swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ojemda

International non-proprietary name:	tovorafenib
Pharmaceutical form:	powder for oral suspension
Dosage strength(s):	Ojemda 25 mg/ml
Route(s) of administration:	oral
Marketing authorisation holder:	IPSEN Pharma Schweiz GmbH
Marketing authorisation no.:	70241
Decision and decision date:	temporary authorisation in accordance with Art. 9a TPA approved on 5 May 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)

TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for tovorafenib in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 19 June 2025.

Temporary authorisation for human medicinal products
The applicant requested temporary authorisation in accordance with Article 9*a* TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Ojemda is indicated as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have received one or more prior systemic therapy.

2.2.2 Approved indication

Ojemda is indicated for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, that has progressed after one or more prior systemic therapies.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The proposed recommended dose is 380 mg/m^2 orally once weekly (QW) according to body surface area (not to exceed 600 mg orally QW) to be taken with or without food. A recommended dose for patients with a body surface area (BSA) of less than 0.3 m^2 has not been established. The recommended duration of treatment with tovorafenib is until disease progression or loss of clinical benefit or unacceptable toxicity.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	3 June 2025
Formal control completed	6 June 2025
List of Questions (LoQ)	31 July 2025
Response to LoQ	28 November 2025
Preliminary decision	16 January 2026
Response to preliminary decision	6 April 2026
Final decision	5 May 2026
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

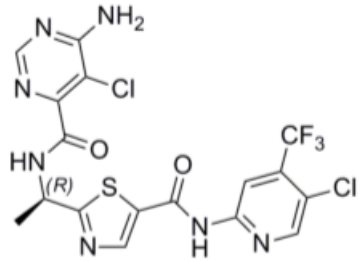
Paediatric low-grade gliomas (pLGGs) account for 30% of all childhood brain tumours. They are usually treated by surgical resection, chemotherapy and/or radiation, and generally have a favourable prognosis with a 10-year overall survival (OS) rate of 85–96%. Nevertheless, patients who relapse are at risk of severe comorbidity, including neurocognitive impairment, vision or hearing loss, endocrinopathies, or other complications that can result from traditional treatment.

The vast majority of pLGGs share alterations in the BRAF gene, including KIAA1549-BRAF fusion (observed in approximately 65% of cases) and BRAF V600E mutation (approximately 30%). These BRAF altered tumours are potentially life-threatening diseases with limited treatment options. Therefore, safe and effective treatment options are needed.

4 Quality aspects

4.1 Drug substance

INN: tovorafenib
Chemical name: 6-amino-5-chloro-N-[(1R)-1-[5-[[[5-chloro-4- (trifluoromethyl)-2-pyridinyl]amino]carbonyl]-2-thiazolyl]ethyl]-4-pyrimidinecarboxamide
Molecular formula: $C_{17}H_{12}Cl_2F_3N_7O_2S$
Molecular mass: 506.29 g/mol
Molecular structure:



Physicochemical properties:
Tovorafenib is a white to off-white powder with one stereogenic centre in the R-absolute configuration, non-hygroscopic and practically insoluble under physiological conditions (pH 1.2-8.0). It is present in its stable polymorph form A.

Synthesis:
The drug substance is manufactured by multiple-step chemical synthesis. The synthesis process involves amide bond formation steps and isolated intermediates. Adequate information is provided regarding the manufacturing process, materials, critical steps, and intermediates.

Specification:
The drug substance specification includes tests for appearance, identification, assay, chiral purity, chromatographic purity, water content, residual solvents, elemental impurities, residue on ignition, and microbial purity. The applied limits are justified and in line with the relevant guidelines and the European Pharmacopoeia, if applicable. The proposed acceptance criteria and analytical methods were considered appropriate for quality control of the drug substance.

Stability:
Appropriate stability data have been generated, resulting in a suitable retest period. Based on the results, a satisfactory retest period has been established when stored in double low-density

polyethylene (LDPE) bags with desiccant between the two LDPE bags and placed in high-density polyethylene (HDPE) drums.

4.2 Drug product

Description and composition:
The tovorafenib drug product is a powder for oral suspension. The drug product is a white to off-white powder in a glass bottle closed by a cap with a heat induction seal liner. The bottle is overfilled to allow delivery of 300 mg active strength. After reconstitution with 14 mL of water, the obtained suspension of 25 mg/mL active concentration is dosed with an oral syringe. The necessary 20 ml oral syringe and bottle adapter are provided in the commercial package.
In addition to the drug substance tovorafenib, the following excipients are present in the powder for oral suspension: Copovidone, cellulose, microcrystalline, mannitol, sodium lauryl sulphate, simethicone, maltodextrin, colloidal anhydrous silica, sucralose, artificial strawberry flavour.

Manufacture:
The drug product is manufactured using a controlled multi-step process.
An intermediate is used during manufacture.

Specification:
Adequate tests and acceptance criteria for release and shelf-life have been established for the control of the finished product and the reconstituted suspension, including appearance, identification, assay, syringeability, reconstitution time, content uniformity, enantiomer content, related substances, dissolution, water content, crystallinity, and microbial purity.

Stability:
Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines. A shelf-life was established on the basis of these data. The storage recommendation is “Store below 25°C and in the original package” and “Store out of reach of children”.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

For the review of the MAA for Ojemda, the Division Nonclinical Assessment conducted an abridged evaluation that was essentially based on the publicly available FDA assessment report (“NDA/BLA Multi-Disciplinary Review and Evaluation - NDA 217700 and 218033 - Tovorafenib (DAY101)”) provided by the applicant. Since the report on the carcinogenicity study in transgenic rasH2 mice was not part of the original submission to the FDA, a full assessment of that study was conducted by Swissmedic. Impurities and ERA were also subject to a full review.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Ojemda in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption

Tovorafenib is rapidly absorbed, with a median Tmax of 3 hours (1.5–4 hours).

Effect of food

A high-fat meal had no clinically relevant effect on Cmax or AUC, although Tmax was delayed to 6.5 hours, indicating that tovorafenib can be taken irrespective of food.

Dose proportionality

Tovorafenib exposure (Cmax and AUC) increases approximately proportionally with dose across the studied ranges (20–280 mg Q2D and 400–800 mg QW).

PK after multiple dosing

At steady state (reached after approximately 12 days), mean Cmax is 6.9 µg/mL and AUC is 508 µg·h/mL following 380 mg/m² QW dosing. Accumulation is minimal and not clinically relevant.

Distribution

The apparent volume of distribution for tovorafenib is 60 L/m² (23%), indicating distribution beyond the plasma compartment. *In vitro* plasma protein binding of tovorafenib is high, with approximately 97.5% bound to human plasma proteins.

Metabolism & elimination

Tovorafenib is primarily metabolised by aldehyde oxidase and CYP2C8, with minor contributions from CYP3A, CYP2C9, and CYP2C19.

After a single oral dose of radiolabelled tovorafenib, total radioactivity (parent drug and metabolites) was primarily recovered in faeces (65%) and to a lesser extent in urine (27%). Excretion of unchanged tovorafenib in urine was negligible (0.147%).

The terminal half-life is approximately 56 hours and apparent clearance is 0.7 L/h/m^2.

Special populations

No dedicated studies in renal or hepatic impairment were conducted. Population PK analysis (345 patients) showed that tovorafenib PK are adequately described by a 1-compartment model.

