

Summary of the Risk Management Plan (RMP)

Name of the medicinal product:	OJEMDA
Active substance:	Tovorafenib
Version number of the current RMP:	1.0
Name of the marketing authorisation holder:	Ipsen Pharma Schweiz GmbH
Date of RMP:	27 February 2026

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of OJEMDA is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittel information / Information sur le médicament” approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of OJEMDA in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Ipsen Pharma Schweiz GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of OJEMDA.

Summary of Risk Management Plan for OJEMDA (tovorafenib)

This is a summary of the RMP for tovorafenib. The RMP details important risks of tovorafenib, how these risks can be minimised and how more information will be obtained about tovorafenib's risks and uncertainties (missing information).

Tovorafenib's Summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how tovorafenib should be used.

This summary of the RMP for tovorafenib should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of tovorafenib RMP.

I. The Medicine and What is it Used for

Tovorafenib is authorised for treatment of patients 6 months of age and older with paediatric low-grade glioma harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies. Tovorafenib is the active substance and it is given orally.

Further information about the evaluation of tovorafenib's benefits can be found in EPAR, including in its plain-language summary, available on the European Medicines Agency website under the medicine's webpage Medicines European Medicines Agency (europa.eu).

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of tovorafenib, together with measures to minimise such risks and the proposed studies for learning more about tovorafenib's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update reports (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of tovorafenib is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of tovorafenib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of tovorafenib. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information

Important identified risks	<ul style="list-style-type: none"> • Growth retardation • Intratumoral haemorrhage
Important potential risks	<ul style="list-style-type: none"> • Decreased fertility risk
Missing information	<ul style="list-style-type: none"> • Long-term safety

II.B Summary of Important Risks

Important identified risk, Important potential risk and Missing information

Important identified risk: Growth retardation	
Evidence for linking the risk to the medicine	<p>Paediatric patients treated with tovorafenib in study FIRFELY-1 tended to have lower than expected annualised growth velocity relative to normative curves in age- and gender-matched children without cancer. Patients' height percentiles tended to decrease overtime when plotted on the US Centres for Disease Control and Prevention normative growth charts.</p> <p>As of the data cutoff date, 61 (44.5%) patients in Arms 1 and 2 of FIREFLY-1 from 24 different study sites have reported TEAEs of decrease in growth velocity. Three (2.2%) patients had dose reduction, seven (5.1%) patients had dose interruption, and four (2.9%) patients permanently discontinued tovorafenib treatment due to decrease in growth velocity. Forty-five (32.8%) patients had decrease in growth velocity considered CTCAE Grade 3, and 1 (0.7%) patient had CTCAE Grade 4.</p> <p>In Arms 1 and 2 of the FIREFLY-1, the most commonly reported Grade ≥ 3 TEAE in children was growth retardation (32.1% patients). The growth retardation was one of the most commonly reported treatment related SAEs reported in nine patients. Decrease in growth velocity (PT: Growth retardation) was more commonly reported as serious and treatment related among younger patients (14.8%, 6.1%, 3.8%, and 0% among patients ages 2 to <6 years, 6 to <12 years, 12 to <16 years and 16 to ≤ 25 years, respectively). Four patients withdrew from the study as a result of growth retardation. Three patients had TEAEs of growth retardation leading to dose reduction. Six patients had TEAEs of growth retardation leading to dose interruption.</p>
Risk factors and risk groups	Patients ≤ 18 years of age.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL section 4
Additional pharmacovigilance activities	None
Important identified risk: Intratumoral haemorrhage	
Evidence for linking the risk to the medicine	While spontaneous tumour haemorrhages are known to occur commonly in high grade gliomas [Fehler! Verweisquelle konnte nicht gefunden werden.], intratumoral haemorrhage is also reported to occur in low-grade pilocytic astrocytomas in 8 to 20% of cases [Fehler! Verweisquelle konnte nicht gefunden werden. , Fehler! Verweisquelle konnte nicht gefunden werden. , Fehler! Verweisquelle konnte nicht gefunden werden.].

