall Response Rate	
ORR (CR+PR+MR) 95% CI[a]	52.6% (40.8, 64.2)
Complete Response (CR), n (%)	0 (0)
Partial Response (PR), n (%)	29 (38.2)
Minor Response (MR), n (%)	11 (14.5)
Duration of Response (DoR)	**N=40**
Median (95% CI)[b], Months	18.0 (12.0, 22.8)
DoR rate at 12 months[b]	65.0%
DoR rate at 24 months[b]	25.6%

Abbreviations: RAPNO-LGG = Response Assessment in Pediatric Neuro-Oncology for Low-Grade Glioma; CI = confidence interval.
*At least one measurable lesion by the relevant imaging criteria at baseline based on RAPNO-LGG criteria.
[a] Based on Clopper-Pearson exact confidence interval.
[b] Based on Kaplan-Meier estimate.

Based on RAPNO-LGG criteria, among responders, the median time to response was 5.4 months (range 1.6 to 17.5 months). Based on exploratory subgroup analyses, the ORR was 53.1% (95% CI: 40.2, 65.7) among patients with *BRAF* fusion or rearrangement (n=64), and 50.0% (95% CI: 21.1, 78.9) among patients with *BRAF* V600E mutation (n=12), respectively. The ORR was 51.1% (95% CI: 35.8, 66.3) among patients who had received prior MAPK-targeted therapy (n=45), and 54.8% (95% CI: 36.0, 72.7) among patients who had not received prior MAPK-targeted therapy (n=31).

Based on RANO-LGG criteria (N=76), the ORR was 53.9% (95% CI: 42.1, 65.5). No patients had CR, 30.3% had PR, and 23.7% had MR.

Based on RANO-HGG criteria (N=69), the ORR was 71.0% (95% CI: 58.9, 81.3), including 23.2% of patients with CR and 47.8% with PR. RANO-HGG-based response was assessed on T1-enhancing lesions and should be interpreted with caution.

Per protocol, patients were permitted to enter an optional drug holiday, during which time they could be re-treated with OJEMDA if there was clinical or radiographic evidence of disease progression. In Arm 1, 33 (43%) patients were on a drug holiday after completing 26 cycles of therapy (24 months of treatment), and 11 (14%) patients remained on treatment by the data cutoff.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General Toxicology

In repeat- dose toxicology studies in rats of up to 3 months duration, tovorafenib-related findings in male and female rats included persistent follicular cell atrophy of the thyroid gland at ≥ 150 mg/kg once every other day (approximately 0.3-fold and 0.7-fold the human exposure at the recommended dose based on AUC in males and females, respectively). In repeat-dose toxicology studies in monkeys of up to 3 months duration, tovorafenib-related findings in male and female monkeys included reversible

increase in myeloid-to-erythroid ratio in the sternal bone marrow at ≥ 3 mg/kg once every other day (approximately 0.3-fold and 0.2-fold the human exposure at the recommended dose based on AUC in males and females, respectively).

Carcinogenicity

Tovorafenib was not carcinogenic in a 26-week (or 6-month) study in transgenic rasH2 mice following oral administration at doses up to 100 mg/kg/day, at exposures approximately 0.6-fold the human exposure (AUC) at the recommended human dose.

Genotoxicity

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.

Reproductive and Developmental Toxicology

In a fertility and early embryonic development study in female rats, tovorafenib decreased the number of pregnancies, corpora lutea, and live embryos, as well as increased post-implantation losses at doses as low as 37.5 mg/kg/day (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 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).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOJEMDA™

Tovorafenib tablets

Tovorafenib for oral suspension

This Patient Medication Information is written for the person who will be taking **OJEMDA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **OJEMDA** talk to a healthcare professional.

What OJEMDA is used for:

For the following indication OJEMDA has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- OJEMDA is used in patients 6 months of age and older to treat a type of brain tumour called pediatric low-grade glioma. The glioma:
  - must have been treated with one or more other treatments, and
  - has come back after previous treatment or has not responded to previous treatment.

OJEMDA should only be used for people who have a tumour that has a certain change in a gene called "*BRAF*". Before taking OJEMDA, you should have your tumour tested for this change.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How OJEMDA works:

OJEMDA targets tumors in the brain. It works by blocking specific proteins that cause tumour to grow. This helps slow or stop the growth of the tumour.

