PDL DRUG REVIEW

Proprietary Name: Ojemda®
Common Name: tovorafenib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Mekinist (trametinib)	Non-Recommended with Conditions
Tafinlar (dabrafenib)	Non-Recommended with Conditions

Pharmacology/Usage: Tovorafenib, the active ingredient of Ojemda®, is a kinase inhibitor. It is a Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases.

Indication: For the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Ojemda® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women. Advise pregnant women of the potential risk to a fetus. As Ojemda® can cause fetal harm when administered to a pregnant woman, verify pregnancy status in females of reproductive potential prior to starting Ojemda®. Advise females of reproductive potential to use effective nonhormonal contraception during treatment and for 28 days after the last dose. Ojemda® can render hormonal contraceptives infective. 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. The safety and efficacy of use in the pediatric population younger than 6 months of age have not been established.

Dosage Form:

- Film-Coated Tablets: 100mg. Do not chew, cut, or crush.
- Oral Suspension: 25mg/ml. After reconstitution, each ml of strawberry flavored tovorafenib suspension contains 25mg of tovorafenib. Each bottle delivers 300mg of tovorafenib in 12ml.

Recommended Dosage: Confirm the presence of BRAF fusion or rearrangement, or BRAF V600 mutation prior to the start of Ojemda® treatment. An FDA approved test for the detection of BRAF fusion or rearrangement, or BRAF V600 mutation in relapsed or refractory pediatric LGG is not currently available.

Before starting Ojemda®, assess liver function tests, including AST, ALT, and bilirubin.

The recommended dosage based on body surface area (BSA) is 380mg/m^2 PO QW (the maximum recommended dosage is 600mg PO QW) with or without food until disease progression or intolerable toxicity. Ojemda® may be administered as an immediate release tablet or as an oral suspension. A recommended dosage for patients with BSA less than 0.3m^2 has not been established. Refer to the prescribing information for further information.

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. If a dose is missed by 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.

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.

There are recommended dosage modifications for adverse reactions. Refer to the prescribing information for additional information.

Dosage adjustments are not recommended with mild hepatic impairment. Ojemda® has not been studied in patients with moderate to severe hepatic impairment. Dose adjustments are not recommended with mild to moderate renal impairment. Ojemda® has not been studied in patients with severe renal impairment.

Drug Interactions: Tovorafenib is a CYP2C8 substrate. Avoid the co-administration of Ojemda® with a strong or moderate CYP2C8 inhibitor.

Avoid the coadministration of Ojemda® with a strong or moderate CYP2C8 inducer.

Tovorafenib is a CYP3A inducer. Avoid the 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®.

Avoid the 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.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ojemda®) for all grades. There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included rash (77%), hair color changes (76%), dry skin (36%), dermatitis acneiform (31%), pruritus (26%), fatigue (55%), pyrexia (39%), edema (26%), viral infection (55%), upper respiratory tract infection (31%), paronychia (26%), vomiting (50%), constipation (33%), nausea (33%), abdominal pain (28%), diarrhea (22%), stomatitis (20%), headache (45%), hemorrhage (42%).

Listed % incidence for select laboratory abnormalities= reported % incidence for drug (Ojemda®) for all grades. There was no placebo data in the prescribing information to compare with. The most frequently reported laboratory abnormalities included decreased hemoglobin (90%), decreased lymphocytes (50%), decreased leukocytes (31%), increased lymphocytes (23%), decreased phosphate (87%), increased AST (83%), increased creatine phosphokinase (83%), increased LDH (73%), decreased potassium (51%), increased ALT (50%), increased bilirubin (22%), decreased albumin (24%), and decreased sodium (20%).

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

Ojemda® can cause rash, including maculopapular rash and photosensitivity. Monitor for new or worsening skin reactions and consider dermatologic consultation and initiate supportive care as clinically indicated. Withhold, reduce the dose, or permanently discontinue Ojemda® based on severity of adverse reactions. In addition, advise patients to use precautionary measures against ultraviolet exposure such as use of sunscreen, sunglasses, and/or protective clothing during Ojemda® treatment. Again, withhold, reduce the dose, or permanently discontinue Ojemda® based on severity of adverse reactions.

Ojemda® can cause hepatotoxicity. The median time to onset of increased ALT or AST was 14 days. Monitor liver function tests, including ALT, AST, and bilirubin, before the start of Ojemda®, one month after

initiation and then every 3 months thereafter and as clinically indicated. Withhold and resume at the same or reduced dose upon improvement, or permanently discontinue Ojemda® based on severity.

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

Based on nonclinical data in NF1 models without BRAF alterations, tovorafenib may promote tumor growth in patients with NF1 tumors. Confirm evidence of BRAF alteration prior to the start of Ojemda® treatment.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Day One Biopharmaceuticals, Inc.

Analysis: The efficacy of Ojemda® was assessed in a multicenter, open-label, single-arm study (FIREFLY-1), that included patients (N=76) 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.

All received Ojemda® approximately 420mg/m^2 PO QW per body surface area with a maximum dose of 600mg until disease progression or unacceptable toxicity. While the Ojemda® dosages administered during this study were between 290mg/m^2 and 476mg/m^2, the recommended Ojemda® dosage is 380mg/m^2 PO QW as 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 BRAV V600 mutation. Tumor assessments were performed every 12 weeks.

The efficacy population included patients who had measurable disease at baseline (N=76). The median age was 8.5 years (range 2 to 21 years), while 53% were male, 53% were white, and 93% had Karnofsky/Lansky performance status of 80 to 100. Patients received a median of 3 prior systemic regimens, and 45 patients (59%) received prior treatment with a MAP kinase pathway inhibitor.

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) determined 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. Efficacy results are presented in the table below, which was adapted from the prescribing information.

Efficacy Parameter	RAPNO-LGG N=76*
Overall Response Rate	
ORR	51%
CR, n (%)	0
PR, n (%)	28 (37%)
MR, n (%)	11 (14%)
Duration of Response (DoR) (N=39)	
Median, months	13.8
% with observed DoR ≥6 months	85%

Efficacy Parameter	RAPNO-LGG N=76*
% with observed DoR ≥12 months	23%

*At least one measurable lesion at baseline on RAPNO-LGG criteria

Among responders, the median time to response was 5.3 months. 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, the ORR was 53%, including 20 patients each with PR and MR, respectively.

Place in Therapy: 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. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). Confirm the presence of BRAF fusion or rearrangement, or BRAF V600 mutation prior to the start of Ojemda® treatment. An FDA approved test for the detection of BRAF fusion or rearrangement, or BRAF V600 mutation in relapsed or refractory pediatric LGG is not currently available. Before starting Ojemda®, assess liver function tests, including AST, ALT, and bilirubin. The efficacy of Ojemda® was assessed in an open-label, single-arm study that included patients required to have a relapsed or refractory pediatric LGG harboring an activating BRAF alteration based on local laboratory testing. The major efficacy outcome measure was ORR, which was 51%. Ojemda® is the first FDA-approved once weekly oral treatment for this indication.

Summary

It is recommended that Ojemda® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Recommended**
- ☒ **Non-Recommended with Conditions**

References

[1] Ojemda [package insert]. Brisbane, CA: Day One Biopharmaceuticals, Inc.; 2024.