	<p>gefunden werden.,Fehler! Verweisquelle konnte nicht gefunden werden.].</p> <p>As of the clinical cutoff date, 20 (14.6%) patients in Arms 1 and 2 of FIREFLY-1 have reported events meeting search criteria for intratumoral haemorrhage. No patients had dose reduction, five (3.6%) patients had dose interruption and four (2.9%) patients, including three patients with Grade 1 intratumoral haemorrhage, permanently discontinued tovorafenib treatment due to intratumoral haemorrhage events. Two (1.5%) patients had maximum CTCAE Grade 3 serious events, of which one was considered treatment related (leading to interruption and ultimately discontinuation of tovorafenib) and the other as not related (with no change in study treatment). Three (2.2%) subjects (including the subject with the event of subdural haemorrhage) had maximum CTCAE Grade 4 serious events and one subject had a fatal (Grade 5) event. The fatal case involved a 14-year-old subject in Arm 2 who had a serious TEAE of Grade 4 tumour haemorrhage on Day 226, which worsened to Grade 5 on Day 239, 21 days after the last dose of tovorafenib. The event was noted by the investigator to be attributable to disease progression and considered not related to tovorafenib treatment.</p>
Risk factors and risk groups	<p>Review of all reported events found them to be consistent in frequency and severity with the natural history of pilocytic astrocytomas in this population [Fehler! Verweisquelle konnte nicht gefunden werden.,Fehler! Verweisquelle konnte nicht gefunden werden., Fehler! Verweisquelle konnte nicht gefunden werden., Fehler! Verweisquelle konnte nicht gefunden werden.,Fehler! Verweisquelle konnte nicht gefunden werden.,Fehler! Verweisquelle konnte nicht gefunden werden.]. Several factors such as tumour vascularity, prior radiation, and age at first radiation can contribute to the risk of intratumoral haemorrhage [Fehler! Verweisquelle konnte nicht gefunden werden.,Fehler! Verweisquelle konnte nicht gefunden werden.]. Case series to date have been limited to identification of spontaneous tumour haemorrhage either at the time of resection, as a presenting characteristic, or prior to any surgical intervention on the tumour. While some risk factors are identified among the literature, there are no case series exploring the prevalence of tumour haemorrhage among patients with relapsed or refractory paediatric low-grade glioma, particularly those who are as heavily pretreated as the FIREFLY-1 population. Important recognised risks predisposing this high-risk population to intratumoral haemorrhage include having had one or more tumour resections, non-pilocytic histology, leptomeningeal or disseminated disease, and treatment with multiple therapeutic regimens including vascular endothelial growth factor receptor inhibitors.</p>
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>SmPC sections 4.4 and 4.8.</p> <p>PL section 4.</p>
Additional pharmacovigilance activities	None
Important potential risk: Decreased fertility risk	
Evidence for linking the risk to the medicine	In a fertility and early development study in mature rats, female rats were administered the vehicle control article or tovorafenib

	beginning 14 days before cohabitation with untreated males, during cohabitation, and continuing until gestation Day 6. In treated female rats mated with untreated males, there were tovorafenib-related effects on female fertility parameters which were evident as fewer pregnancies, corpora lutea, implantation sites, and live embryos. For male rats treated until Day 64, fewer pregnancies, corpora lutea, implantation sites, live embryos and increased post-implantation loss occurred at all doses. Ovarian weights and numbers of estrous cycles were unaffected and there were no macroscopic abnormalities observed at necropsy evaluation at any dose level. In repeat- dose toxicology studies in rats of up to three months duration, 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 approximately 0.3-fold the human exposure at the recommended dose based on AUC.
Risk factors and risk groups	Males and females of reproductive potential
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.6 and 5.3. PL section 2.
Additional pharmacovigilance activities	None
Missing information: Long-term safety	
Risk minimisation measures	None
Additional pharmacovigilance activities	None

Abbreviations: AUC=area under the curve; CTCAE=common terminology criteria for adverse events; PL=package leaflet; PT=preferred term; RAF=rapidly accelerated fibrosarcoma; SAE=serious adverse event; SmPC=summary of product characteristics; TEAE=treatment-emergent adverse event; US=United States.

II.C Post-authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation in European Union (EU)

The following study is a condition of the marketing authorisation:

DAY101-002: LOGGIC/FIREFLY-2

Study short name and title:

A Phase III, Randomised, International Multicenter Trial of DAY101 Monotherapy Versus Standard of Care Chemotherapy in Patients with Paediatric Low-Grade Glioma Harbouring an Activating RAF Alteration Requiring First-Line Systemic Therapy

Purpose of the Study:

To compare the ORR, event-free survival, assessed per response assessment in paediatric neuro-oncology criteria by IRC of tovorafenib monotherapy versus standard of care chemotherapy in patients with paediatric LGG harbouring an activating RAF alteration requiring first-line systemic therapy.

To compare the OS of tovorafenib monotherapy versus standard of care chemotherapy.

LTFU period that includes a 30-day safety follow-up visit. Upon completion of the treatment phase (including EOT visit), ongoing safety, disease stability/progression, survival status, and subsequent anticancer therapies will be assessed in the LTFU period. For each patient, study participation is up to five years, inclusive of the Treatment phase and a LTFU period.

II.C.2 Other studies in post-authorisation development plan

There are no other studies required for tovorafenib.