ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ojemda 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg tovorafenib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Orange, oval film-coated tablets (16 mm in length and 9 mm width) debossed with “100” on one side and “D101” on the opposite side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 progressed after one or more prior systemic therapies (for biomarkers-based patient selection, see section 4.2).

4.2 Posology and method of administration

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

Patient selection

Before taking tovorafenib, patients must have confirmation of BRAF fusion or rearrangement, or BRAF V600 mutation assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, confirmation of BRAF fusion or rearrangement, or BRAF V600 mutation should be assessed by an alternative validated test.

Posology

The recommended dose of tovorafenib based on body surface area (BSA) is 380 mg/m^2 once weekly. The maximum recommended dose is 600 mg once weekly (see Table 1).
Ojemda may be administered as an immediate release tablet (see Table 1) or as an oral suspension (see tovorafenib 25 mg/ml powder for oral suspension SmPC).
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

Body surface area	**Recommended dose** (once weekly)
0.30-0.89 m^2	See tovorafenib powder for oral suspension SmPC
0.90-1.12 m^2	400 mg
1.13-1.39 m^2	500 mg
≥ 1.40 m^2	600 mg

Duration of treatment
Treatment with tovorafenib should be continued once weekly until disease progression, loss of clinical benefit, or unacceptable toxicity.

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 4 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 2.

Table 2: Recommended dose reductions for adverse reactions

Body surface area	**First dose reduction**	**Second dose reduction**
0.30-1.12 m^2	Administer the oral suspension once weekly (see tovorafenib powder for oral suspension SmPC)	Administer the oral suspension once weekly (see tovorafenib powder for oral suspension SmPC)
1.13-1.39 m^2	400 mg once weekly	Administer the oral suspension once weekly (see tovorafenib powder for oral suspension SmPC)
≥ 1.40 m^2	500 mg once weekly	400 mg once weekly

The recommended dose modifications for adverse reactions for tovorafenib are in Table 3.

Table 3: Recommended dose modifications for adverse reactions

Severity of ADR[a]	Dose modification[b]
Haemorrhage 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 2 for recommended dose reductions.

Special populations

Hepatic impairment
No dose adjustment is recommended for patients with mildly abnormal liver function tests (defined as bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or bilirubin > 1x to 1.5x ULN and any AST). Tovorafenib has not been studied in patients with moderately abnormal liver function tests (defined as bilirubin > 1.5x to 3x ULN and any AST) or severely abnormal liver function tests (defined as bilirubin > 3x ULN and any AST) (see section 5.2). Patients with moderately or severely abnormal liver function tests 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 5.2).

Paediatric population
Tovorafenib paediatric clinical experience is limited, particularly in the specific age range 6 months to 2 years. The safety and efficacy of tovorafenib in children below 6 months of age have not been established. No data are available.

Method of administration

Ojemda is for oral use.
The tablets should be swallowed whole with water and must not be chewed, cut, or crushed.
Ojemda can be taken with or without food (see section 5.2). and should be taken at a regularly scheduled time once weekly.
Ojemda should be administered to paediatric patients under adult supervision.

The film-coated tablets and powder for oral suspension may be used interchangeably (see tovorafenib powder for oral suspension SmPC). For patients who are not able to swallow or with BSA less than 0.9 m^2 the oral suspension should be provided (see tovorafenib powder for oral suspension SmPC).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Intratumoural haemorrhage

Intratumoural haemorrhage (including the terms tumour haemorrhage and intracranial tumour haemorrhage) events have been reported very commonly in patients treated with tovorafenib (see section 4.8). 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 4.2).

Other haemorrhage events

Haemorrhagic events have been reported very commonly in patients taking tovorafenib. If haemorrhage occurs, patients should be treated as clinically indicated (see section 4.8). Patients and caregivers should be advised of the risk of haemorrhage 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 haemorrhage, 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 4.2).

Effect on growth

Reductions in growth velocity have been reported very commonly in patients treated with tovorafenib (see section 4.8). 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.

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 4.8).
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 4.2).

Skin toxicity including photosensitivity

Rash, including photosensitivity events, have been reported very commonly in patients treated with tovorafenib (see section 4.8). 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 $\geq$ 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 4.2 and section 4.8).

Women of childbearing potential/ Contraception in females and males

Before initiating treatment in women of childbearing potential, appropriate advice on effective methods of contraception should be provided. Women of childbearing potential must use effective non-hormonal contraception such as a barrier method during therapy and for 28 days after the last dose of tovorafenib (see section 4.5 and section 4.6). Male patients with female partners of reproductive potential must use condoms and effective contraception during treatment with tovorafenib and for 2 weeks after the last dose (see section 4.6).

Neurofibromatosis type 1(NF1) associated tumours

Based on non-clinical data in NF1 models without BRAF alterations, tovorafenib may promote tumour growth in patients with NF1-associated tumours (see section 5.3). Evidence of a BRAF alteration prior to initiation of treatment with tovorafenib should be confirmed.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg film-coated tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on tovorafenib

Tovorafenib is a substrate for the metabolising 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 5.2). Coadministration of tovorafenib with a strong or moderate CYP2C8 inhibitor (e.g. gemfibrozil) 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 5.2). Coadministration of tovorafenib with a strong or moderate CYP2C8 inducer (e.g. carbamazepine) should be avoided.

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 (see section 5.2). Coadministration of tovorafenib with certain CYP3A substrates (e.g. tacrolimus) where minimal concentration changes may lead to serious therapeutic failures should be avoided. If coadministration cannot be avoided, monitor patients for loss of efficacy unless otherwise recommended in the SmPC for CYP3A substrates.

Coadministration of tovorafenib with hormonal contraceptives (CYP3A substrates) may render hormonal contraceptives ineffective (see sections 4.4, 4.6 and 5.2). Coadministration of hormonal contraceptives with tovorafenib should be avoided. If coadministration cannot be avoided, an additional effective non-hormonal contraceptive method must be used during coadministration and for 28 days following discontinuation of tovorafenib.

CYP1A2, CYP2B6, CYP2C8 and CYP2C9 substrates
In vitro data indicated that tovorafenib may have the potential to induce CYP1A2 and CYP2B6 and to inhibit CYP2C8, CYP2C9. The clinical relevance of these findings is unknown. When tovorafenib is co-administered with medicinal products metabolised by these enzymes, appropriate monitoring is recommended

Transporters substrates
In vitro data indicated that 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.

4.6 Fertility, pregnancy and 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 non-hormonal contraception such as a barrier method should be used (see section 4.5). 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 5.3). Tovorafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. Pregnant women should be advised of the potential risk to a foetus. If a patient becomes pregnant while taking tovorafenib, the patient should be informed of the potential hazard to the foetus.

Breastfeeding

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 and may not be reversible (see section 5.3).

4.7 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.

4.8 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 harbouring 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); 3 (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 adverse drug reactions by individual MedDRA preferred term were hair colour changes (77.4%), blood creatine phosphokinase increased (62.0%), fatigue (60.6%), anaemia (60.6%), vomiting (56.2%), hypophosphataemia (52.6%), headache (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%) and paronychia (29.9%).

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

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 growth retardation (2.9%) and tumour haemorrhage (2.9%).

Tabulated list of adverse reactions

Adverse reactions reported in patients treated with tovorafenib monotherapy in FIREFLY-1 (n=137) are listed in Table 4. Adverse reactions are listed below by MedDRA body system organ class and the following frequency convention: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse drug reactions reported in paediatric LGG patients in FIREFLY-1 (n=137)

Infections and infestations	
Very common	Upper respiratory tract infection, paronychia, viral infection
Blood and lymphatic system disorders	
Very common	Anaemia[a]
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypokalaemia, hypoalbuminemia, hyponatraemia
Nervous system disorders	
Very common	Headache
Eye disorders	
Common	Blepharitis, dry eye
Vascular disorders	
Very common	Haemorrhage[b], intratumoural haemorrhage[c], flushing
Gastrointestinal disorders	
Very common	Vomiting, nausea, constipation, abdominal pain[d], stomatitis[e], diarrhoea[f]
Skin and subcutaneous tissue disorders	
Very common	Rash[g], hair colour changes, dry skin[h], dermatitis acneiform[i], pruritus, skin discolouration[j], alopecia, photosensitivity reaction
Musculoskeletal and connective tissue disorders	
Very common	Growth retardation[k], pain in extremity, myalgia, arthralgia
General disorders	
Very common	Fatigue, pyrexia, oedema[l]
Investigations	
Very common	Blood phosphorus decreased[m], blood creatine phosphokinase increased, blood lactate dehydrogenase increased, aspartate aminotransferase increased, weight decreased, alanine aminotransferase increased, lymphocyte count decreased, blood bilirubin increased, white blood cell count decreased.
Common	Eosinophilia

[a] Includes term haemoglobin decreased
[b] Includes terms epistaxis, contusion, gingival bleeding, haematoma, petechiae, gastrointestinal haemorrhage, haematemesis, haematochezia, lower gastrointestinal haemorrhage, purpura, subdural haemorrhage, vaginal haemorrhage
[c] Includes terms tumour haemorrhage, intracranial tumour haemorrhage
[d] Includes term abdominal pain upper
[e] Includes terms aphthous ulcer, mouth ulceration, cheilitis, angular cheilitis, lip ulceration
[f] Includes term enterocolitis
[g] 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
[h] Includes terms chapped lips, lip dry, xeroderma
[i] Includes term acne
[j] Includes terms skin depigmentation, skin hyperpigmentation, skin hypopigmentation, melanocytic nevus
[k] Includes term growth failure
[l] Includes terms face oedema, swelling face, periorbital oedema, eye swelling, oedema peripheral, peripheral swelling, lip oedema, vulval oedema
[m] Includes term hypophosphataemia

Description of selected adverse reactions

Intratumoural haemorrhage (ITH)
In FIREFLY-1, 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 days-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: 1-672 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 increased
In FIREFLY-1, 62% of patients reported events of blood creatine phosphokinase (CPK) increased. 12.4% of patients reported Grade ≥ 3 events. All events were non-serious. 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 days to 701 days). The mean duration of the of the initial occurrence of the event was 238.4 days (median: 122 days; range: 8 days-926 days).