The ingredients in OJEMDA are:

Medicinal ingredient(s): tovorafenib

Non-medicinal ingredients:

Tablet: 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 orange).

Powder: artificial strawberry flavor, colloidal silicon dioxide, copovidone, maltodextrin, mannitol, microcrystalline cellulose, simethicone, sodium lauryl sulfate, and sucralose.

OJEMDA comes in the following dosage form(s):

Tablets; 100 mg.

Powder; 25 mg/mL

Do not use OJEMDA if:

- You are allergic to tovorafenib.
- You are allergic to any of the other ingredients in OJEMDA or to any part of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OJEMDA. Talk about any health conditions or problems you may have, including if you:

- Have or have had bleeding problems
- Have or have had skin problems
- Have or have had liver problems

Other warnings you should know about:

Hemorrhage (severe bleeding problems including tumour bleeding): OJEMDA can cause severe bleeding problems. This includes bleeding in the brain. Your healthcare professional will monitor you for signs of bleeding problems.

Liver problems: OJEMDA can cause liver problems. You will have blood tests done before starting and during treatment with OJEMDA. These blood tests will tell your healthcare professional how your liver is working.

Skin problems including photosensitivity: OJEMDA can cause skin problems like rash and acne. Your healthcare professional will check your skin during treatment. OJEMDA can also make your skin more sensitive to light (photosensitivity). Use sunscreen (SPF 50 or higher), sunglasses and protective clothing during treatment with OJEMDA.

Slowed growth: OJEMDA can slow down growth in children. Your healthcare professional will routinely monitor you or your child's growth while you are taking OJEMDA. Growth may recover after treatment is paused or stopped. Talk to your healthcare professional if you notice any changes in you or your child's growth.

See the "Serious side effects and what to do about them" table, below, for more information on these and other serious side effects.

Pregnancy and Breastfeeding:

Female patients:

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- You must not take OJEMDA if you are pregnant or are planning to become pregnant. OJEMDA may harm your unborn baby.
- If you are able to get pregnant:
  - Your healthcare professional will make sure you are not pregnant before you start taking OJEMDA.
  - Use effective birth control while you are taking OJEMDA and for 28 days after you stop taking it. You must use a non-hormonal birth control method like a condom. If you take hormonal birth control you must also use a non-hormonal birth control method. Talk to your healthcare provider about effective birth control methods.
  - Tell your healthcare professional right away if you get pregnant or think you may be pregnant while you are taking OJEMDA.
- Do not breastfeed your baby while you are taking OJEMDA and for 2 weeks after you stop taking it.

Male patients:

- During your treatment with OJEMDA, use a condom each time you have sex with a woman who is pregnant, may be pregnant or could get pregnant. Continue using condoms for 2 weeks after your last dose.
- If during your treatment with OJEMDA, your sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.

Fertility:

- Treatment with OJEMDA may affect your ability to father or have a child. If you have questions about this, talk to your healthcare professional.

Driving and using machines: OJEMDA can cause fatigue. If you feel tired while taking OJEMDA, you should not drive, use machinery or do tasks that require special attention.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OJEMDA:

- Gemfibrozil, a medicine used to treat high cholesterol
- Methotrexate, a medicine used to treat various cancers, arthritis, skin problems
- Medicines used to treat various cancers such as topotecan, irinotecan
- Hormonal birth control
- Clopidogrel, a medicine used to prevent heart attacks and strokes
- Deferasirox, a medicine used to manage iron levels in the blood
- Teriflunomide, a medicine used to treat multiple sclerosis, a disease affecting the brain and spinal cord
- Rifampin, a medicine used to treat tuberculosis, a disease caused by bacteria affecting the lungs
- Phenytoin, a medicine used to treat seizures

How to take OJEMDA:

- Your healthcare provider will either prescribe you or your child OJEMDA tablets or OJEMDA for oral suspension.
- Take OJEMDA exactly as your healthcare professional tells you to. Talk to your healthcare professional if you are not sure.
- You can take OJEMDA with or without food.
- OJEMDA Tablets: Swallow tablets whole with water. Do not chew, cut, or crush the tablet.
- OJEMDA for oral suspension:
    - OJEMDA powder for oral suspension must be reconstituted / prepared before use to make an oral suspension.
    - Suspension must be used within 15 minutes after reconstitution.
    - See the Instructions for Use for instructions on how to prepare, measure and take or give a dose of OJEMDA for oral suspension. Talk to your healthcare professional if you are not sure.