Only body surface area (BSA) and sex were identified as covariates, with BSA affecting clearance and volume, and males showing slightly higher clearance; however, these effects were not clinically relevant.

No clinically meaningful impact on exposure was observed for age (1–94 years), sex, race, or mild-to-moderate renal or mild hepatic impairment, nor for other investigated covariates. Significant uncertainty surrounds use in patients under 1 year of age due to the lack of PK data and incomplete understanding of metabolic maturation, which has led to the granting of temporary marketing authorisation pending the provision of additional data in patients aged 6 to 12 months.

Renal excretion of unchanged tovorafenib is negligible. No dose adjustment is necessary in patients with mild to moderate renal impairment or mild hepatic impairment. However, data are lacking in patients with severe renal impairment and in those with moderate or severe hepatic impairment.

Interactions
Effect of other drugs on tovorafenib
In vitro data
Tovorafenib is a CYP2C8 substrate.
Strong or moderate CYP2C8 inhibitors are expected to increase tovorafenib exposure, which may increase the risk of adverse reactions. Coadministration should be avoided.
Strong or moderate CYP2C8 inducers are expected to decrease tovorafenib exposure, which may reduce efficacy. Coadministration should be avoided.

Effect of tovorafenib on other drugs
Clinical data
Tovorafenib is a CYP3A inducer.
Tovorafenib may decrease the exposure of CYP3A substrates, which may lead to reduced efficacy. The steady-state maximum concentration (Cmax) and area under the curve (AUC) of midazolam, a CYP3A4 substrate, are predicted to decrease by at least 20% following coadministration with tovorafenib.

Implications:
Coadministration with hormonal contraceptives may result in contraceptive failure; therefore, it should be avoided or an additional nonhormonal contraceptive method should be used.
Coadministration with other sensitive CYP3A substrates should be avoided or patients should be monitored for reduced therapeutic effect.

Pharmacodynamics
Mechanism of action and primary pharmacology
Tovorafenib is a type II RAF kinase inhibitor that targets components of the MAPK signalling pathway, including BRAF and CRAF, and thereby inhibits tumour cell proliferation. Potent in vitro activity was demonstrated, with low nanomolar IC50 values against BRAF V600E, wild-type BRAF, and wild-type CRAF.

Secondary pharmacology (safety)
The effect of tovorafenib on cardiac repolarisation was evaluated. At the recommended dose of 380 mg/m² once weekly (not exceeding 600 mg), no mean increase in QT interval greater than 20 milliseconds was observed.

Exposure efficacy/safety relationship
Exposure to tovorafenib was positively associated with the occurrence of adverse events. Statistically significant correlations were identified between exposure levels (notably Cmin,ss or time-averaged exposure) and several toxicities, including skin rash (Grade ≥2/≥3), elevations in liver enzymes (ALT, AST), fatigue, anaemia, increased CPK, myalgia, ocular events, and overall treatment-emergent adverse events (TEAEs). Younger age was identified as an additional risk factor for certain toxicities (particularly skin rash, ALT, and CPK elevations).
Graphical analyses confirmed that higher exposure is associated with an increased risk of adverse events, including severe and serious events, suggesting that reducing exposure could improve the safety profile. A dose reduction from 420 to 380 mg/m² once weekly was estimated to decrease the risk of adverse events by 15–32%. This dose adjustment may also help mitigate the impact on growth in paediatric patients, especially if implemented early.
In contrast, no significant relationship was observed between tovorafenib exposure and efficacy outcomes (tumour response rate or change in tumour size based on various assessment criteria).

Exposure–safety analyses further confirmed specific associations: time-averaged exposure was linked to an increased risk of Grade ≥1 ocular events and facial oedema, while Cmin was associated with Grade ≥2 skin rash and Grade ≥3 adverse events. No correlation was found between exposure and serious adverse events.

Finally, a decrease in height-for-age z-scores was observed in treated children, particularly in younger patients and females. Modelling suggests that dose reduction may mitigate this effect and that growth recovery may occur after treatment discontinuation, although data remain limited.

6.2 Dose finding and dose recommendation

The proposed dose for the submitted indication is 380mg/m2 once weekly (not to exceed 600 mg). This dose was selected to optimise the benefit-risk profile. It was chosen based on a safety and efficacy analysis performed on data from FIREFLY-1, which support an improvement in safety with the 380mg/m2 dosage without compromising the overall response rate (ORR). The choice was further supported by the flat exposure-response (E-R) relationship for ORR that was observed across the different dosage ranges.

6.3 Efficacy

The applicant submitted FIREFLY-1 as the pivotal study for the current application.

FIREFLY-1 is an ongoing phase 2, multicentre, multi-arm, uncontrolled, open-label study evaluating tovorafenib in patients 6 months to 25 years of age, with relapsed or refractory (pLGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation (arm 1 and arm 2 [expansion cohort of arm 1]) and advanced solid tumours (arm 3). The efficacy analysis for this application was based on data from arm 1; arm 2 data supported this application.

This study included a 2-year treatment period during which all patients were treated with tovorafenib and a 3-year follow-up period (long-term extension) during which patients may continue treatment with tovorafenib or opt to enter a drug holiday. Patients continued to undergo routine radiographic evaluations during the drug holiday period. Re-treatment with tovorafenib was permitted upon clinical or radiographic evidence of disease progression. For further details regarding the included patient population and the study design, please refer to the attached Information for healthcare professionals.

The primary endpoint of arm 1 was overall response rate (ORR) as assessed by an independent radiology review committee (IRC) according to Response Assessment in Neuro-Oncology High-Grade Glioma (RANO-HGG) criteria. PFS (based on RANO-HGG and RAPNO criteria), ORR (based on RAPNO criteria), and OS were secondary endpoints.

A total of 137 patients were enrolled in arm 1 and 2 of the study (n=77 in arm 1 and n=60 in arm 2). Overall, their baseline characteristics reflected the disease under the study. Patients enrolled in this study were spread across all age groups (range: 11 months to 24 years), however, and, as would be expected for the disease, limited number of patients (n=3) were below 2 years of age. Arm 1 patients had a median age of 8 years (range: 2-21). The majority (72.7%) of these patients had a KIAA1549: BRAF fusion, while 16.9% of them had a BRAF V600E mutation. Please refer to the attached Information for healthcare professionals for additional details regarding demographics and baseline characteristics.

The results of the analysis supporting this application were submitted as per a data cut-off date of May 2024, which represents a median follow-up of 28 months.

As of this cut-off date, ORR was 71% (95% CI:58.8, 81.3) according to RANO-HGG and 52.6% (40.8, 64.2) according to the RAPNO criteria in arm 1. The median duration of response was approximately similar according to the response criteria (19.7 months, 18.0 months, and 16.8 months based on RANO-HGG, RAPNO, and RANO-LGG). Response rates were similar across subgroups defined by

BRAF alteration. For detailed efficacy results, please refer to the Information for healthcare professionals.

Uncertainties exist though for efficacy assessment in the lowest age group (<2 years of age) due to the limited number of patients (n=3) treated for a maximum of 20 months with a response ranging between stable and complete response based on investigator assessment as per RANO-HGG criteria.

6.4 Safety

The safety data are based on data collected for the 137 patients enrolled in arm 1 and 2 of the FIREFLY-1 study and treated with at least one dose of tovorafenib. These patients were treated for a median of 22 months.