Anaemia
In FIREFLY-1, anaemia was reported in 61.3% of patients. 13.1% of patients reported anemia 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 patients 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 days-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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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, haemodialysis is likely to be ineffective in the treatment of overdose with tovorafenib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, protein kinase inhibitor, B-Raf serine-threonine kinase (RAF) inhibitor, ATC code: L01EC04

Mechanism of action

Tovorafenib is a central nervous system (CNS) penetrant, selective small molecule Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases, including RAF monomers and dimers and BRAF fusion, suppressing activation of the mitogen-activated protein kinase (MAPK) pathway (see section 5.3).

Pharmacodynamic effects

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 and safety

The efficacy of tovorafenib was evaluated in patients 6 months of age and older in a multicentre, open-label, single-arm clinical study (FIREFLY-1 [Arm 1]). Eligible patients (n=76), from 6 months to 25 years of age, were required to have a relapsed or refractory paediatric low-grade glioma (LGG) harbouring 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 tumours harbouring additional activating molecular alteration(s) (e.g., IDH1/2 mutations, FGFR mutations) or patients with known or suspected diagnosis of neurofibromatosis type 1 (NF1) were excluded.
Patients received 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.

Tumour assessments were performed every 12 weeks.
The major efficacy endpoints were overall response rate (ORR) of patients assessed by independent review based on RANO-HGG (Response Assessment in Neuro-Oncology for High-Grade Glioma), the primary endpoint, and RAPNO-LGG (Response Assessment in Paediatric Neuro-Oncology) criteria. Additional efficacy outcome measures were duration of response, time to response, ORR and progression-free survival (PFS) by independent review based on RANO-LGG (2011) criteria.
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. Most common prior systemic therapies were chemotherapy regimens (carboplatin and vincristine).
46 patients (60%) received prior treatment with a MAP kinase pathway inhibitor. The most common tumour locations were the optic pathway (51%), deep midline structures (12%), brain stem (8%), cerebellum (7%), and cerebral hemisphere (5%). 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, 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.
Based on RANO-HGG criteria per independent review, out of the 69 evaluable patients, the ORR was 71.0% (58.8, 81.3; 95% CI), with 23.2% of patients were in complete response, 47.8% in partial response and 21.7% in stable disease. The median duration of response was 19.7 months (95% CI: 13.7, NE [not estimable]).

Efficacy results based on RAPNO-LGG are shown in Table 5.

Table 5: Efficacy results based on independent review in FIREFLY-1 (Arm-1)

Efficacy parameter	**RAPNO-LGG N=76***
Overall response rate	
ORR (CR+PR+MR) 95% CI[a]	52.6% (40.8, 64.2)
Best overall response	
Complete response (CR), n (%)	0 (0)
Partial response (PR), n (%)	29 (38.2%)
Minor response (MR), n (%)	11 (14.5%)
Stable disease (SD), n (%)	22 (28.9%)
Progressive disease (PD), n (%)	13 (17.1%)
Duration of response (DoR)	**N=40**
Median (95% CI)[b], months	18.0 (12.0, 22.8)
DoR rate at ≥ 12 months (95% CI)[b]	65.0% (48.2%, 77.6%)
DoR rate at ≥ 24 months (95% CI)[b]	25.6% (11.4%, 42.6%)

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of FIREFLY-2 study until July 2030 with Ojemda in one or more subsets of the paediatric population in the treatment of paediatric low-grade glioma (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so -called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Tovorafenib pharmacokinetic parameters are presented as mean (CV%) unless otherwise indicated. Based on pop-PK modelling, 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

Based on clinical study in healthy volunteers, 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
Based on clinical study in healthy volunteers, 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

Based on pop-PK modelling, tovorafenib apparent volume of distribution is 60 L/m^2 (23%). Tovorafenib is 97.5% bound to human plasma proteins *in vitro*. Tovorafenib is highly protein-bound to albumin (≈ 95%) and moderately bound to alpha-1 acid glycoprotein (AAG) (≈42%).

Biotransformation

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

Drug interaction studies

In vitro studies

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

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. Tovorafenib inhibits BCRP, OATP1B1, OATP1B3 and MATE1 potentially at clinically relevant concentrations.

Elimination

Based on pop-PK modelling, tovorafenib terminal half-life is approximately 56 hours (33%) and the apparent clearance is 0.7 L/h/m^2 (31%). Based on clinical study in healthy volunteers, following a single oral dose of radiolabelled tovorafenib, 66.1% of the total radiolabelled dose was recovered in the faeces (8.6% unchanged) and 28.7% of the dose was recovered in the urine (0.2% unchanged).

Special populations

Paediatric population
Based on pop-PK modelling, no clinically significant differences in the pharmacokinetics 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.

Patients with renal impairment
Based on pop-PK modelling, 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). Tovorafenib has not been studied in patients with severe (eGFR <30 ml/min/1.73 m^2) renal impairment.

Patients with hepatic impairment
Based on pop-PK modelling of PK data derived from clinical studies, no clinically significant differences of tovorafenib were observed in patients with mildly abnormal liver functions tests (defined as 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 moderately abnormal liver functions tests (defined as bilirubin > 1.5x to 3x ULN and any AST) or severely abnormal liver functions tests (defined as total bilirubin > 3 x ULN and any AST) (see section 4.2).

Race
No clinically significant differences in the pharmacokinetics of tovorafenib were observed based on race (White, Black, Asian).

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

Pharmacokinetic/pharmacodynamic relationship

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 was associated with increased risk of adverse reactions such as skin rash and elevated liver enzymes (AST and ALT) (see section 4.8). The exposure-response relationship for overall response rate based on RAPNO-LGG was not clinically significant over the dose range of 290 to 476 mg/m^2 (0.76-1.25 times the recommended dose).

5.3 Preclinical safety data

In vitro, tovorafenib increased phosphorylation of extracellular signal-regulated kinase (ERK) at clinically relevant concentrations in cells with neurofibromatosis Type 1loss 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 antitumour activity (see section 4.4) and while not statistically significant, an increase in tumour volume was noted in 2/12 mice (approximately 17%).

In hERG-transfected HEK293 cells, hERG channel was inhibited indicating potential for QT prolongation. Half-maximal inhibitory concentration was 8.9 μM which is 32-fold higher than the clinical plasma unbound concentration in adults.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:
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. Based on *in vitro* and *in vivo* studies, tovorafenib is not considered genotoxic at clinically relevant exposures.
In a preliminary embryofetal development study in rats, total litter loss due to early resorptions was observed in all females at exposure levels lower than the recommended dose in human. This resulted in no foetus available for further examination, and explains the absence of further developmental studies (pivotal embryofetal development studies and prenatal and postnatal development study).
In a fertility and early embryonic development study in female rats, tovorafenib decreased the number of pregnancies, corpora lutea, and live embryos, as well as increased post-implantation losses at doses as low as 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 haemorrhagicum and haemorrhage, and non-reversible cystic follicles, decreased corpora lutea, and interstitial cell hyperplasia were observed in ovaries at doses 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 approximately 0.3-fold the human exposure at the recommended dose based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content

Silica, colloidal anhydrous
Copovidone
Croscarmellose sodium
Magnesium stearate
Cellulose, microcrystalline

Film-coating

Hypromellose
Macrogol
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Ojemda is supplied in blisters of PCTFE laminated between polyvinyl chloride (PVC) and aluminium foil backing containing either 4, 5 or 6 film-coated tablets. Each carton contains 16, 20 or 24 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2025/001
EU/1/26/2025/002
EU/1/26/2025/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ojemda 25 mg/ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One bottle of Ojemda contains 300 mg of tovorafenib. After reconstitution, one bottle of oral suspension delivers 12 ml of tovorafenib at a concentration of 25 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 progressed after one or more prior systemic therapies (for biomarkers-based patient selection, see section 4.2).

4.2 Posology and method of administration

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

Patient selection

Before taking tovorafenib, patients must have confirmation of BRAF fusion or rearrangement, or BRAF V600 mutation assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, confirmation of BRAF fusion or rearrangement, or BRAF V600 mutation should be assessed by an alternative validated test.

Posology

The recommended dose of tovorafenib based on body surface area (BSA) is 380 mg/m^2 once weekly. The maximum recommended dose is 600 mg once weekly (see Table 1).
Ojemda may be administered as an oral suspension (see Table 1) or as an immediate release tablet (see tovorafenib 100 mg film-coated tablets SmPC).
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:

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

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

Duration of treatment
Treatment with tovorafenib should be continued once weekly until disease progression, loss of clinical benefit, or unacceptable toxicity.

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 4 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 oral suspension are provided in Table 2.

Table 2: Recommended dose reductions for adverse reactions

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
$\geq$ 1.40 m^2	20 ml	500 mg	16 ml	400 mg

The recommended dose modifications for adverse reactions for tovorafenib are in Table 3.

Table 3: Recommended dose modifications for adverse reactions

Severity of ADR[a]	Dose modification[b]
Haemorrhage 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 2 for recommended dose reductions.

Special populations

Hepatic impairment
No dose adjustment is recommended for patients with mildly abnormal liver function tests (defined as bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or bilirubin > 1x to 1.5x ULN and any AST). Tovorafenib has not been studied in patients with moderately abnormal liver function tests (defined as bilirubin > 1.5x to 3x ULN and any AST) or severely abnormal liver function tests (defined as bilirubin > 3x ULN and any AST) (see section 5.2). Patients with moderately or severely abnormal liver function tests 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 m² 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 5.2).