Usual dose:

- Your healthcare professional will decide the right dose for you to take once a week.

Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:

- experience serious or unwanted side effects, or
- your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much OJEMDA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a weekly dose of OJEMDA by:

- **3 days or less**: take the missed dose as soon as you remember. Take the next dose of OJEMDA on the next regular scheduled day.
- **More than 3 days**: skip the missed dose and take the next dose of OJEMDA on the next regular scheduled day.

If you vomit right after taking OJEMDA, you should take another dose. Talk to your healthcare professional if you are not sure.

Possible side effects from using OJEMDA:

These are not all the possible side effects you may have when taking OJEMDA. If you experience any side effects not listed here, tell your healthcare professional.

- Being sick (vomiting), feeling sick (nausea)
- Constipation
- Decreased appetite
- Diarrhea
- Dry or itching skin
- Fever

- Cold symptoms (sore throat, runny nose)
- Hair changes (colour, texture and hair loss)
- Headache
- Joint pain
- Muscle pain
- Nail bed infection
- Nose and throat infection
- Pain in legs and arms
- Reddening of the skin (flushing)
- Skin colour changes
- Sore mouth, redness and swelling of mouth
- Stomach pain
- Swelling
- Tiredness
- Weight loss

OJEMDA can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment. These will tell your healthcare professional how OJEMDA is affecting your blood and liver.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
Very common			
Blood problems (low or high white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, frequent or recurrent infections, getting sick easily, fever, chills, irregular heartbeats, shortness of breath, skin itching or hives, asthma-like symptoms (wheezing, cough), nasal congestion, diarrhea, fever, swelling, muscle weakness		X	
Hemorrhage (severe bleeding problems including tumour bleeding): sudden tingling, weakness, numbness or sudden and severe headache, nausea or vomiting, seizures, confusion, loss of consciousness, collapse, unsteadiness, dizziness, or slurred speech.			X
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling,		X	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
nausea or vomiting, unusual dark urine, unusual tiredness, unexplained loss of appetite, dark-colored urine, pale stools, fatigue, confusion, loss of consciousness, itching without a rash.			
Severe vomiting	**X**		
Skin problems, including photosensitivity (sensitivity to sunlight): burning, itching, or stinging of the skin after sun exposure, appearance of red patches or blisters, increased sensitivity to sunlight, or unusual pigmentation changes on exposed areas, rash.	**X**		
Slowed growth: slow growth, growth failure.		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C to 30°C). Keep out of reach and sight of children.

If you want more information about OJEMDA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website www.ipsen.ca; or by calling 1-855-215-2288.

This leaflet was prepared by Ipsen Biopharmaceuticals Canada Inc.

Date of Authorization: 2026-07-13

INSTRUCTIONS FOR USE: OJEMDA for Oral Suspension

Read these Instructions for Use carefully.

Your healthcare professional will show you how to prepare, measure, and take or give a dose of OJEMDA for oral suspension correctly. Always use OJEMDA for oral suspension exactly as your healthcare professional tells you to. Talk to your healthcare professional if you have any questions.

- You will receive the OJEMDA for oral suspension in a box that contains a bottle with powder, a 20 mL oral dosing syringe, and a bottle adaptor. Contact your healthcare professional if you do not have one or more of these items. Each bottle is for single use only.
- The bottle is made of glass. Do not use the bottle if it is broken or damaged. Do not use OJEMDA if the safety seal under the cap is broken or missing. Contact your healthcare professional for a new bottle.
- Do not use OJEMDA after the expiry date which is stated on the bottle and box after EXP. Contact your healthcare professional if the expiry date has passed.