Treatment emergent adverse events (TEAEs) were reported for all patients enrolled in arm 1 and 2 of the FIREFLY-1 study. The most common TEAEs (experienced by more than 40% of patients) were changes in hair colour (77.4%), increased creatine phosphokinase in the blood (62.0%), fatigue (60.6%), anaemia (60.6%), vomiting (56.2%), headache (52.6%), hypophosphatemia (52.6%), maculo-papular rash (50.4%), fever (46.7%), growth retardation (43.1%), and dry skin (40.9%).

Serious adverse events were reported for 55% of patients; at least one Grade ≥ 3 TEAEs were reported for 81.8% of patients; and Grade 4 TEAEs for 14.6% of patients.

TEAEs were generally managed by treatment interruption or dose reduction; 32.1% of patients experienced TEAEs leading to dose reduction, 65.7% experienced a TEAE leading to dose interruption. A total of 10.9% experienced TEAEs leading to discontinuation of treatment. The most common adverse event leading to a dose reduction of tovorafenib in > 5% of patients was maculopapular rash (5.1%). The most common reported adverse events leading to discontinuation of tovorafenib dose in > 5% of patients were fever (13.9%), maculopapular rash (10.2%), vomiting (10.2%), fatigue (5.8%), nausea (5.1%), headache (5.1%), and alanine aminotransferase (5.1%). Adverse events that resulted in permanent discontinuation of tovorafenib in more than one patient were tumour bleeding (2.9%) and growth retardation (2.9%).
A total of 8 death cases were reported in FIREFLY-1. These cases occurred across arms 1, 2, and 3 and included two deaths >30 days after the last dose of study treatment.
The events leading to death in arm 1 and 2 were: one case of brain death due to progressive disease (in arm 1), one grade 5 non-treatment-emergent AE of hydrocephalus (in arm 1), one case of unexplained death (in arm 1), one case of death due to progressive disease (arm 1), one case of grade 5 TEAE of tumour haemorrhage (in arm 2) and one case of grade 5 pneumonia (in arm 2). Tumour haemorrhage, anaemia and decrease in growth velocity were among the most frequent adverse events of special interest reported in FIREFLY-1; they occurred in 7.3%, 13.1% and 43.1% of patients, respectively.

The safety data is considered non-conclusive in the youngest patients due to the limited number of patients treated with the drug.

6.5 Final clinical benefit risk assessment

Paediatric LGG is a seriously debilitating disease, with a high unmet need and limited treatment options.

The non-randomised non-controlled FIREFLY-1 data from arm 1 has shown promising efficacy results in paediatric and young adult patients diagnosed with paediatric LGG (pLGG) and harbouring a BRAF alteration including BRAF mutations or BRAF fusions. However, only a limited number of patients below 2 years were included in this study, with response assessment based solely on RANO-HGG

criteria and assessed by the investigator, which limits the available evidence for efficacy in this age group.

The toxicity of tovorafenib is considered acceptable and manageable by treatment interruption or dose reductions. Nevertheless, considering the anticipated long-term use of the drug, additional safety data characterising the long-term impact of the drug on growth and development is needed and are requested as post-authorisation requirements.

Therefore, in view of the serious nature of pLGG, the unmet medical need, and the limited treatment options, the benefit-risk in the requested age group (6 months to 25 years) is considered positive for temporary authorisation, pending confirmation from the ongoing FIREFLY 2 study.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Ojemda was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼This medicinal product is subject to additional monitoring. This enables a fast identification of new findings regarding safety. Healthcare professionals are asked to report any suspected new or serious adverse reactions. Refer to section «Undesirable effects» for how to report adverse reactions.
OJEMDA has been authorised temporarily, see «Indications/Uses» section.

OJEMDA® film-coated tablets/powder for oral suspension

Composition

Active substances

Tovorafenib

Excipients

Powder for oral suspension: strawberry flavor (containing maltodextrin, triacetin, artificial flavour), colloidal silicon dioxide, copovidone K-28, maltodextrin, mannitol (E421), microcrystalline cellulose, simethicone, sodium lauryl sulfate, sucralose
One bottle contains max. 2.5 mg sodium.
Film-coated tablets: Colloidal silicon dioxide, copovidone K-28, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, orange film coating (Hypromellose, macrogol 8000, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172))
One film-coated tablet contains max. 8.46 mg sodium.

Pharmaceutical form and active substance quantity per unit

Powder for oral suspension: each bottle contains 300 mg tovorafenib once reconstituted. 1 ml of the reconstituted suspension contains 25 mg of tovorafenib. White to off white powder.

Immediate release film-coated tablets: each film-coated tablet contains 100 mg tovorafenib. Film-coated, oval tablets debossed with «100» on one side and «D101» on the opposite side.

Indications/Uses

OJEMDA is indicated for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, that has progressed after one or more prior systemic therapies.
This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

Dosage/Administration

Treatment with tovorafenib should be initiated and supervised by a qualified physician experienced in the use of anti-cancer medicinal products.

Before taking tovorafenib, patients must have confirmation of BRAF fusion, BRAF rearrangement, or BRAF V600 mutation by a validated test.

Dosage

The recommended dose of tovorafenib based on body surface area (BSA) is 380 mg/m^2 orally once weekly (the maximum recommended dose is 600 mg orally once weekly).

Tovorafenib 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
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).

Duration of treatment

Continue once weekly dosing until disease progression, loss of clinical benefit, or unacceptable toxicity (see «Clinical Efficacy»).

Missed or delayed doses

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.

Vomiting

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

Dose modifications

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

The recommended dose reductions for adverse reactions for tovorafenib tablets are provided in Table 3 and tovorafenib 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 tovorafenib are in Table 5.

Table 5: Recommended Dose Modifications for Adverse Reactions

Severity of ADR[a]	Dose Modification[b]
Hemorrhage and intratumoural haemorrhage	
• Intolerable Grade 2 • Grade 3	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider permanent discontinuation.
• First occurrence of any Grade 4	- Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider permanent discontinuation.

• Recurrent Grade 4	Permanent discontinuation.
Skin toxicity, including photosensitivity	
• Intolerable Grade 2 • Grade 3 or 4	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider permanent discontinuation.
Liver related events	
• Grade 3 AST or ALT • Grade 3 bilirubin	Withhold administration. 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 lower dosage.
• First occurrence of any Grade 4	Withhold administration. - If improved to Grade 0-1, resume at lower dosage. - If not improved, consider permanent discontinuation.
• Recurrent Grade 4	Permanent discontinuation.
Other adverse reactions	
• Intolerable Grade 2 • Grade 3	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider permanent discontinuation.
• Grade 4	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider discontinuation.

[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. Tovorafenib 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 Section «Pharmacokinetics»). Patients with moderate or severe hepatic impairment should be monitored carefully when treated with tovorafenib.

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. Tovorafenib has not been studied in patients with severe (eGFR <30 mL/min/1.73 m^2) renal impairment (see Section «Pharmacokinetics»).

Paediatric population

The safety and efficacy of tovorafenib in children below 6 months of age or Body Surface Area < 0.3 m^2 have not been evaluated in clinical studies. For children between 6 month - 2 year of age, limited safety and efficacy data are available (see sections «Undesirable Effects» and «Clinical Efficacy»).