Paediatric population
Tovorafenib paediatric clinical experience is limited, particularly in the specific age range 6 months to 2 years. The safety and efficacy of tovorafenib in children below 6 months of age have not been established. No data are available.

Method of administration

Ojemda is for oral use.

If the patient is unable to swallow and has a nasogastric tube in situ, the powder for oral suspension can be administered via the tube (see section 6.6).
Ojemda can be taken with or without food (see section 5.2) and should be taken at a regularly scheduled time once weekly.

Ojemda should be administered to paediatric patients under adult supervision.
Ojemda powder for oral suspension must be reconstituted prior to being administered (see section 6.6). Prior to first time use of the oral suspension, caregivers (and if appropriate, patients) should be instructed on the proper preparation, dose, and administration of Ojemda.

Detailed instructions on the preparation and administration of the powder for oral suspension are given in section 6.6 and at the end of the package leaflet.

The powder for oral suspension and the film-coated tablets may be used interchangeably (see tovorafenib 100 mg film-coated tablets SmPC). For patients who are not able to swallow or with BSA less than 0.9 m^2 the oral suspension should be provided.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Intratumoural haemorrhage

Intratumoural haemorrhage (including the terms tumour haemorrhage and intracranial tumour haemorrhage) events have been reported very commonly in patients treated with tovorafenib (see section 4.8). 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 4.2).

Other haemorrhage events

Haemorrhagic events have been reported very commonly in patients taking tovorafenib. If haemorrhage occurs, patients should be treated as clinically indicated (see section 4.8). Patients and caregivers should be advised of the risk of haemorrhage 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 haemorrhage, 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 4.2).

Effect on growth

Reductions in growth velocity have been reported very commonly in patients treated with tovorafenib (see section 4.8). 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.

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 4.8).
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 4.2).

Skin toxicity including photosensitivity

Rash, including photosensitivity events, have been reported very commonly in patients treated with tovorafenib (see section 4.8). 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 $\geq$ 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 4.2 and section 4.8).

Women of childbearing potential/ Contraception in females and males

Before initiating treatment in women of childbearing potential, appropriate advice on effective methods of contraception should be provided. Women of childbearing potential must use effective non-hormonal contraception such as a barrier method during therapy and for 28 days after the last dose of tovorafenib (see section 4.5 and section 4.6). Male patients with female partners of reproductive potential must use condoms and effective contraception during treatment with tovorafenib and for 2 weeks after the last dose (see section 4.6).

Neurofibromatosis type 1 (NF1) associated tumours

Based on non-clinical data in NF1 models without BRAF alterations, tovorafenib may promote tumour growth in patients with NF1-associated tumours (see section 5.3). Evidence of a BRAF alteration prior to initiation of treatment with tovorafenib should be confirmed.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per bottle, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on tovorafenib

Tovorafenib is a substrate for the metabolising 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 5.2). Coadministration of tovorafenib with a strong or moderate CYP2C8 inhibitor (e.g. gemfibrozil) 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 5.2). Coadministration of tovorafenib with a strong or moderate CYP2C8 inducer (e.g. carbamazepine) should be avoided.

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 (see section 5.2). Coadministration of tovorafenib with certain CYP3A substrates (e.g. tacrolimus) where minimal concentration changes may lead to serious therapeutic failures should be avoided. If coadministration cannot be avoided, monitor patients for loss of efficacy unless otherwise recommended in the SmPC for CYP3A substrates.

Coadministration of tovorafenib with hormonal contraceptives (CYP3A substrates) may render hormonal contraceptives ineffective (see sections 4.4, 4.6 and 5.2). Coadministration of hormonal contraceptives with tovorafenib should be avoided. If coadministration cannot be avoided, an additional effective non-hormonal contraceptive method must be used during coadministration and for 28 days following discontinuation of tovorafenib.

CYP1A2, CYP2B6, CYP2C8 and CYP2C9 substrates
In vitro data indicated that tovorafenib may have the potential to induce CYP1A2 and CYP2B6 and to inhibit CYP2C8, CYP2C9. The clinical relevance of these findings is unknown. When tovorafenib is co-administered with medicinal products metabolised by these enzymes, appropriate monitoring is recommended

Transporters substrates
In vitro data indicated that 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.

4.6 Fertility, pregnancy and 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 non-hormonal contraception such as a barrier method should be used (see section 4.5). 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 5.3). Tovorafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. Pregnant women should be advised of the potential risk to a foetus. If a patient becomes pregnant while taking tovorafenib, the patient should be informed of the potential hazard to the foetus.

Breastfeeding

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 and may not be reversible (see section 5.3).

4.7 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.

4.8 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 harbouring 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); 3 (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 adverse drug reactions by individual MedDRA preferred term were hair colour changes (77.4%), blood creatine phosphokinase increased (62.0%), fatigue (60.6%), anaemia (60.6%), vomiting (56.2%), hypophosphataemia (52.6%), headache (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%) and paronychia (29.9%).

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

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 growth retardation (2.9%) and tumour haemorrhage (2.9%).

Tabulated list of adverse reactions

Adverse reactions reported in patients treated with tovorafenib monotherapy in FIREFLY-1 (n=137) are listed in Table 4. Adverse reactions are listed below by MedDRA body system organ class and the following frequency convention: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse drug reactions reported in paediatric LGG patients in FIREFLY-1 (n=137)

Infections and infestations	
Very common	Upper respiratory tract infection, paronychia, viral infection
Blood and lymphatic system disorders	
Very common	Anaemia[a]
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypokalaemia, hypoalbuminemia, hyponatraemia
Nervous system disorders	
Very common	Headache
Eye disorders	
Common	Blepharitis, dry eye
Vascular disorders	
Very common	Haemorrhage[b], intratumoural haemorrhage[c], flushing
Gastrointestinal disorders	

Very common	Vomiting, nausea, constipation, abdominal pain[d], stomatitis[e], diarrhoea[f]
Skin and subcutaneous tissue disorders	
Very common	Rash[g], hair colour changes, dry skin[h], dermatitis acneiform[i], pruritus, skin discolouration[j], alopecia, photosensitivity reaction
Musculoskeletal and connective tissue disorders	
Very common	Growth retardation[k], pain in extremity, myalgia, arthralgia
General disorders	
Very common	Fatigue, pyrexia, oedema[l]
Investigations	
Very common	Blood phosphorus decreased[m], blood creatine phosphokinase increased, blood lactate dehydrogenase increased, aspartate aminotransferase increased, weight decreased alanine aminotransferase increased, lymphocyte count decreased, blood bilirubin increased,, white blood cell count decreased
Common	Eosinophilia

[a] Includes term haemoglobin decreased
[b] Includes terms epistaxis, contusion, gingival bleeding, haematoma, petechiae, gastrointestinal haemorrhage, haematemesis, haematochezia, lower gastrointestinal haemorrhage, purpura, subdural haemorrhage, vaginal haemorrhage
[c] Includes terms tumour haemorrhage, intracranial tumour haemorrhage
[d] Includes term abdominal pain upper
[e] Includes terms aphthous ulcer, mouth ulceration, cheilitis, angular cheilitis, lip ulceration
[f] Includes term enterocolitis
[g] 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
[h] Includes terms chapped lips, lip dry, xeroderma
[i] Includes term acne
[j] Includes terms skin depigmentation, skin hyperpigmentation, skin hypopigmentation, melanocytic nevus
[k] Includes term growth failure
[l] Includes terms face oedema, swelling face, periorbital oedema, eye swelling, oedema peripheral, peripheral swelling, lip oedema, vulval oedema
[m] Includes term hypophosphataemia

Description of selected adverse reactions

Intratumoural haemorrhage (ITH)
In FIREFLY-1, 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 days-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: 1–672 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 increased
In FIREFLY-1, 62% of patients reported events of blood creatine phosphokinase (CPK) increased. 12.4% of patients reported Grade ⩾ 3 events. All events were non-serious. 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 days to 701 days). The mean duration of the of the initial occurrence of the event was 238.4 days (median: 122 days; range: 8 days-926 days).

Anaemia
In FIREFLY-1, anaemia was reported in 61.3% of patients. 13.1% of patients reported anemia 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 patients 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 days-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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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, haemodialysis is likely to be ineffective in the treatment of overdose with tovorafenib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, protein kinase inhibitor, B-Raf serine-threonine kinase (RAF) inhibitor, ATC code: L01EC04

Mechanism of action

Tovorafenib is a central nervous system (CNS)-penetrant, selective small molecule Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases, including RAF monomers and dimers and BRAF fusion, suppressing activation of the mitogen-activated protein kinase (MAPK) pathway (see section 5.3).

Pharmacodynamic effects

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 and safety

The efficacy of tovorafenib was evaluated in patients 6 months of age and older in a multicentre, open-label, single-arm clinical study (FIREFLY-1 [Arm 1]). Eligible patients (n=76), from 6 months to 25 years of age, were required to have a relapsed or refractory paediatric low-grade glioma (LGG) harbouring 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 tumours harbouring additional activating molecular alteration(s) (e.g., IDH1/2 mutations, FGFR mutations) or patients with known or suspected diagnosis of neurofibromatosis type 1 (NF1) were excluded.
Patients received 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.

Tumour assessments were performed every 12 weeks.
The major efficacy endpoints were overall response rate (ORR) of patients assessed by independent review based on RANO-HGG (Response Assessment in Neuro-Oncology for High-Grade Glioma), the primary endpoint, and RAPNO-LGG (Response Assessment in Paediatric Neuro-Oncology) criteria. Additional efficacy outcome measures were duration of response, time to response, ORR and progression-free survival (PFS) by independent review based on RANO-LGG (2011) criteria.
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. Most common prior systemic therapies were chemotherapy regimens (carboplatin and vincristine).
46 patients (60%) received prior treatment with a MAP kinase pathway inhibitor. The most common

tumour locations were the optic pathway (51%), deep midline structures (12%), brain stem (8%), cerebellum (7%), and cerebral hemisphere (5%). 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, 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.
Based on RANO-HGG criteria per independent review, out of the 69 evaluable patients, the ORR was 71.0% (58.8, 81.3; 95% CI), with 23.2% of patients were in complete response, 47.8% in partial response and 21.7% in stable disease. The median duration of response was 19.7 months (95% CI: 13.7, NE [not estimable]).