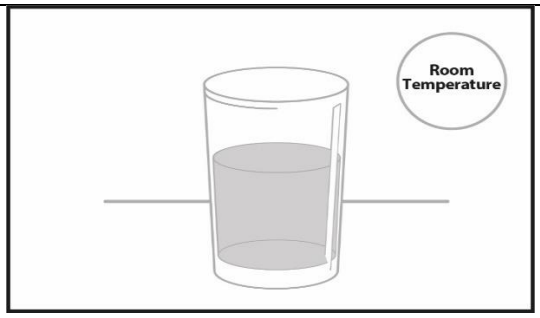
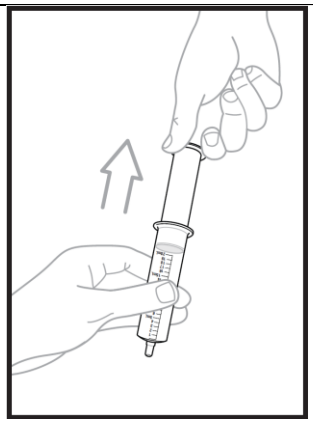
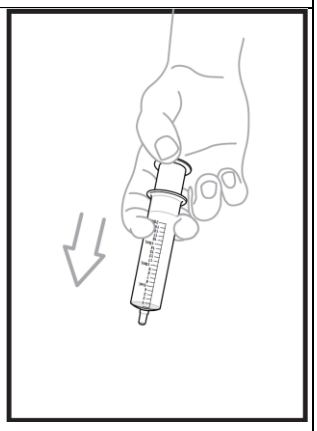
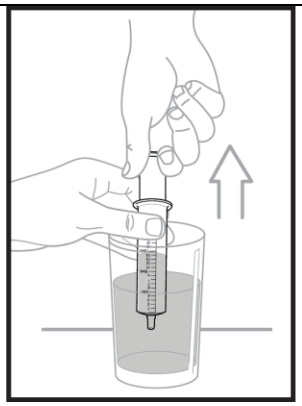
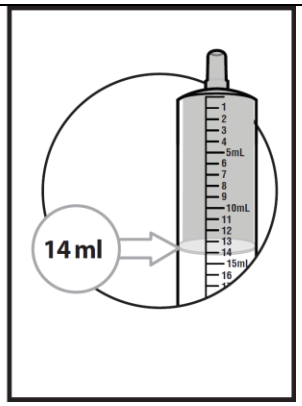
Get the following supplies ready:	
Included in a box of OJEMDA for Oral Suspension: 	**Not included in the box:** • 1 empty clean cup • room temperature water • ENFIT syringe and ENFIT adaptor (if taking or giving OJEMDA oral suspension through a feeding tube)

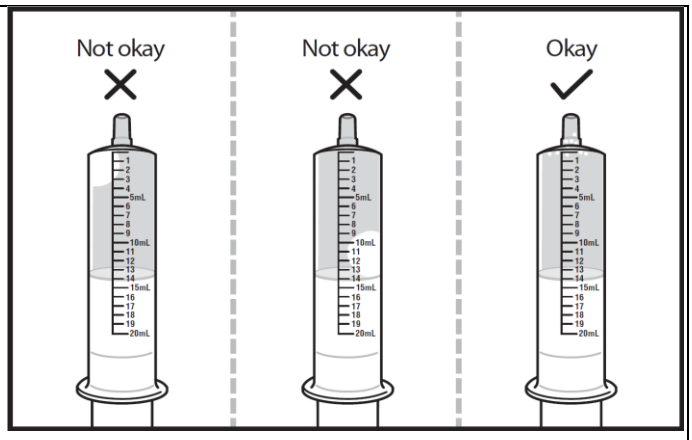
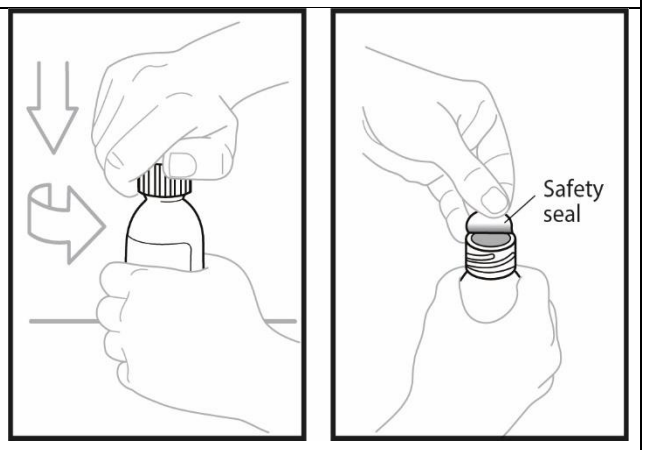
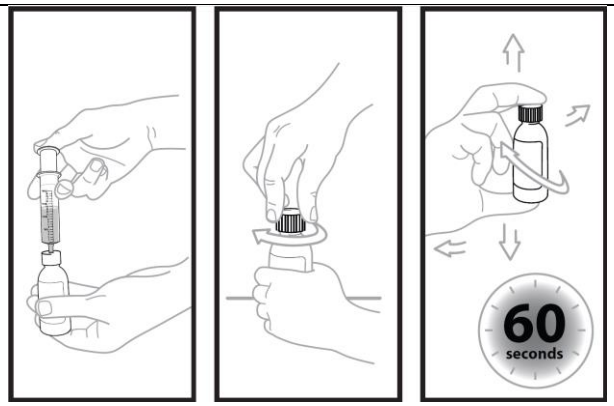
- **Always use the oral dosing syringe provided** to measure your dose.
- The 20 mL oral dosing syringe is marked to help you correctly measure your dose. It has markings in milliliters (mL).
- **Add exactly 14 mL** of room temperature water to the bottle to prepare the OJEMDA oral suspension. Only 12 mL will be taken or given from each prepared bottle.
- Each dose **must be given within 15 minutes** after the medicine has been prepared.