Administration

OJEMDA is for oral use. The film-coated tablets and powder for oral suspension may be used interchangeably. For patients who are not able to swallow or with BSA less than 0.9 m2 the oral suspension should be provided. If the patient is unable to swallow and has a nasogastric tube in situ, the OJEMDA oral suspension can be administered via the tube.

OJEMDA may be taken with or without food (see Section «Pharmacokinetics») and should be taken at a regularly scheduled time once weekly.

OJEMDA should be administered to paediatric patients under adult supervision.

Tablets:

The tablets should be swallowed whole with water and must not be chewed, cut or crushed.

Powder for oral suspension:

OJEMDA powder must be reconstituted to the oral suspension prior to being dispensed. Prior to use of the oral suspension for the first time, caregivers (and if appropriate, patients) should be instructed 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 tovorafenib in 12 ml (25 mg/ml).

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.

Administer the oral suspension using the supplied oral dosing syringe (co-packaged) by mouth or through a feeding tube (not included, minimum 12 Charrière, polyurethan; compatibility shown) immediately after preparation per the Instructions for Use.

If the oral suspension is not administered within 15 minutes after preparation, instruct the patient to discard it. Delay in administration above 15 minutes could lead to gel formation.

Instructions on the reconstitution of OJEMDA powder for oral suspension are provided at the end of this Information for healthcare professionals and in the patient information.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section «Composition».

Warnings and precautions

Intratumoural haemorrhage

Intratumoural haemorrhage (including the term tumour haemorrhage and intracranial tumour haemorrhage) events have been reported very commonly in patients treated with tovorafenib (see Section «Undesirable effects»).

Patients and caregivers should be advised of the risk of intratumoural haemorrhage during treatment with tovorafenib. The risk of tumour haemorrhage may be increased with concomitant use of anticoagulants and antiplatelet therapy. Monitoring for signs and symptoms of haemorrhage and evaluation as clinically indicated should be done routinely. The occurrence of haemorrhagic events should be managed with dose interruption or treatment discontinuation (see section «Dosage/Administration»).

Other haemorrhage events

Hemorrhagic events have been reported very commonly in patients taking tovorafenib. If haemorrhage occurs, patients should be treated as clinically indicated (see Section «Undesirable effects»).

Patients and caregivers should be advised of the risk of hemorrhage during treatment with tovorafenib. The risk of haemorrhage may be increased with concomitant use of anticoagulants and

antiplatelet therapy. Monitoring for signs and symptoms of hemorrhage and evaluation as clinically indicated should be done routinely. The occurrence of haemorrhagic events should be managed with dose interruption, dose reduction or treatment discontinuation (see Section «Dosage/Administration»).

Effect on growth

Reductions in growth velocity have been reported very commonly in patients treated with tovorafenib. (see Section «Undesirable effects»). Patients and caregivers should be advised of the risk of effect on growth during treatment with Tovorafenib. Monitoring for growth and development should be done prior to initiation, routinely during and following discontinuation of treatment with tovorafenib (see Section «Dosage/Administration»).

Liver related events

Liver related events specifically increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin have been reported very commonly in patients treated with tovorafenib (see section «Undesirable effects»).

Monitoring of liver function tests including AST, ALT, bilirubin levels should be done prior to initiation, 1 month after initiation and routinely during treatment with tovorafenib. Treatment should be withheld and resumed at the same or reduced dose upon improvement, or permanently discontinued based on the severity (see section «Dosage/Administration»).

Skin toxicity, including photosensitivity

Rash, including photosensitivity events, have been reported very commonly in patients treated with tovorafenib (see Section «Undesirable effects»). Patients should be monitored for new or worsening skin reactions. Dermatologic consultation and initiation of supportive care should be considered as clinically indicated. Patients and caregivers should be advised of the risk of rash and photosensitivity during treatment with tovorafenib. The use of precautionary measures against ultraviolet exposure such as use of sunscreen (SPF ≥50), sunglasses, and/or protective clothing during treatment with tovorafenib is recommended. Treatment should be withheld, resumed at reduced dose, or permanently discontinued based on severity of adverse reaction (see Section «Dosage/Administration»).

Embryo-Fetal Toxicity and Women of childbearing potential/ Contraception in females and males

Based on findings from animal studies and its mechanism of action, OJEMDA may cause fetal harm when administered to pregnant women (see Section «Pregnancy, Lactation» and «Preclinical Data»). Accordingly, women of childbearing potential should undergo a pregnancy test before initiating tovorafenib treatment. Before initiating treatment in women of childbearing potential or in male patients with female partners of reproductive potential, appropriate advice on effective methods of contraception (inclusive non-hormonal methods) should be provided (see Section «Pregnancy, lactation»).

Neurofibromatosis type 1 (NF1) associated tumors

Based on nonclinical data in NF1 models without BRAF alterations, tovorafenib may promote tumor growth in patients with NF1-associated tumors (see Section «Properties/Effects»). Evidence of a BRAF alteration prior to initiation of treatment with tovorafenib must be confirmed.

Sodium

OJEMDA film-coated tablets contain less than 1 mmol sodium (23 mg) per film-coated tablet, i.e. essentially «sodium-free».
OJEMDA oral suspension contains less than 1 mmol sodium (23 mg) per bottle of OJEMDA, powder for oral suspension, i.e. essentially «sodium-free».

Interactions

In Vitro Studies
Effects of other medicinal products on tovorafenib
Tovorafenib is a substrate for the metabolizing enzyme CYP2C8.
Strong or Moderate CYP2C8 Inhibitors
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 (see Section «Pharmacokinetics»). Coadministration of tovorafenib with a strong or moderate CYP2C8 inhibitor should be avoided.
Strong or Moderate CYP2C8 Inducers
Strong or moderate CYP2C8 inducers are predicted to decrease tovorafenib exposure based on a mechanistic understanding of its elimination, which may reduce tovorafenib efficacy (see Section «Pharmacokinetics»). Coadministration of tovorafenib with a strong or moderate CYP2C8 inducer should be avoided.
Transporter systems

Tovorafenib is not a substrate of breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1 and OATP1B3. Tovorafenib has not been evaluated as a substrate of OAT1, OAT3, MATE1, MATE2-K and OCT2.

Effects of tovorafenib on other medicinal products
CYP3A Substrates
Tovorafenib is a CYP3A inducer. Coadministration of tovorafenib is expected to decrease exposure of certain CYP3A substrates, which may reduce the effectiveness of these substrates. Coadministration of tovorafenib with certain CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures should be avoided. If coadministration is unavoidable, monitor patients for loss of efficacy unless otherwise recommended in the product labeling for CYP3A substrates.

Coadministration of tovorafenib with hormonal contraceptives (CYP3A substrates) may render hormonal contraceptives ineffective (see Section «Pregnancy, lactation» and Section «Pharmacokinetics»). Coadministration of hormonal contraceptives with tovorafenib should be avoided. If coadministration is unavoidable, an additional effective nonhormonal contraceptive method must be used during coadministration and for 28 days following discontinuation of tovorafenib.

CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 substrates

Tovorafenib inhibits CYP2C8, CYP2C9, CYP2C19 and CYP3A, but does not inhibit CYP1A2, CYP2B6 and CYP2D6 at clinically relevant concentrations. Tovorafenib induces CYP2C8, CYP1A2, CYP2B6, CYP2C9 and CYP2C19 at clinically relevant concentrations. The clinical relevance of these findings is unknown. When tovorafenib is co-administered with medicinal products metabolised by these enzymes, appropriate monitoring is recommended.