Efficacy results based on RAPNO-LGG are shown in Table 5.

Table 5: Efficacy results based on independent review in FIREFLY-1 (Arm-1)

Efficacy parameter	**RAPNO-LGG N=76***
Overall response rate	
ORR (CR+PR+MR) 95% CI[a]	52.6% (40.8, 64.2)
Best overall response	
Complete response (CR), n (%)	0 (0)
Partial response (PR), n (%)	29 (38.2%)
Minor response (MR), n (%)	11 (14.5%)
Stable disease (SD), n (%)	22 (28.9%)
Progressive disease (PD), n (%)	13 (17.1%)
Duration of response (DoR)	**N=40**
Median (95% CI)[b], months	18.0 (12.0, 22.8)
DoR rate at ≥ 12 months (95% CI)[b]	65.0% (48.2%, 77.6%)
DoR rate at ≥ 24 months (95% CI)[b]	25.6% (11.4%, 42.6%)

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of FIREFLY-2 study until July 2030 with Ojemda in one or more subsets of the paediatric population in the treatment of paediatric low-grade glioma (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Tovorafenib pharmacokinetic parameters are presented as mean (CV%) unless otherwise indicated. Based on pop-PK modelling, 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

Based on clinical study in healthy volunteers, 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
Based on clinical study in healthy volunteers, 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

Based on pop-PK modelling, tovorafenib apparent volume of distribution is 60 L/m^2 (23%). Tovorafenib is 97.5% bound to human plasma proteins *in vitro*. Tovorafenib is highly protein-bound to albumin (≈ 95%) and moderately bound to alpha-1 acid glycoprotein (AAG) (≈ 42%).

Biotransformation

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

Drug interaction studies

In vitro studies

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

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. Tovorafenib inhibits BCRP, OATP1B1, OATP1B3 and MATE1 potentially at clinically relevant concentrations.

Elimination

Based on pop-PK modelling, tovorafenib terminal half-life is approximately 56 hours (33%) and the apparent clearance is 0.7 L/h/m^2 (31%). Based on clinical study in healthy volunteers, following a single oral dose of radiolabelled tovorafenib, 66.1% of the total radiolabelled dose was recovered in the faeces (8.6% unchanged) and 28.7% of the dose was recovered in the urine (0.2% unchanged).

Special populations

Paediatric population
Based on pop-PK modelling, no clinically significant differences in the pharmacokinetics 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.

Patients with renal impairment
Based on pop-PK modelling, 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). Tovorafenib has not been studied in patients with severe (eGFR <30 ml/min/1.73 m^2) renal impairment

Patients with hepatic impairment
Based on pop-PK modelling of PK data derived from clinical studies, no clinically significant differences of tovorafenib were observed in patients with mildly abnormal liver functions tests (defined as 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 moderately abnormal liver functions tests (defined as bilirubin > 1.5x to 3x ULN and any AST) or severely abnormal liver functions tests (defined as total bilirubin >3 x ULN and any AST) (see section 4.2).

Race
No clinically significant differences in the pharmacokinetics of tovorafenib were observed based on race (White, Black, Asian).

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

Pharmacokinetic/pharmacodynamic relationship

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 was associated with increased risk of adverse reactions such as skin rash and elevated liver enzymes (AST and ALT) (see section 4.8). The exposure-response relationship for overall response rate based on RAPNO-LGG was not clinically significant over the dose range of 290 to 476 mg/m^2 (0.76-1.25 times the recommended dose).

5.3 Preclinical safety data

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 antitumour activity (see section 4.4) and while not statistically significant, an increase in tumour volume was noted in 2/12 mice (approximately 17%).

In hERG-transfected HEK293 cells, hERG channel was inhibited indicating potential for QT prolongation. Half-maximal inhibitory concentration was 8.9 μM which is 32-fold higher than the clinical plasma unbound concentration in adults.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:
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. Based on *in vitro* and *in vivo* studies, tovorafenib is not considered genotoxic at clinically relevant exposures.
In a preliminary embryofetal development study in rats, total litter loss due to early resorptions was observed in all females at exposure levels lower than the recommended dose in human. This resulted in no foetus available for further examination, and explains the absence of further developmental studies (pivotal embryofetal development studies and prenatal and postnatal development study).
In a fertility and early embryonic development study in female rats, tovorafenib decreased the number of pregnancies, corpora lutea, and live embryos, as well as increased post-implantation losses at doses as low as 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 haemorrhagicum and haemorrhage, and non-reversible cystic follicles, decreased corpora lutea, and interstitial cell hyperplasia were observed in ovaries at doses 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 approximately 0.3-fold the human exposure at the recommended dose based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone
Cellulose, microcrystalline
Mannitol (E421)
Sodium Lauril sulfate
Simeticone
Maltodextrin
Silica, colloidal anhydrous
Sucralose
Artificial strawberry flavour (containing maltodextrin, triacetin, artificial flavour)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Powder for oral suspension:
3 years.

Reconstituted oral suspension:
15 minutes

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

30 ml clear Type III glass bottle with induction-seal and a white polypropylene cap.

Each pack contains one bottle, a 20 ml oral dosing syringe, and a bottle adaptor.

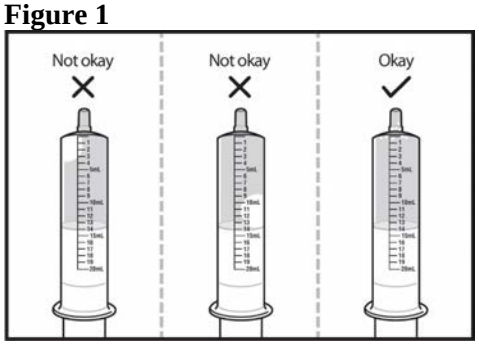
6.6 Special precautions for disposal and other handling

- The instructions for use 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 bottle is made of glass. This medicine should not be used if the bottle is broken or damaged, or if the safety seal under the cap is broken or missing.
- Only 14 ml of room temperature water should be used for preparing Ojemda.
- Only use up to 12 ml of Ojemda from each prepared bottle. If the prescribed dose is more than 12 ml (300 mg), split the dose as equally as possible between each prepared bottle (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.
- Each dose must be given within 15 minutes after the medicine has been prepared.

Instruction for reconstitution of Ojemda powder for oral suspension

Note: if more than one bottle is needed for the prescribed dose, bottles should be constituted one by one. Split the dose as equally as possible between each prepared bottle.
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 exactly 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 the 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

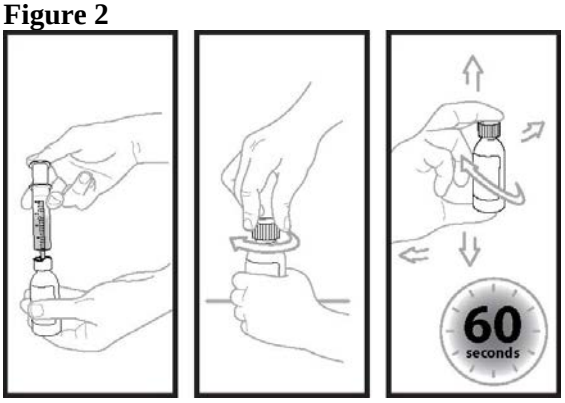
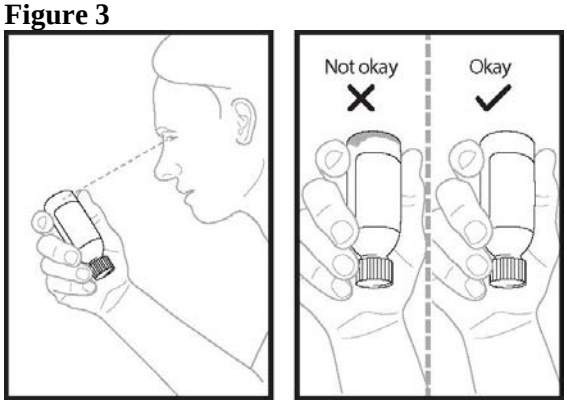
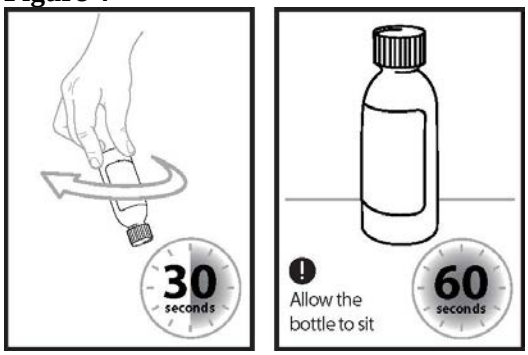


Figure 3



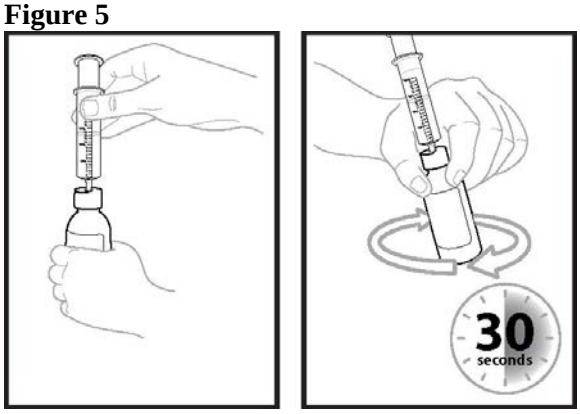
Step 6: Turn the bottle upside down again and swirl for 30 seconds (see Figure 4). Remove the cap and check that no solids are stuck in the bottle neck. If you see solids in the bottle neck when removing the cap, recap the bottle, turn the bottle upside down, and swirl for an additional 15 seconds.
Allow 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