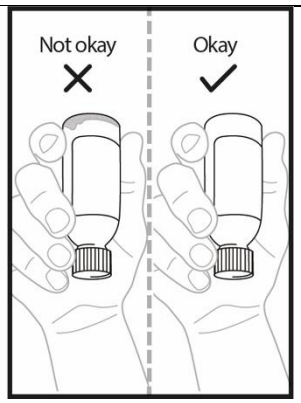
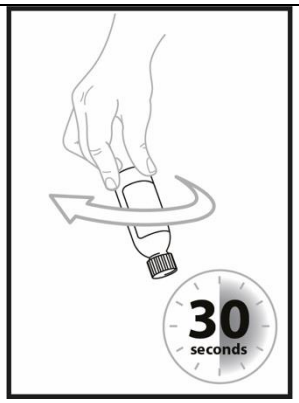
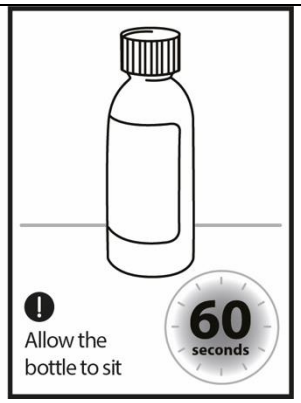
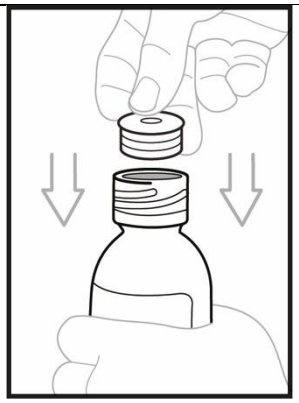
Note: You may need to prepare 2 bottles to give your dose of OJEMDA oral suspension. If 2 bottles are required:

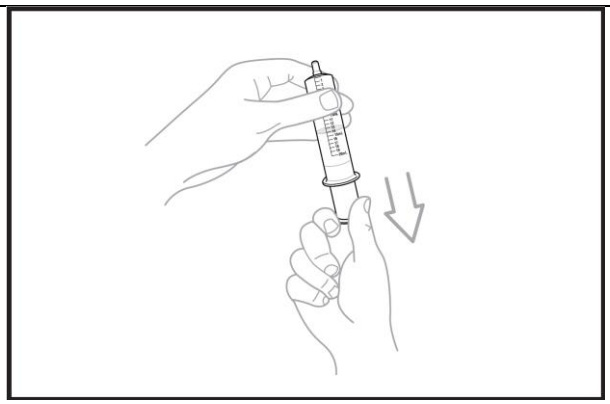
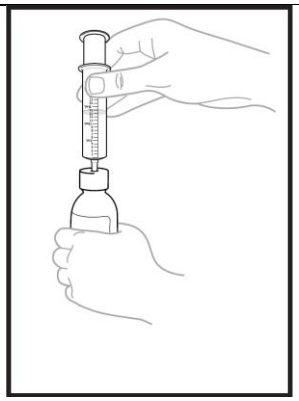
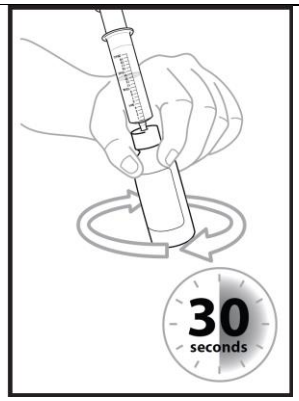
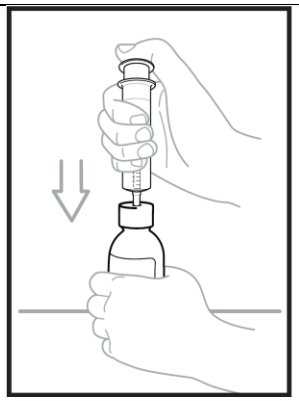
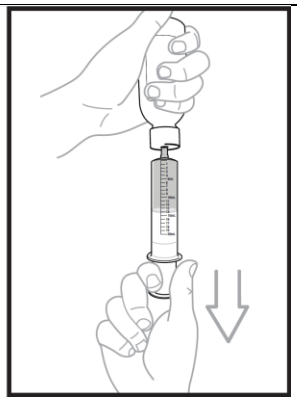
  - always add exactly 14 mL of room temperature water to each bottle, and
  - prepare, take or give the dose from the first bottle. Repeat the same steps to prepare, take or give the dose from the second bottle.

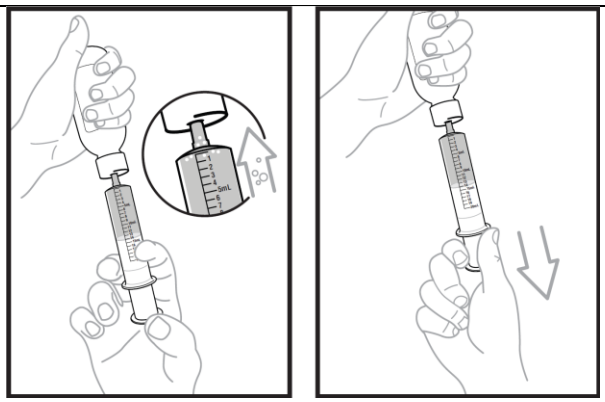
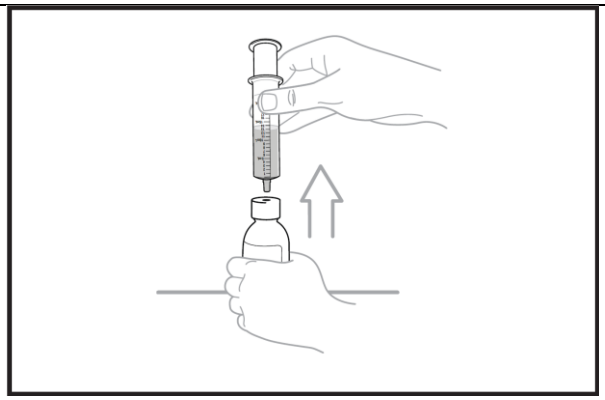
- Take or give OJEMDA oral suspension by mouth using the 20 mL oral dosing syringe, or through a feeding tube with a **minimum** size of 12 French using an ENFIT syringe.
  - If you are taking or giving OJEMDA oral suspension **by mouth,** follow Section A, **Steps 1 to**