Transporter Substrates

Tovorafenib may have the potential to inhibit BCRP, OATP1B1, OATP1B3 and MATE1. The clinical relevance of these findings is unknown. When tovorafenib is co-administered with medicinal products that are substrates of these transporters, appropriate monitoring is recommended.

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.

Pregnancy, lactation

Women of childbearing potential/ contraception in females and males

Women of childbearing potential should have a pregnancy test prior to starting treatment with tovorafenib.

Women of childbearing potential must use effective methods of contraception during therapy and for 28 days following discontinuation of tovorafenib. Tovorafenib may decrease the efficacy of hormonal contraceptives, and effective nonhormonal contraception should be used (see Section «Interactions»). Male patients with female partners of reproductive potential must use condoms and effective methods of contraception during treatment with tovorafenib and for 2 weeks after the last dose.

Pregnancy

There are no data on the use of tovorafenib in pregnant women. Animal studies have shown reproductive toxicity (see Section «Preclinical data»). Tovorafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus

Lactation

It is not known whether tovorafenib is excreted in human milk. A risk to the breastfed child cannot be excluded, therefore breastfeeding should be discontinued 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 Section «Preclinical Data»).

Effects on ability to drive and use machines

Tovorafenib has minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of tovorafenib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should be made aware of the potential for tovorafenib to cause fatigue, which may affect these activities.

Undesirable effects

Summary of the safety profile

The safety profile of tovorafenib is based on pooled data from 137 patients 6 months of age and older with relapsed or refractory paediatric LGG harboring a BRAF alteration in one clinical study (FIREFLY-1, Arm 1 and 2). The median duration of treatment was 22.5 months (range 0.7 to 32.1 months). The safety population characteristics were comprised of patients with a median age of 9 years (range 1 to 24 years); three (2%) patients were 6 months to < 2 years of age, 93 (68%) patients were 2 years to < 12 years of age, and 41 (30%) patients were >12 years of age.

The most common serious adverse drug reactions were growth retardation (6.6%), vomiting (6.6%), and tumor haemorrhage (5.1%).

The most common adverse reactions by individual MedDRA preferred term were hair color changes (77.4%), blood creatine phosphokinase increased (62.0%), fatigue (60.6%), anaemia (60.6%), vomiting (56.2%), headache (52.6%), hypophosphataemia (52.6%), rash maculo-papular (50.4%), pyrexia (46.7%), growth retardation (43.1%), dry skin (40.9%), aspartate aminotransferase increased (38.0%), blood lactate dehydrogenase increased (38.0%), nausea (37.2%), constipation (36.5%),

upper respiratory tract infection (35.8%), dermatitis acneiform (34.3%), epistaxis (32.1%), decreased appetite (29.9%), paronychia (29.9%).

The most commonly reported adverse reaction leading to dose reduction of tovorafenib in >5% of patients was rash maculo-papular (5.1%). The most commonly reported adverse reactions leading to dose interruption of tovorafenib in >5% of patients were pyrexia (13.9%), rash maculo-papular (10.2%), vomiting (10.2%), fatigue (5.8%), nausea (5.1%), headache (5.1%) and alanine aminotransferase increased (5.1%). Adverse reactions which resulted in permanent discontinuation of tovorafenib in more than one patient were tumor hemorrhage (2.9%) and growth retardation (2.9%).

Tabulated list of adverse reactions

Within the system organ class, the adverse reactions are listed by frequency using the following categories: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1 000, <1/100), rare (≥1/10 000 , <1/1 000), very rare (<1/10 000), not known (frequency cannot be estimated from the available data).

Table 6: Adverse drug reactions reported in paediatric LGG patients in the pivotal clinical study (n=137)

Infections and Infestations	
Very common	Upper respiratory tract infection (35.8%), paronychia (29.9%), viral infection (11.7%)
Blood and lymphatic system disorders	
Very common	Anaemia[a] (61.3%), lymphocyte count decreased (16.8%), white blood cell counts decreased (11.7%)
Common	Eosinophilia
Metabolism and Nutrition Disorders	
Very common	Decreased appetite (29.9%), hypokalaemia (28.5%), hypoalbuminemia (14.6%), hyponatremia (13.9%)
Nervous system disorders	
Very common	Headache (52.6%)
Eye disorders	
Common	Blepharitis, dry eye
Cardiac disorders	
Common	Ventricular arrythmia[b]
Vascular disorders	
Very common	Haemorrhage[c] (40.1%), intratumoural haemorrhage[d] (13.9%), flushing (10.2%)

Gastrointestinal disorders	
Very common	Vomiting (56.2%), nausea (37.2%), constipation (36.5%), abdominal pain[e] (29.2%), stomatitis[f] (28.5%), diarrhoea[g] (26.3%)
Hepatobiliary disorders	
Very common	Alanine aminotransferase (ALT) increased (24.8%), blood bilirubin increased (14.6%)
Skin and subcutaneous tissue disorders	
Very common	Rash[h] (83.2%), hair colour changes (77.4%), dry skin[i] (47.4%), dermatitis acneiform[j] (38.0%), pruritus (27.7%), skin discolouration[k] (20.4%), alopecia (20.4%), photosensitivity reaction (14.6%)
Musculoskeletal and connective tissue disorders	
Very common	growth retardation[l] (44.5%), pain in extremity (20.4%), myalgia (16.1%), arthralgia (13.9%)
General disorders	
Very common	Fatigue (60.6%), pyrexia (46.7%), oedema[m] (33.6%)
Investigations	
Very common	blood creatine phosphokinase (CPK) increased (62.0%), blood phosphorus decreased[n] (55.5%), aspartate aminotransferase (AST) increased (38.0%), blood lactate dehydrogenase (LDH) increased (38.0%), weight decreased (25.5%)

[a] Includes term haemoglobin decreased

[b] Includes term ventricular extrasystoles

[c] Includes terms epistaxis, contusion, gingival bleeding, haematoma, petechiae, gastrointestinal hemorrhage, haematemesis, haematochezia, lower gastrointestinal hemorrhage, purpura, subdural hemorrhage, vaginal hemorrhage

[d] Includes terms tumour haemorrhage, intracranial tumour haemorrhage

[e] Includes term abdominal pain upper

[f] Includes terms cheilitis, angular cheilitis, aphthous ulcer, mouth ulceration, lip ulceration

[g] Includes terms enterocolitis

[h] 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

[i] Includes terms chapped lips, lip dry, xeroderma

[j] Includes term acne

[k] Includes terms skin depigmentation, skin hyperpigmentation, skin hypopigmentation, melanocytic nevus

[l] Includes term growth failure

[m] Includes terms face oedema, swelling face, periorbital oedema, eye swelling, oedema peripheral, peripheral swelling, lip oedema, vulval oedema

[n] Includes term hypophosphataemia

Description of selected adverse reactions

Intratumoural haemorrhage (ITH)

In FIREFLY1, intratumoural haemorrhage (including terms tumour haemorrhage and intracranial tumour haemorrhage) were observed in 13.9% patients, 3.6% patients reported Grade ≥ 3 events, 0.7% patient reported a Grade 5 event. Tovorafenib was permanently discontinued due to ITH events in 2.9% of patients. The mean time to onset since initiating treatment with tovorafenib was 239.2 days (median: 206 days; range 23 -671 days) and the mean duration of the initial occurrence of ITH was 30.8 days (median: 19.5 days; range: 1 day to 88 days).