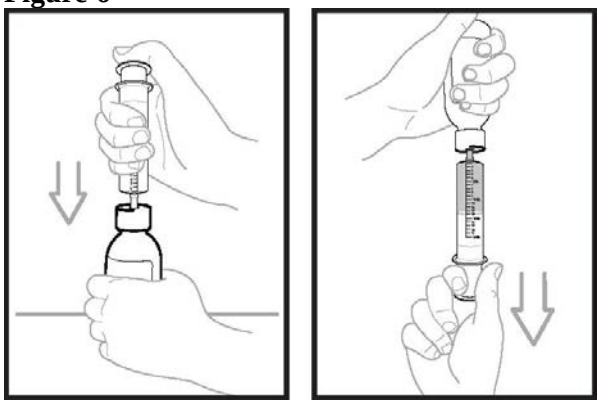
Step 7: Firmly insert the bottle adaptor into the bottle by pushing it tightly into the top of the bottle. The top edge of the bottle adaptor should be even with the bottle top.
Do not remove the bottle adaptor after it is inserted into the bottle.
Step 8: Check the prescribed dose in millilitres (ml). 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.**

Administration using an oral syringe
Once the suspension is prepared, place the tip of the oral dosing syringe towards the inside of the mouth with the tip touching the inside of either cheek then slowly push the medicine into the mouth by pressing down on the plunger.
Do not forcefully push the plunger. This may cause choking. Allow the child to swallow while giving Ojemda

Administration using a feeding tube
Only use a feeding tube with a minimum size of 12 French. Flush the feeding tube according to the manufacturer's instructions before administering the suspension. Use an ENFit syringe to draw up the suspension from the bottle then dispense the suspension into the feeding tube with an ENFit adaptor. Finally, flush the feeding tube after administering as per the manufacturer's instructions.

If 2 bottles are required to prepare the required dose, repeat Step 1 to 12 and give the remainder of the dose right away. Be sure to give the entire dose of Ojemda.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2025/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD month YYYY
Date of latest renewal: DD month YYYY

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Ipsen Pharma Biotech
Parc d´Activites Du Plateau De Signes
Chemin Departemental 402
Signes 83870
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of tovorafenib in 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, the MAH shall conduct and submit the final report of the phase III randomised, parallel-group, two-arm study (FIREFLY-2) to evaluate the efficacy and safety of tovorafenib monotherapy versus standard of care (SoC) chemotherapy in patients with paediatric low-grade glioma harbouring an activating rapidly accelerated fibrosarcoma gene (RAF) alteration requiring first-line systemic therapy.	30 April 2032
The MAH shall generate additional PK data in paediatrics patients below 2 years of age and submit an updated population PK model incorporating these data, including an assessment of systemic exposure and, if necessary, revised dosing recommendations for this subgroup of patients.	30 April 2032

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ojemda 100 mg film-coated tablets
tovorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of tovorafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

16 film-coated tablets
20 film-coated tablets
24 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2025/001 16 film-coated tablets
EU/1/26/2025/002 20 film-coated tablets
EU/1/26/2025/003 24 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ojemda 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ojemda 100 mg tablets
tovorafenib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ojemda 25 mg/ml powder for oral suspension
tovorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one bottle of oral suspension delivers 300 mg in 12 ml of tovorafenib at 25 mg/ml.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.
Contains 1 bottle, 1 bottle adaptor, 1 oral dosing syringe.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 15 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2025/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ojemda 25 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ojemda 25 mg/ml powder for oral suspension
tovorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, one bottle of oral suspension delivers 300 mg in 12 ml of tovorafenib at 25 mg/ml.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.
For single use.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the instructions for use before reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 15 minutes of reconstitution.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2025/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ojemda 100 mg film-coated tablets
tovorafenib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child starts using this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor, pharmacist or nurse.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child's.
- If your child get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- The information in this leaflet is for you or your child – but in the leaflet it will just say "your child".

What is in this leaflet

1. What Ojemda is and what it is given for

Ojemda contains the active substance tovorafenib and belongs to a group of medicines known as protein kinase inhibitors.

It is used in patients aged 6 months and older to treat paediatric low-grade glioma. This is a type of brain tumour that forms in the glial cells which support and protect the nerve cells in the brain and spinal cord. Gliomas are assigned a grade from 1 to 4, which indicates how aggressive the tumour cells are. Grade 1 and 2 are considered as low-grade gliomas.

Ojemda is used in patients aged 6 months and older, whose brain tumour:
- has an abnormality in the BRAF gene (BRAF fusion or rearrangement, or BRAF V600 mutation), and;
- has come back after previous treatment or has not responded to previous treatment.

The doctor will perform a test to make sure that Ojemda is right for your child before starting treatment.

2. What you need to know before you give Ojemda

Do not give Ojemda
- if your child is allergic to tovorafenib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your child's doctor before giving Ojemda. The doctor needs to know if your child:

- has **bleeding problems. Ojemda may cause bleeding problems, including bleeding inside the tumour.** The use of medicines that prevent the blood from clotting, such as anticoagulants or antiplatelet therapy, can increase the risk of these bleeding problems during treatment with Ojemda. If bleeding problems occur, the doctor may withhold, resume at reduced dose, or permanently stop treatment with Ojemda based on their severity. Tell your doctor right away if your child develops symptoms, including:
    - nose bleeds;
    - headaches;
    - coughing up blood or blood clots;
    - vomiting blood or vomit that looks like coffee grounds;
    - red or black stools that look like tar;
    - confusion;
    - slurred speech;
    - dizziness;
    - feeling weak

- has **skin problems**. Omjeda may cause rash, including photosensitivity (a condition in which the skin becomes very sensitive to sunlight or other forms of ultraviolet light and may burn easily).You should try to avoid your child being directly exposed to the sun as this may lead to skin reactions. Use precautionary measures such as sunscreen (SPF $\geq$ 50), sunglasses and/or protective clothing during treatment with Ojemda. The doctor may withhold, reduce the dose or permanently stop the treatment based on severity of the reaction. Tell your doctor right away if your child develops symptoms including
    - raised bumps on discoloured patches of skin;
    - peeling, redness or skin irritation;
    - blisters;
    - rash.

What your child's doctor will check before and during the treatment

- Your child will have blood tests to check how well the liver is working before starting treatment, one month after starting and regularly during treatment with Ojemda. This is because Ojemda can cause problems with the liver. If this occurs the doctor may withhold or permanently stop treatment or reduce the dose.
- The doctor will monitor your child's growth before starting treatment, regularly during treatment and once treatment has been stopped. This is because Ojemda can slow down the rate at which your child grows.

Children younger than 6 months old
Ojemda is not recommended for use in children younger than 6 months old. It has not been studied in this age group.

Other medicines and Ojemda
Talk to your doctor, pharmacist, or nurse if your child is taking, has recently taken or might take any other medicines before starting treatment with Ojemda. This includes medicines obtained without a prescription.

This is very important as some medicines may affect how Ojemda works or make it more likely that your child will have side effects. Ojemda can also affect how some other medicines work.

- gemfibrozil, a medicine used to treat high cholesterol and fat levels in the blood
- carbamazepine, a medicine used for stopping seizures
- tacrolimus : a medicine used to suppress your body's immune system, or stopping your body from rejecting an organ transplant
- birth control: if you are using hormonal oral contraceptives, you must also use a reliable barrier method of contraception (see Pregnancy, breast-feeding and fertility)

Tell the doctor, pharmacist or nurse if your child is taking any of these medicines (or if you are not sure). The doctor may decide to adjust the dose.

Pregnancy, breast-feeding and fertility

Pregnancy

Although this medicine will primarily be used in young children, it may be used in older patients who are able to conceive. This section is directed at these patients

- If you are pregnant, or if you think you may be pregnant, ask the doctor or nurse for advice before taking this medicine. Ojemda may potentially harm an unborn baby.
- If you become pregnant while taking this medicine, tell the doctor immediately. Data from animal studies have shown that Ojemda may harm the unborn baby.

If your child can become pregnant, the doctor will do a test before they start treatment with Ojemda.

Contraception

If your child could become pregnant, they must use a reliable method of birth control (contraception) during treatment with Ojemda and for at least 28 days following the last dose of Ojemda.
Birth control methods containing hormones (such as birth control pills, injections, or patches) may not work well during treatment with Ojemda. An effective non-hormonal barrier method of birth control (e.g. condom) should be used to avoid the risk of pregnancy while taking Ojemda. Ask the doctor or nurse for advice.

If your male child is able to conceive a child, your child should use effective non-hormonal birth control (contraception) during treatment with Ojemda and for 2 weeks after the last dose of Ojemda.

Breastfeeding

It is not known if Ojemda can pass into breast milk. Your child should not breastfeed during treatment and for 2 weeks after treatment is stopped. Talk to the doctor about the best way to feed the baby during this time.

Fertility

The effects of Ojemda on fertility are not known. This medicine may potentially impact the fertility of men and women and effects may not be reversible. Options to improve your child's chances to have children in the future should be discussed with your child's doctor.

Driving and using machines

Ojemda can have side effects that may affect your child's ability to drive, ride a bike/scooter, use machines, or take part in other activities that need alertness. If your child has problems with vision or feels tired or weak, or their energy levels are low, they should avoid such activities.

Descriptions of these effects can be found in section 4.

Discuss with the doctor, pharmacist or nurse if you are unsure about anything. Your child's disease, symptoms and treatment situation may also affect their ability to take part in such activities.

Ojemda contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg tablet, that is to say essentially 'sodium-free'.