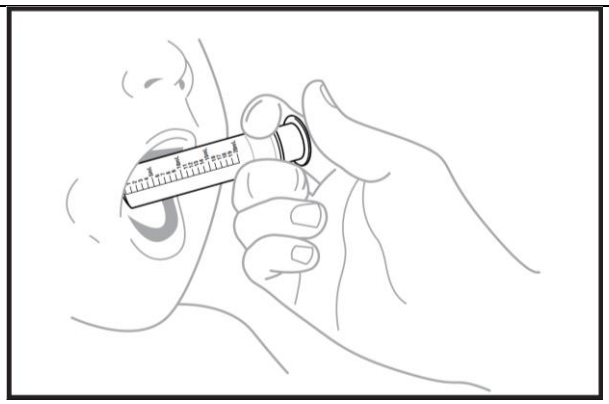
19. ▪ If taking or giving OJEMDA oral suspension **by a feeding tube,** follow Section B, **Steps 20 to 25**.	
Section A: Preparing, measuring, and taking or giving a dose of OJEMDA oral suspension	
Step 1. Wash and dry your hands before preparing, measuring, and taking or giving a dose of OJEMDA.	
Step 2. Place your supplies on a clean, flat work surface.	
Step 3. Fill a cup half-way with room temperature water. **Do not use cold water.**	
Step 4. Remove air from the oral dosing syringe. Pull the plunger up into the oral dosing syringe as far as it will go, and then push the plunger back down into the oral dosing syringe as far as it will go. This will help to remove all the air inside.	 
Step 5. Place the oral dosing syringe tip in the water. Pull up on the plunger to draw water into the oral dosing syringe to the 14 mL mark. **Note: Add exactly 14 ml** of water to the bottle with powder.	 

Step 6. Remove the oral dosing syringe from the cup. Turn the oral dosing syringe tip upward and check for air bubbles. If large air bubbles appear in the oral dosing syringe, push the water back into the cup and then pull up on the plunger again to draw up the water to the **14 mL** mark. **Repeat Step 6** until there are no large air bubbles present. Small air bubbles are ok. Set the oral dosing syringe aside.	
Step 7. Open the bottle with powder by pushing down firmly on the cap and turning it to the left (counter-clockwise). • **Do not** throw away the cap. • Remove the Safety seal. **Do not** use the bottle with powder if the safety seal under the cap is broken or missing. Call your healthcare professional if the safety seal is broken.	
Step 8. Insert the tip of the oral dosing syringe into the opening of the bottle. Push down on the plunger and inject 14 mL of water into the bottle. • Remove the tip of the emptied oral dosing syringe from the bottle and set it aside. • Right away, replace the cap back onto the bottle by pushing down while twisting the cap to the right (clockwise). • Shake the bottle well for 60 seconds in all directions.	

Step 9: Turn bottle upside down to check for any powder stuck to the inside of the bottle. • If you still see powder in the bottle, continue to shake the bottle for another 15 seconds until you no longer see the powder inside the bottle. • **Do not shake the bottle for more than 2 minutes total time.** • Check the bottle to make sure all of the powder is no longer visible. • If you still see powder in the bottle, contact your healthcare professional and ask for a new bottle.	
Step 10. Turn the bottle upside down again and swirl for 30 seconds. • Place the bottle on a flat, clean, work surface. • Remove the cap and check that no solids are stuck in the bottle neck. • If you see solids in the bottle neck, recap the bottle, turn the bottle upside down, and swirl for an additional 15 seconds. • Allow the bottle to sit for 60 seconds to allow most of the foam to settle. **Note:** Foaming in the bottle will reduce the amount of OJEMDA for oral suspension.	 
Step 11. Open the bottle by firmly pressing down on the cap and turning it to the left (counterclockwise). **Do not** throw away the cap. Firmly insert the bottle adaptor into the bottle by pushing it tightly into the top of the bottle. The top edge of the bottle adaptor should be even with the bottle top. **Do not** remove the bottle adaptor after it	

is inserted into the bottle.	
Step 12. Check your or your child's dose in milliliters (mL) as prescribed by your healthcare professional. Pick up the oral dosing syringe again. Each mark on the oral dosing syringe is equal to 1 mL. Draw air into the oral dosing syringe by pulling the plunger out to your prescribed dose. For example, if your dose is 12 mL, you would draw the oral dosing syringe by pulling the plunger out to the 12 mL mark.	
Step 13. Insert the tip of the oral dosing syringe into the bottle adaptor. • The tip of the oral dosing syringe should fit snugly into the hole of the bottle adaptor. • Keep the oral dosing syringe attached to the bottle. Hold the bottle where the oral dosing syringe tip inserts into bottle adaptor. Swirl the oral suspension for 30 seconds with the oral dosing syringe in place.	 
Step 14. Inject the air from the oral dosing syringe into the bottle. Hold the oral dosing syringe in place and turn the bottle upside down. To measure the dose, keep the tip of the oral dosing syringe facing up and pull down on the plunger until the top of the plunger lines up with the prescribed dose in mLs.	 