Other haemorrhage events

In FIREFLY-1 other haemorrhage events were observed in 40.1% of paediatric patients, with Grade ≥3 events occurring in 2.2%. The most frequent haemorrhagic event (epistaxis) was reported in 32.1% of patients and the majority were Grade 1. 1 patient had a Grade 3 event of epistaxis. The mean time to onset since initiating treatment with tovorafenib was 124.5 days (median: 77 days; range 4 -617 days), and the mean duration of the initial occurrence of haemorrhage was 78.1 days (median: 9 days; range: 1 day – 428 days).

Growth retardation

Patients treated with tovorafenib for up to 24 months showed reductions from baseline in Z-scores for height compared to age and sex-matched normative data, although children with paediatric LGG may be expected to have altered growth rates compared to children without cancer. In FIREFLY-1, growth retardation was reported in 44.5% of patients 18 years of age or younger. Growth retardation resulted in dose interruption in 5.1% of patients and dose reduction in 2.2% of patients. Among those patients who experienced growth retardation 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. Growth retardation resulted in permanent discontinuation in 2.9% of patients. Patients followed after interruption of treatment with tovorafenib showed recovery of growth velocity and increase in Z-scores.

Liver related events

In FIREFLY-1, increased ALT was reported in 24.8% of patients taking tovorafenib. Increased AST occurred in 38% of patients taking tovorafenib. Grade ≥3 elevations in ALT and AST were observed in 5.8% and 2.9% of patients, respectively. Additionally, increased bilirubin was reported in 14.6% of patients. The mean time to onset of increased ALT was 215.3 days (range 1 day – 672 days), increased AST was 123.4 days (range 12 –813 days), and increased bilirubin was 79.6 days (range 13 –645 days). Increased ALT leading to dose interruption occurred in 5.1% of patients and dose reduction in 1.5% of patients, and increased AST leading to dose interruption occurred in 2.9% of

patients, and dose reduction in 0.7% of patients. Increased bilirubin leading to dose interruption occurred in 0.7% of patients, with no dose reduction required in any patients.

Blood creatine phosphokinase (CPK) increased

In FIREFLY-1, 62.0% of patients reported events of CPK increased. 12.4% of patients reported Grade ≥ 3 events. All events were nonserious. Of those who reported an increase in CPK, the majority (61.2%), reported an increase within the first 4 weeks of initiation of tovorafenib. Some patients had multiple episodes. Increased CPK led to a dose interruption in 3.6% of patients. The mean time to onset since initiating treatment with tovorafenib was 98.5 days (median: 29 days; range: 4 – 701 days). The mean duration of the initial occurrence of the event was 238.4 days (median: 122 days; range: 8 – 926 days).

Anaemia

In FIREFLY-1, anaemia was reported in 61.3% of patients. 13.1% of patients reported anaemia events Grade ≥ 3. The majority of these patients (54.8%) reported an event of anaemia within 60 days of tovorafenib initiation. One patient experienced a serious event. No patients discontinued treatment due to anaemia; 2.2% of patient reported anaemia which required dose interruption or dose modification. The mean time to onset since initiating treatment with tovorafenib was 107.4 days (median: 57 days; range 8 -737 days) The mean duration of the initial occurrence of the anaemia was 207.1 days (median 89.5 days; range 1 day – 826 days).

Skin toxicity, including photosensitivity

In FIREFLY-1, rash occurred in 83.2% of patients. Most events were mild, with Grade ≥ 3 events reported in 12.4% of patients. Rash resulted in dose interruption in 16.1% of patients and dose reduction in 8.8% of patients, and 1 (0.7 %) patient discontinued treatment due to rash pruritic. The mean time to onset of rash since initiating treatment with tovorafenib was 87.6 days (median: 14.5 days; range 1 day – 617 days), and the mean duration of the initial occurrence of rash was 103 days (median: 43 days; range: 1 day - 777 days). Photosensitivity occurred in 14.6% of patients, including one Grade 3 event in a single patient (0.7%) and resulted in dose interruption in one patient (0.7%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no information on overdose with tovorafenib. If overdose occurs, tovorafenib 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 tovorafenib.

Properties/Effects

ATC code

L01EC04

Mechanism of action

Tovorafenib is a Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases, with IC_{50}-values of 7.1, 10.1, and 0.7 nM, respectively.

Tovorafenib exhibited antitumor activity in cultured cells and xenograft tumor models harboring BRAF V600E and V600D mutations. Tovorafenib also exhibited antitumor activity in a xenograft tumor model harboring a BRAF fusion. Preclinical studies in tumor models with BRAF alterations suggest that tovorafenib does not induce paradoxical activation of the mitogen-activated protein kinase (MAPK), as observed with type I BRAF inhibitors.

In vitro, tovorafenib increased phosphorylation of extracellular signal-regulated kinase (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%).

Pharmacodynamics

Exposure Response Relationships

Tovorafenib exposure is associated with reduction in height-for-age Z-scores in paediatric 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 Paediatric 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.

Clinical efficacy

The efficacy of tovorafenib was evaluated in paediatric patients 6 months of age and older in a phase II, multicenter, open-label, single-arm clinical study (FIREFLY-1 [Arm 1]). Eligible patients (n=76) were required to have relapsed or refractory paediatric 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) or patients with known or suspected diagnosis of neurofibromatosis type 1 (NF1) were excluded.

Patients received tovorafenib approximately 420 mg/m^2 orally once weekly (range: 290 to 476 mg/m^2, 0.76-1.25 times the recommended dose) according to body surface area with a maximum dose of 600 mg until disease progression, loss of clinical benefit, or unacceptable toxicity. Although the tovorafenib doses administered in FIREFLY-1 (Arm 1) were between 290 mg/m^2 to 476 mg/m^2, the recommended tovorafenib 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 paediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation (see Section «Dosage/Administration»).

Tumor assessments were performed every 12 weeks.

The primary endpoint was overall response rate (ORR) of patients assessed by independent review based on RANO-HGG (Response assessment in Neuro-Oncology for High-Grade Glioma) and criteria. The ORR was assessed by RAPNO-LGG as a secondary endpoint and by RANO-LGG as an exploratory endpoint. Additional efficacy outcome measures were assessed by the 3 response assessments.

The median age was 8.5 years (range 2 to 21 years); 14 patients were below 6 years old, 42 between 6 and 12 years old, 15 between 12 and 16 years old and 6 patients older than 16, and below 25 years old; 53% were male; 61% 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), including 22%, 26%, 21%, and 30% who received 1, 2, 3, and >3 prior systemic regimens, respectively. 46 patients (60%) 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%), cerebellum (7%), and

cerebral hemisphere (5%). 63 patients (83%) had a BRAF fusion or rearrangement, and 13 patients (17%) had a V600 mutation.

The median duration of treatment was 23.7 months (range 0.7 to 32.1 months). Per protocol, patients could also enter an optional drug holiday after completing 26 cycles of therapy/24 months of treatment and at the investigator discretion: 43% (33/76) patients were on a drug holiday, and 14% (11/76) patients remained on treatment. Out of the patients who entered a drug holiday, 3 patients (9.1%) were retreated with tovorafenib following clinical or radiographic evidence of disease progression. Efficacy results based on the 2-year follow-up period are shown in Table 7.