3. How to give Ojemda

Always use this medicine exactly as the doctor or pharmacist has told you. Check with the doctor or pharmacist if you are not sure.

How much to give
The doctor will decide on the correct dose of Ojemda based on your child's body size, including their weight and height.
The doctor may decide that your child should be given a lower dose if they get side effects.
Treatment will continue as long as your child benefits from it and no unacceptable side effects occur.

How to give it
Your child should swallow the tablets whole with water. The tablets must not be chewed, cut, or crushed. If your child cannot swallow the tablets, Ojemda is also available in powder for oral suspension.
Give Ojemda once a week with or without food.

If you give more Ojemda than you should
If you gave too much Ojemda, **contact the doctor, pharmacist or nurse** for advice. If possible, show them the Ojemda pack and this leaflet.

If you forget to give Ojemda
- If the weekly dose of Ojemda is delayed by 3 days or less, give it as soon as you remember. Give the next dose to your child on the next regularly scheduled day.
- If the dose of Ojemda is delayed by more than 3 days, skip it and give the next dose to your child on the next regularly scheduled day.

If your child vomits after taking Ojemda
If your child vomits immediately after taking Ojemda, give the dose to your child again. If you are not sure if you should give another dose, contact your doctor or pharmacist.

If you stop giving Ojemda
Give Ojemda for as long as the doctor recommends. Do not stop unless the doctor advises you to.
If you have any further questions on the use of this medicine, ask the doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using this medicine and seek urgent medical attention if your child has any of the following symptoms:
- Severe bleeding, such as a nosebleed that does not stop.
- Signs of tumour bleeding, such as sudden tingling, weakness, numbness or sudden and severe headache, nausea or vomiting, confusion or slurred speech.
- Rash, acne-like rash, peeling, redness of skin or irritation, bumps or tiny papules, blisters. These may be signs of serious skin rashes.
- Sunburn after exposure to sun. It is recommended to use precautionary measures against exposure to light, such as use of sunscreen (SPF $\geq$ 50), sunglasses, and/or protective clothing.

Other possible side effects

Very common (*may affect more than 1 in 10 people*)
- Hair colour changes
- Tiredness (fatigue)
- Low levels of red blood cells which can cause tiredness and pale skin (anaemia)
- Increased level of enzymes (blood creatine phosphokinase increased) an enzyme released into the blood when muscle is damaged
- Being sick (vomiting)
- Low levels of phosphate in the blood (hypophosphataemia)
- Headache

- Dry skin
- Fever (pyrexia)
- Slow growth (growth retardation)
- Acne
- Increase levels of enzymes found in your child's liver (aspartate aminotransferase increased)
- Increased levels of enzymes (blood lactate dehydrogenase increased) which can show that your child has some type of tissue damage.
- Feeling sick (nausea)
- Constipation
- Nose and throat infection (upper respiratory tract infection)
- Swelling (oedema)
- Nail bed infection (paronychia)
- Decreased appetite
- Belly pain (abdominal pain)
- Low levels of potassium in the blood (hypokalaemia)
- Inflammation of the lining of the mouth (stomatitis)
- Itching skin (pruritus)
- Diarrhoea
- Weight loss (weight decreased)
- Increase levels of enzymes found in your child's liver (alanine aminotransferase increased)
- Pain in legs and arms (pain in extremity)
- Skin colour changes (skin discolouration)
- Hair loss (alopecia)
- Muscle pain (myalgia)
- Decrease in lymphocyte count, a type of white blood cell
- Increase levels of a breakdown product of red blood cells (blood bilirubin increased)
- Low levels of albumin in the blood (hypoalbuminemia)
- Low levels of sodium in the blood (hyponatraemia)
- Joint pain (arthralgia)
- Viral infection
- Decrease in white blood cell count
- Reddening of the skin (flushing)

Common (*may affect up to 1 in 10 people*)
- Increase in eosinophil count, a type of white blood cell
- Inflammation of the eyelid margins (blepharitis)
- Dry eye

Reporting of side effects
If your child gets any side effects, talk to the doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ojemda

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister foil and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.
Do not use this medicine if you notice that the package is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ojemda contains

- The active substance is tovorafenib. Each film-coated tablet contains 100 mg of tovorafenib.
- The other ingredients are:
  Tablet core: silica, colloidal anhydrous, copovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose.
  Film-coating: hypromellose, macrogol, titanium dioxide, iron oxide yellow, iron oxide red.

This medicine contains less than 1 mmol sodium (23 mg) per tablet , that is to say essentially 'sodium-free'

What Ojemda looks like and contents of the pack
Ojemda 100 mg tablets are orange, oval, film-coated tablets, debossed with "100" on one side and "D101" on the opposite side. They are supplied in blisters of 4, 5 or 6 film-coated tablets. Each carton contains 16, 20 or 24 film-coated tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Ipsen Pharma
70 rue Balard
75015 Paris
France

Manufacturer
Ipsen Pharma Biotech
Parc d´Activites Du Plateau De Signes,
Chemin Departemental 402
Signes 83870
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Ireland
Ipsen Pharmaceuticals Limited
Tel: + 44 (0)1753 62 77 77

This leaflet was last revised in MM/YYYY

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Package leaflet: Information for the patient

Ojemda 25 mg/ml powder for oral suspension
tovorafenib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child starts using this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor, pharmacist or nurse.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child's.
- If your child get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- The information in this leaflet is for you or your child – but in the leaflet it will just say "your child".

What is in this leaflet

1. What Ojemda is and what it is given for

Ojemda contains the active substance tovorafenib and belongs to a group of medicines known as protein kinase inhibitors.

It is used in patients aged 6 months and older to treat paediatric low-grade glioma. This is a type of brain tumour that forms in the glial cells which support and protect the nerve cells in the brain and spinal cord. Gliomas are assigned a grade from 1 to 4, which indicates how aggressive the tumour cells are. Grade 1 and 2 are considered as low-grade gliomas.

Ojemda is used in patients aged 6 months and older whose brain tumour:
- has an abnormality in the BRAF gene (BRAF fusion or rearrangement, or BRAF V600 mutation) and;
- has come back after previous treatment or has not responded to previous treatment.

The doctor will perform a test to make sure that Ojemda is right for your child before starting treatment.

2. What you need to know before you give Ojemda

Do not give Ojemda
- if your child is allergic to tovorafenib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your child's doctor before giving Ojemda. The doctor needs to know if your child:

- has **bleeding problems. Ojemda may cause bleeding problems, including bleeding inside the tumour.** The use of medicines that prevent the blood from clotting, such as anticoagulants or antiplatelet therapy, can increase the risk of these bleeding problems during treatment with Ojemda. If bleeding problems occur, the doctor may withhold, resume at reduced dose, or permanently stop treatment with Ojemda based on their severity. Tell your doctor right away if your child develops symptoms, including
    - nose bleeds;
    - headaches;
    - coughing up blood or blood clots;
    - vomiting blood or vomit that looks like coffee grounds;
    - red or black stools that look like tar;
    - confusion;
    - slurred speech;
    - dizziness;
    - feeling weak.

- has **skin problems**. Omjeda may cause rash, including photosensitivity (a condition in which the skin becomes very sensitive to sunlight or other forms of ultraviolet light and may burn easily). You should try to avoid your child being directly exposed to the sun as this may lead to skin reactions. Use precautionary measures such as sunscreen (SPF $\geq$ 50), sunglasses and/or protective clothing during treatment with Ojemda. The doctor may withhold, reduce the dose or permanently stop the treatment based on severity of the reaction. Tell your doctor right away if your child develops symptoms including
    - raised bumps on discoloured patches of skin;
    - peeling, redness or skin irritation;
    - blisters;
    - rash.

What your child's doctor will check before and during the treatment

- Your child will have blood tests to check how well the liver is working before starting treatment, one month after starting and regularly during treatment with Ojemda. This is because Ojemda can cause problems with the liver. If this occurs the doctor may withhold or permanently stop treatment or reduce the dose.
- The doctor will monitor your child's growth before starting treatment, regularly during treatment, and once treatment has been stopped. This is because Ojemda can slow down the rate at which your child grows.

Children younger than 6 months old
Ojemda is not recommended for use in children younger than 6 months old. It has not been studied in this age group.

Other medicines and Ojemda
Talk to your doctor, pharmacist, or nurse if your child is taking, has recently taken or might take any other medicines before starting treatment with Ojemda. This includes medicines obtained without a prescription.

This is very important as some medicines may affect how Ojemda works or make it more likely that your child will have side effects. Ojemda can also affect how some other medicines work.

- gemfibrozil, a medicine used to treat high cholesterol and fat levels in the blood
- carbamazepine, a medicine used for stopping seizures
- tacrolimus : a medicine used to suppress your body's immune system, or stopping your body from rejecting an organ transplant
- birth control: if you are using hormonal oral contraceptives, you must also use a reliable barrier method of contraception (see Pregnancy, breast-feeding and fertility)

Tell the doctor, pharmacist or nurse if your child is taking any of these medicines (or if you are not sure). The doctor may decide to adjust the dose.

Pregnancy, breast-feeding and fertility

Pregnancy

Although this medicine will primarily be used in young children, it may be used in older patients who are able to conceive. This section is directed at these patients

- If you are pregnant, or if you think you may be pregnant, ask the doctor or nurse for advice before taking this medicine. Ojemda may potentially harm an unborn baby.
- If you become pregnant while taking this medicine, tell the doctor immediately. Data from animal studies have shown that Ojemda may harm the unborn baby.

If your child can become pregnant, the doctor will do a test before they start treatment with Ojemda.

Contraception

If your child could become pregnant, they must use a reliable method of birth control (contraception) during treatment with Ojemda and for at least 28 days following the last dose of Ojemda.
Birth control methods containing hormones (such as birth control pills, injections, or patches) may not work well during treatment with Ojemda. An effective non-hormonal barrier method of birth control (e.g. condom) should be used to avoid the risk of pregnancy while taking Ojemda. Ask the doctor or nurse for advice.