Step 15. Remove any air bubbles in the oral dosing syringe: • While the oral dosing syringe is still in the bottle, gently push the suspension back into the bottle and then pull down on the plunger again to draw up your dose. Repeat **Step 15** until you see that few or no air bubbles remain or if you draw up the wrong dose in the oral dosing syringe. **Note:** If you need 2 bottles: Only use up to 12 mL of OJEMDA from each prepared bottle. • If the dose is more than 12 mL (300 mg): split the dose as equally as possible between each prepared bottle. • For example, if your dose is 13 mL, draw 6 mL from the first prepared bottle, and 7 mL from the second prepared bottle.	
Step 16: Leave the tip of the oral dosing syringe in the bottle adaptor and carefully turn the bottle upright. Put the bottle onto your flat work surface again. Slowly remove the oral dosing syringe tip from the bottle adaptor by gently pulling straight up on the barrel of the syringe. **Do not** hold the oral dosing syringe by the plunger because the plunger may come out.	
Step 17: Check again to be sure the plunger of the oral dosing syringe is at your prescribed mL dose mark on the barrel. If you do not have the correct prescribed mL dose, repeat **Steps 15 to 17.** If you are taking or giving a dose of OJEMDA **by mouth, continue to Step 18**. If you are taking or giving a dose of OJEMDA through a feeding tube, go to **Section B**. OJEMDA oral suspension **must be given within 15 minutes** after prepared for use.	

Step 18. You or your child should sit upright to take or give a dose of OJEMDA. Place the tip of the oral dosing syringe towards the inside of the cheek in your or your child's mouth. • Slowly push the medicine into the mouth by pressing down on the plunger. • **Do not** forcefully push the plunger. This may cause choking. • Allow the child to swallow while giving OJEMDA. You or your child may drink liquids right away after swallowing the OJEMDA oral suspension. • Be sure to take or give the entire dose of OJEMDA. • If 2 bottles of OJEMDA are required to take or give your prescribed dose, repeat **Section A, Steps 1 to 18** for the second bottle. • Throw away the prepared OJEMDA oral suspension if it is not taken or given within 15 minutes.	
Step 19: See **Section C** for instructions on "**How to throw away used bottles, expired or unused OJEMDA oral suspension, and oral dosing syringes"**	
Section B: Taking or giving a dose of OJEMDA through a feeding tube	
Before giving a dose of OJEMDA through a feeding tube, read the following information and talk to your or your child's healthcare professional before continuing to **STEP 20**: • OJEMDA may be given through a feeding tube, as directed by your healthcare professional. • Only use a feeding tube with a minimum size of 12 French. • Always use the 20 mL oral dosing syringe (included in the box) to <u>prepare</u> each dose of OJEMDA. • Always use a 20 mL ENFIT syringe and an ENFIT adaptor (neither included in the box) to <u>measure</u> and <u>give</u> each dose of OJEMDA through the feeding tube.	
Step 20. Flush the feeding tube according to the manufacturer's instructions before giving a dose of OJEMDA.	
Step 21: Follow **Steps 1 to 11** in **Section A** to prepare OJEMDA using the 20 mL oral dosing syringe. Follow **Steps 12 to 17** in **Section A** to draw up your or your child's dose of OJEMDA using the ENFIT syringe and ENFIT adaptor.	

Step 22: Connect the 20 mL ENFIT syringe containing OJEMDA to the feeding tube.
Step 23: Apply steady pressure to the plunger to give the entire dose of OJEMDA through the feeding tube.
Step 24: Flush the feeding tube after giving each dose of OJEMDA according to the manufacturer's instructions. If 2 bottles are required, **repeat Step 21** and give the remainder of the dose right away.
Step 25: Go to **Section C** for instructions on "**How to throw away used bottles, expired or unused OJEMDA, and oral dosing syringes"**
Section C: How to throw away used bottles, expired or unused OJEMDA, and oral dosing syringes
• Throw away your used bottle(s), expired or unused OJEMDA, and oral dosing syringe(s) in your household trash. • **Do not** re-use the oral dosing syringe(s).
How should I store OJEMDA?
• Store the glass bottle containing OJEMDA for oral suspension at room temperature (15°C to 30°C). • **Keep OJEMDA for oral suspension and the oral dosing syringe out of the reach of children.**