Table 7: Efficacy Results Based on Independent Review in FIREFLY-1 (Arm-1)

Efficacy Parameter	**RANO-HGG (primary endpoint) N=69***	**RAPNO-LGG N=76***
Best Overall Response		
Complete Response (CR), n (%)	16 (23,2%)	0 (0)
Partial Response (PR), n (%)	33 (47,8%)	29 (38,2%)
Minor Response (MR), n (%)	**NA**	11 (14,5%)
Stable disease (SD), n (%)	15 (21,7%)	22 (28,9%)
Overall Response Rate		
ORR (CR+PR+MR) 95% CI[a]	71,0% (58,8; 81,3)	52,6% (40,8; 64,2)
Clinical Benefit Rate (95% CI)[ab]	76,8 (65,1; 86,1)	57,9 % (46,0; 69,1)
Duration of Response	**N=49**	**N=40**
Median (95% CI)[c], Months	19,7 (13,7; NE)	18,0 (12,0; 22,8)
DoR rate at ≥12 months[c]	66,0%	65%
DoR rate at ≥24 months[c]	43,4%	25,6%
Progression-free survival (PFS)		

Median PFS (95% CI), Months	22,3 (16,5; 25,1)	16,6 (8,3; 17,1)

Abbreviations: RANO-HGG= Response Assessment in Neuro-Oncology for High-Grade Glioma; RAPNO-LGG= Response Assessment in Paediatric Neuro-Oncology for Low-Grade Glioma; NA= not applicable; CI= confidence interval, NE= not estimable.
*At least one measurable lesion by the relevant imaging criteria at baseline based on RAPNO-LGG and RAPNO-HGG criteria.
[a]Based on Clopper-Pearson exact confidence interval.
[b]Based on CR, PR or stable disease lasting ≥12 months for RANO-HGG criteria. Based on CR, PR, MR or stable disease lasting ≥12 months for RAPNO-LGG criteria.
[c]Based on Kaplan-Meier estimate.

Based on RANO-HGG criteria, among responders, the median time to response was 5.3 months (range 2.6 – 19.4). The ORR was 74,6% among patients with BRAF fusion or rearrangement (n=59), and 50% among patients with BRAF V600E mutation (n=10), respectively. The ORR was 73% among patients who had received prior MAPK-targeted therapy (n=41), and 67,9% among patients who had not received prior MAPK-targeted therapy (n=28).

Based on RAPNO-LGG criteria, among responders, the median time to response was 5.4 months (range 1.6, 17.5). The ORR was 53% (95% CI: 40.2, 65.7) among patients with BRAF fusion or rearrangement (n=64), and 50% (95% CI: 21.1, 78.9) among patients with BRAF V600E mutation (n=12), respectively. The ORR was 51% (95% CI: 35.8, 66.3) among patients who had received prior MAPK-targeted therapy (n=45), and 55% (95% CI: 36.0, 72.7) among patients who had not received prior MAPK-targeted therapy (n=31). The median DOR was 16.6 months (95% CI 11.3, 19.4) for patients who had received prior MAPK-targeted therapy (n=45), and 22.8 months (95% CI 8.4, -) for patients who had not received prior MAPK-targeted therapy (n=31).

Based on RANO-LGG (2011) criteria (n=76), the ORR was 54% [95% CI: (42, 65)], including 23 patients with PR and 18 patients with MR. 22 patients (29%) had stable disease.

3 patients between 11 months and 2 years of age were treated with tovorafenib in Arm-2 had best overall response as stable disease, complete response and partial response (each n=1) respectively based on RANO-HGG criteria assessed by the investigator.

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*.

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 0.7 L/h/m^2 (31%). Following a single oral dose of radiolabeled tovorafenib, 66.1% of the total radiolabeled dose was recovered in the feces (8.6% unchanged) and 28.7% of the dose was recovered in the urine (0.2% unchanged).

Special populations
Paediatric population

No clinically significant differences of tovorafenib were observed based on age (range: 1 to 94 years). C_{max} and AUC in paediatric patients aged 11 months to 17 years were within the range of values observed in adults given the same dose per body surface area.

Renal impairment

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 m2) renal impairment.

Hepatic impairment

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) (see Section «Dosage/Administration»).

Race

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).

Gender

No clinically significant differences in the pharmacokinetics of tovorafenib were observed based on sex.

Preclinical data

Mutagenicity

Tovorafenib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay. *In vitro,* tovorafenib induced chromosomal aberrations in cultured human lymphocytes only with metabolic activation at the highest concentration accompanied by precipitates. Tovorafenib was not genotoxic in an *in vivo* rat bone marrow micronucleus assay. Overall, tovorafenib is therefore not considered to be genotoxic.

Carcinogenicity

Tovorafenib was not carcinogenic in a 26-week (or 6-month) study in transgenic mice at exposures approximately 0.6-fold the human exposure (AUC) at the recommended human dose. A 2-year carcinogenicty rat study is ongoing.

Reproduction toxicity

In an embryofetal development study in pregnant rats, total litter loss due to early resorptions was observed in all animals at doses ≥37.5 mg/kg/day (approximately 0.8-fold the human exposure at the recommended dose based on AUC).

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

Other information

Shelf life

Do not use this medicine after the expiry date marked as «EXP» on the pack.

Special precautions for storage

Keep out of reach of children.
Powder for oral suspension:
Do not store above 25°C and in original pack.
The bottle is made of glass. This medicine should not be used if the bottle is broken, damaged or if the safety seal under the cap is broken or missing.
Use reconstituted oral suspension within 15 minutes of preparation. Delay in administration above 15 minutes could lead to gel formation.
Film-coated Tablets:
Do not store above 25°C and in original pack.
Tablets should not be removed from blisters until immediately before use.

Authorisation number

70241, 70260 (Swissmedic)

Packs

Powder for oral suspension:
1 bottle (300 mg): Clear glass bottle with a child-resistant screw cap, co-packaged with a press-in bottle adaptor and a 20 ml oral dosing syringe in a pack [A]
Film-coated tablets:

16 film-coated tablets: 4 blister cards (4 tablets each) per pack. [A]

20 film-coated tablets: 4 blister cards (5 tablets each) per pack. [A]

24 film-coated tablets: 4 blister cards (6 tablets each) per pack. [A]

Marketing authorisation holder

IPSEN Pharma Schweiz GmbH, Zug

Date of revision of the text

January 2026

OJEMDA Powder for oral suspension – Instructions for Reconstitution

The Instructions for Reconstitution should be read carefully each time before preparing a dose of OJEMDA.

The doctor or pharmacist should show the patient or the caregiver how to prepare, measure and give a dose of OJEMDA correctly. The reconstitution can be given orally or with a nasogastric tube (polyurethan; compatibility shown) with a **minimum size** of 12 Charrière using a ENFIT syringe.

OJEMDA powder for oral suspension is to be reconstituted as follows:

Note: if more than one bottle is needed for the prescribed dose, bottles should be constituted one by one.