If your male child is able to conceive a child, your child should use effective non-hormonal birth control (contraception) during treatment with Ojemda and for 2 weeks after the last dose of Ojemda..

Breastfeeding

It is not known if Ojemda can pass into breast milk. Your child should not breastfeed during treatment and for 2 weeks after treatment is stopped. Talk to the doctor about the best way to feed the baby during this time.

Fertility

The effects of Ojemda on fertility are not known. This medicine may potentially impact the fertility of men and women and effects may not be reversible. Options to improve your child's chances to have children in the future should be discussed with your child's doctor.

Driving and using machines

Ojemda can have side effects that may affect your child's ability to drive, ride a bike/scooter, use machines, or take part in other activities that need alertness. If your child has problems with vision or feels tired or weak, or their energy levels are low, they should avoid such activities.

Descriptions of these effects can be found in section 4.

Discuss with the doctor, pharmacist or nurse if you are unsure about anything. Your child's disease, symptoms and treatment situation may also affect their ability to take part in such activities.

Ojemda contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per bottle of powder for oral suspension, that is to say essentially 'sodium-free'.

3. How to give Ojemda

Always use this medicine exactly as the doctor or pharmacist has told you. Check with the doctor or pharmacist if you are not sure.

How much to give
The doctor will decide on the correct dose of Ojemda based on your child's body size, including their weight and height.
The doctor may decide that your child should be given a lower dose if they get side effects.
Treatment will continue as long as your child benefits from it and no unacceptable side effects occur.

How to give it
Please read the Instructions for Use at the end of this leaflet for details on how to prepare and give the powder for oral suspension.

Give Ojemda once a week with or without food.

If you give more Ojemda than you should
If you gave too much Ojemda, **contact the doctor, pharmacist or nurse** for advice. If possible, show them the Ojemda pack and this leaflet.

If you forget to give Ojemda
- If the weekly dose of Ojemda is delayed by 3 days or less give it as soon as you remember. Give the next dose to your child on the next regularly scheduled day.
- If the dose of Ojemda is delayed by more than 3 days, skip it and give the next dose to your child on the next regularly scheduled day.

If your child vomits after taking Ojemda
If your child vomits immediately after taking Ojemda, give the dose to your child again. If you are not sure if you should give another dose, contact your doctor or pharmacist.

If you stop giving Ojemda
Give Ojemda for as long as the doctor recommends. Do not stop unless the doctor advises you to.
If you have any further questions on the use of this medicine, ask the doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using this medicine and seek urgent medical attention if your child has any of the following symptoms:
- Severe bleeding, such as a nosebleed that does not stop.
- Signs of tumour bleeding, such as sudden tingling, weakness, numbness or sudden and severe headache, nausea or vomiting, confusion or slurred speech.
- Rash, acne-like rash, peeling, redness of skin or irritation, bumps or tiny papules, blisters. These may be signs of serious skin rashes.
- Sunburn after exposure to sun.It is recommended to use precautionary measures against exposure to light such as use of sunscreen (SPF $\geq$ 50), sunglasses, and/or protective clothing.

Other possible side effects

Very common (*may affect more than 1 in 10 people*)
- Hair colour changes
- Tiredness (fatigue)
- Low levels of red blood cells which can cause tiredness and pale skin (anaemia)
- Increased level of enzymes (blood creatine phosphokinase increased) an enzyme released into the blood when muscle is damaged
- Being sick (vomiting)
- Low levels of phosphate in the blood (hypophosphataemia)
- Headache

- Dry skin
- Fever (pyrexia)
- Slow growth (growth retardation)
- Acne
- Increase levels of enzymes found in your child's liver (aspartate aminotransferase increased)
- Increased levels of enzymes (blood lactate dehydrogenase increased) which can show that your child has some type of tissue damage.
- Feeling sick (nausea)
- Constipation
- Nose and throat infection (upper respiratory tract infection)
- Swelling (oedema)
- Nail bed infection (paronychia)
- Decreased appetite
- Belly pain (abdominal pain)
- Low levels of potassium in the blood (hypokalaemia)
- Inflammation of the lining of the mouth (stomatitis)
- Itching skin (pruritus)
- Diarrhoea
- Weight loss (weight decreased)
- Increase levels of enzymes found in your child's liver (alanine aminotransferase increased)
- Pain in legs and arms (pain in extremity)
- Skin colour changes (skin discolouration)
- Hair loss (alopecia)
- Muscle pain (myalgia)
- Decrease in lymphocyte count, a type of white blood cell
- Increase levels of a breakdown product of red blood cells (blood bilirubin increased)
- Low levels of albumin in the blood (hypoalbuminemia)
- Low levels of sodium in the blood (hyponatraemia)
- Joint pain (arthralgia)
- Viral infection
- Decrease in white blood cell count
- Reddening of the skin (flushing)

Common (*may affect up to 1 in 10 people*)
- Increase in eosinophil count, a type of white blood cell
- Inflammation of the eyelid margins (blepharitis)
- Dry eye

Reporting of side effects
If your child gets any side effects, talk to the doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ojemda

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions. The suspension must be used within 15 minutes after reconstitution.

Do not use this medicine if the safety seal under the cap of the bottle is broken or missing.

Do not use this medicine if you notice that the package is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ojemda contains

- The active substance is tovorafenib. One bottle contains 300 mg of tovorafenib. After reconstitution, one bottle of oral suspension delivers 12 ml of tovorafenib at a concentration of 25 mg/ml.
- The other ingredients are: copovidone, cellulose microcrystalline, mannitol (E421) sodium lauril sulfate, simeticone, maltodextrin, silica, colloidal anhydrous, sucralose powder, artificial strawberry flavour (contains maltodextrine, triacetine, artificial flavour).

This medicine contains less than 1 mmol sodium (23 mg) per bottle , that is to say essentially ‘sodium-free’.

What Ojemda looks like and contents of the pack
Ojemda powder for oral suspension 25 mg/ml is a white to off white powder in a clear glass bottle, co-packaged with a press-in bottle adaptor and a 20 ml oral dosing syringe.
Each ml of reconstituted, strawberry flavoured Ojemda powder for oral suspension contains 25 mg of tovorafenib. After reconstitution, one bottle of oral suspension delivers 300 mg in 12 ml of tovorafenib at 25 mg/ml.

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Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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INSTRUCTIONS FOR USE

Read the leaflet first before reading this Instructions for Use.

This Instructions for Use contains important information on how to prepare, measure and give a dose of Ojemda 25 mg/ml powder for oral suspension.

- Read this Instructions for Use carefully before you prepare, measure and give a dose of Ojemda for the first time, and each time you get a refill as there may be new information. This information does not take the place of talking with the doctor about your child's medical treatment or condition.
- The doctor or pharmacist should show you how to prepare, measure and give a dose of Ojemda correctly. Talk to the doctor or pharmacist if you have questions.
- Give Ojemda exactly as the doctor tells you to.
- You will receive Ojemda in a box that contains a bottle with powder, a 20 ml oral dosing syringe, and a bottle adaptor. Contact your doctor or pharmacist if you do not have one or more of these items**.**
- The bottle is made of glass. Do not use the bottle if it is broken or damaged. Do not use Ojemda if the safety seal under the cap is broken or missing. Contact the doctor or pharmacist for a new bottle.
- Do not use Ojemda after the expiry date which is stated on the bottle and box after EXP. Contact your pharmacist if the expiry date has passed.
- Only use room temperature water for preparing Ojemda.
- Each dose **must be given within 15 minutes** after the medicine has been prepared.
- Each bottle, bottle adaptor and syringe of Ojemda are **for single use only**.
- Keep the bottle, bottle adaptor and syringe out of the reach of children.

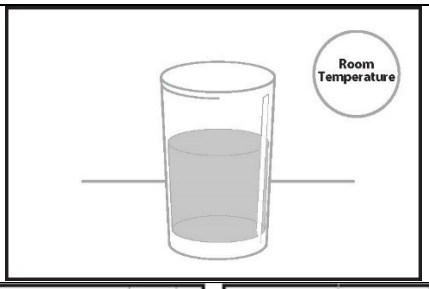
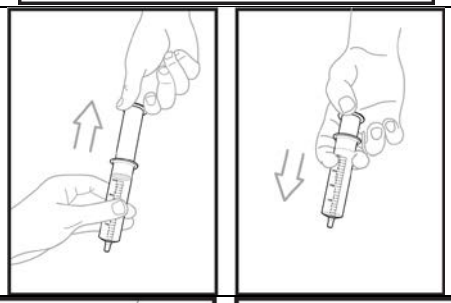
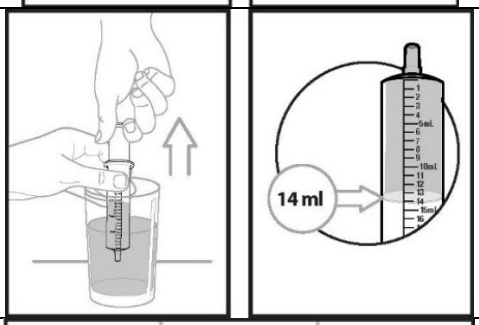
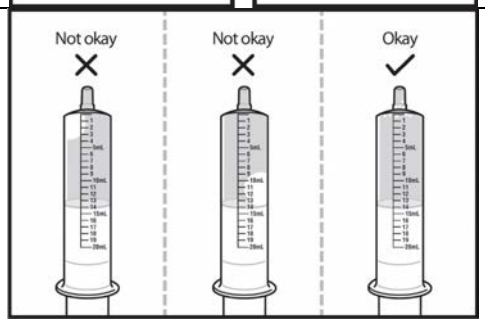
Get the following supplies ready:	
Included in the box:  	**Not included in the box:** • 1 empty clean cup • room temperature water (15 to 30°C) • ENFit syringe and ENFit adaptor (if taking or giving Ojemda powder for oral suspension through a feeding tube)