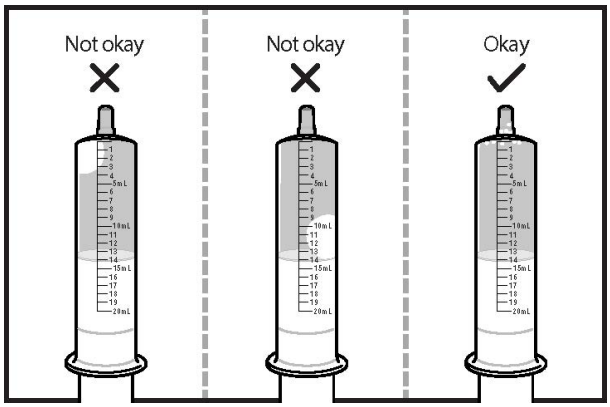
This procedure should be performed on a clean and flat work surface with clean hands.

Step 1: Fill a cup half-way with room temperature water. **Do not use cold water.**

Step 2: Pull up on the plunger of the oral dosing syringe to draw water until the 14 ml mark.

Step 3: 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 draw up the water again to the **14 ml** mark. **Repeat this step** until there are no large air bubbles present. Small air bubbles are fine (see Figure 1).

Figure 1



Step 4: Open the bottle with powder by pushing down firmly on the cap and turning it to the left (counterclockwise). Do not use the product if the bottle is broken, damaged or if the safety seal under the cap is broken or missing. **Do not** throw away the cap.

Step 5: Using the oral dosing syringe, inject exactly 14 ml of water into the bottle (see Figure 2). 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.

Turn bottle upside down to check for any powder stuck to the inside of the bottle (see Figure 3). 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.** If you still see powder in the bottle, ask for a new bottle.

Figure 2

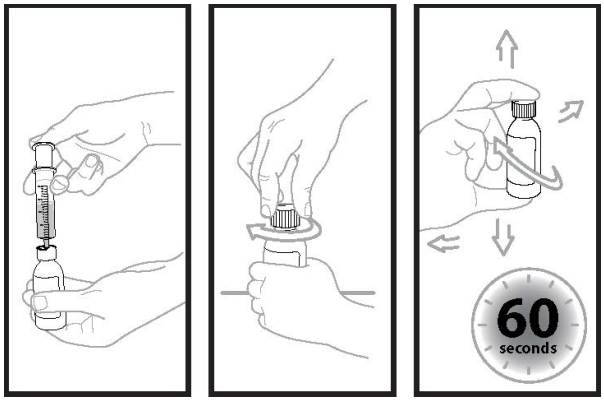
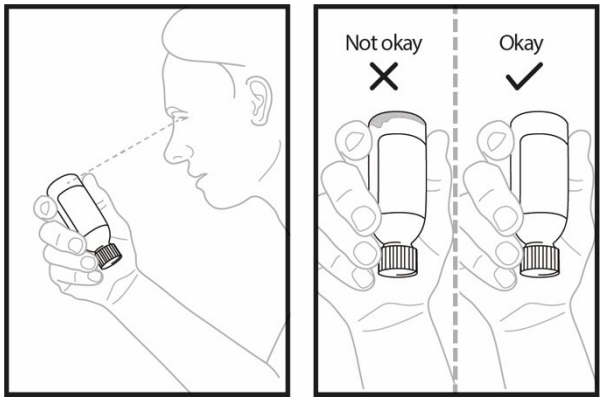


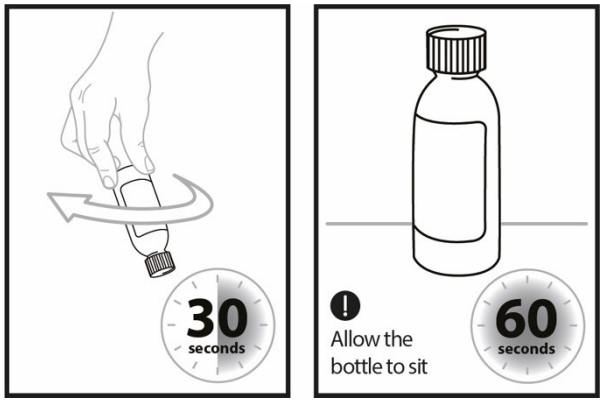
Figure 3



Step 6: Turn the bottle upside down again and swirl for 30 seconds (see Figure 4). Remove the cap and check that no solids are stuck in the bottle neck. If you see solids in the bottle neck when removing the cap, 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.

Figure 4



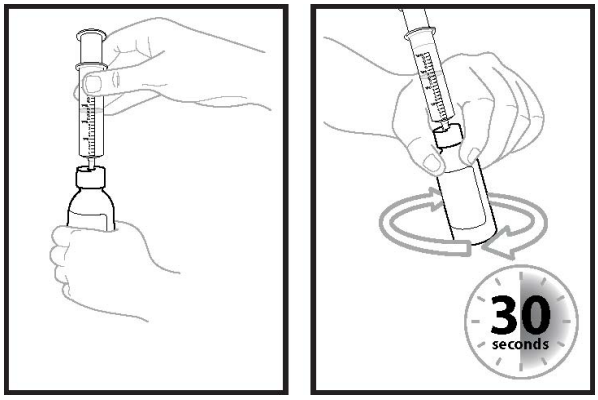
Step 7: Firmly insert the bottle adaptor into the bottle by pushing it tightly into the top of the bottle. The top edge of the bottle adaptor should be even with the bottle top.

Do not remove the bottle adaptor after it is inserted into the bottle.

Step 8: Check the prescribed dose in millilitres (ml). Draw air into the oral dosing syringe by pulling the plunger out until the prescribed dose is reached.

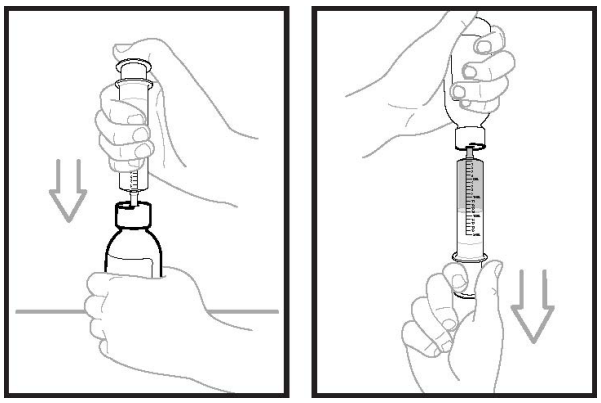
Step 9: Insert the tip of the oral dosing syringe into the bottle adaptor. The tip of the oral dosing syringe should fit snugly into the hole of the bottle adaptor. With the oral dosing syringe in place and holding the bottle where the oral dosing syringe tip inserts into bottle adaptor, swirl the oral suspension for 30 seconds (see Figure 5).

Figure 5



Step 10: Inject the air from the oral dosing syringe into the bottle (see Figure 6). Hold the oral dosing syringe in place and turn the bottle upside down. To measure the prescribed 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 millilitres.

Figure 6



Step 11: While the syringe is still inserted into the adapter in the bottle, remove any air bubbles in the oral dosing syringe by gently pushing the OJEMDA back into the bottle and then pulling down on the plunger again to draw up your prescribed dose.
Repeat this step until you see that few or no air bubbles remain or if you draw up the wrong dose in the oral dosing syringe. Only use up to 12 ml of OJEMDA from each prepared bottle.
Step 12: Leave the tip of the oral dosing syringe in the bottle adaptor and carefully turn the bottle upright. Put the bottle onto a flat work surface again. Slowly remove the oral dosing syringe tip from the bottle adaptor by gently pulling straight up. **OJEMDA is ready for administration.**