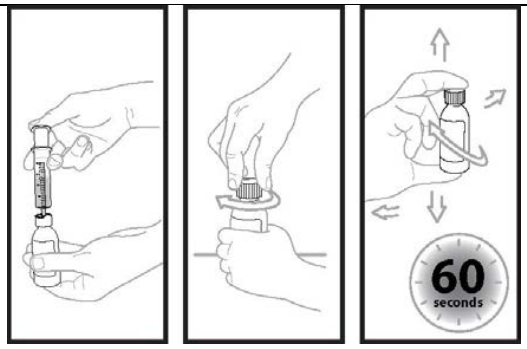
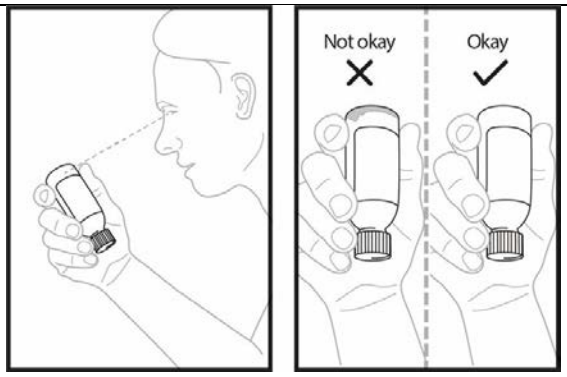
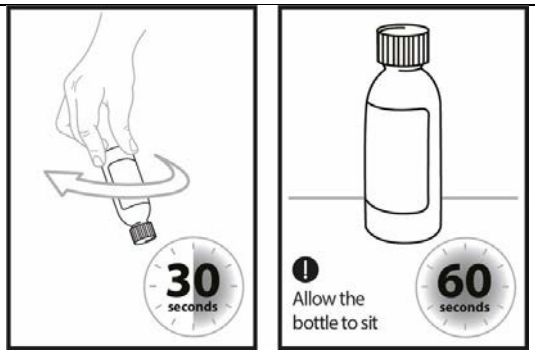
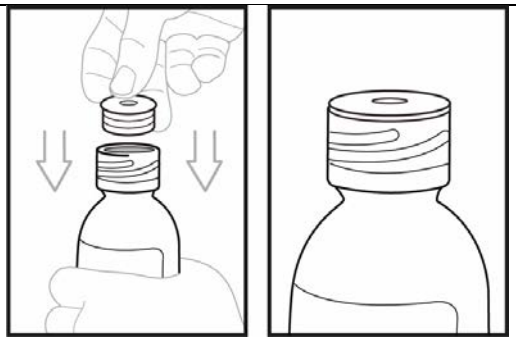
Always use the oral dosing syringe provided to make sure that you correctly measure your prescribed dose. The 20 ml oral dosing syringe is marked to help you correctly measure the prescribed dose of Ojemda. The barrel of the oral dosing syringe has markings in millilitres (ml).

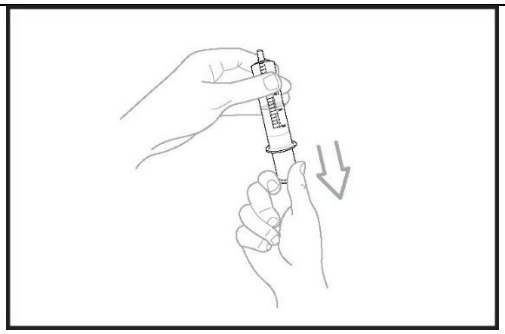
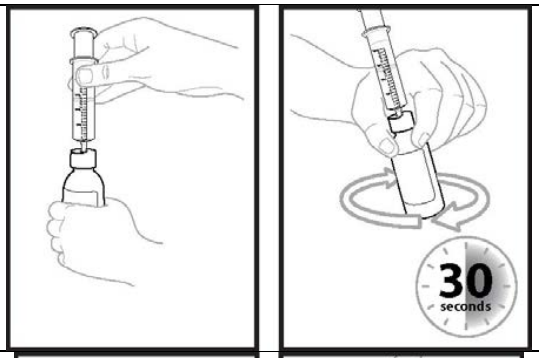
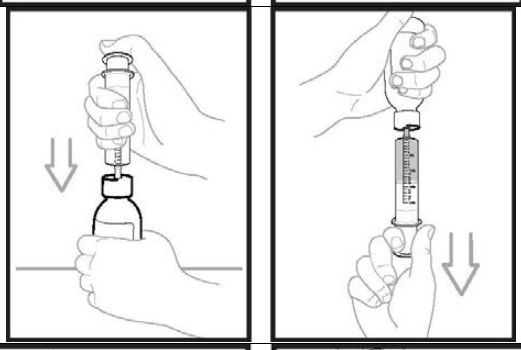
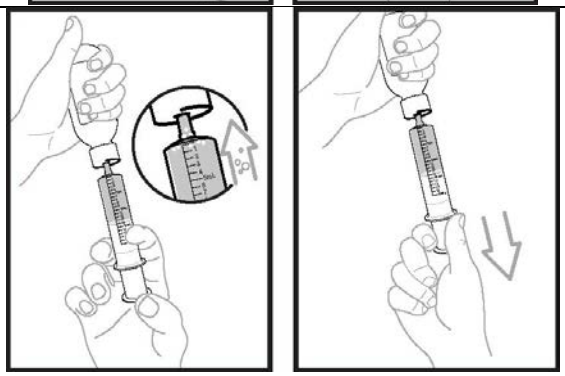
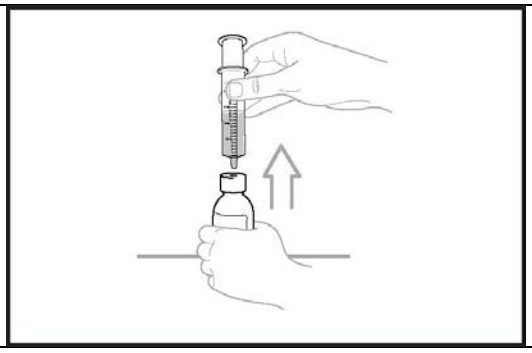
Note: The prescribed dose of Ojemda may require preparing 2 bottles of the powder. If 2 bottles are required:

- always add exactly 14 ml of room temperature water to each bottle, **and**
- prepare and give the dose of Ojemda from the first bottle, and then repeat the same steps to prepare and give the dose of Ojemda from the second bottle.

- Ojemda can be given by mouth using the 20 ml oral dosing syringe, or through a feeding tube with a **minimum** size of 12 French using an ENFit syringe.
    - If you are giving Ojemda **by mouth,** follow Section A, **Steps 1 to 19**.
    - If you are giving Ojemda **by a feeding tube,** follow Section B, **Steps 20 to 25**.

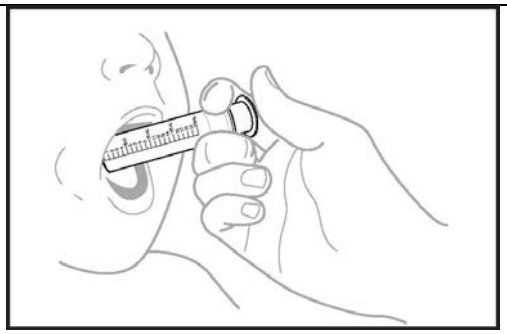
SECTION A: ADMINISTRATION VIA ORAL SYRINGE	
Step 1. Wash and dry your hands before preparing, measuring and giving a dose of Ojemda.	
Step 2. Place your supplies on a clean, flat work surface.	
Step 3. Fill a cup half-way with room temperature water (around 15°C to 30°C). **Do not use cold water.**	
Step 4. Remove air from the oral dosing syringe. Pull the plunger up into the oral dosing syringe as far as it will go and then push the plunger back down into the oral dosing syringe as far as it will go. This will help to remove all the air inside.	
Step 5. Place the oral dosing syringe tip in the water. Pull up on the plunger to draw water into the oral dosing syringe to the 14 ml mark.	
Step 6. Remove the oral dosing syringe from the cup. Turn the oral dosing syringe tip upward and check for air bubbles. If large air bubbles appear in the oral dosing syringe, push the water back into the cup and then pull up on the plunger again to draw up the water to the **14 ml** mark. **Repeat Step 6** until there are no large air bubbles present. Small air bubbles are ok. Set the oral dosing syringe aside.	
Step 7. Open the bottle with powder by pushing down firmly on the cap and turning it to the left (counter-clockwise). • **Do not** throw away the cap. • Remove the Safety seal. **Do not** use the bottle with powder if the safety seal under the cap is broken or missing. Call the doctor or pharmacist if the safety seal is broken.	

Step 8. Insert the tip of the oral dosing syringe into the opening of the bottle. Push down on the plunger and inject exactly 14 ml of water into the bottle. • Remove the tip of the emptied oral dosing syringe from the bottle and set it aside. • Right away, replace the cap back onto the bottle by pushing down while twisting the cap to the right (clockwise). • Shake the bottle well for 60 seconds in all directions.	
Step 9: Turn bottle upside down to check for any powder stuck to the inside of the bottle. • If you still see powder in the bottle, continue to shake the bottle for another 15 seconds until you no longer see the powder inside the bottle. • **Do not shake the bottle for more than 2 minutes total time.** • Check the bottle to make sure all of the powder is no longer visible. • If you still see powder in the bottle, contact the doctor or pharmacist and ask for a new bottle.	
Step 10. Turn the bottle upside down again and swirl for 30 seconds. • Place the bottle on a flat, clean, work surface. • Remove the cap and check that no solids are stuck in the bottle neck. • If you see solids in the bottle neck, recap the bottle, turn the bottle upside down, and swirl for an additional 15 seconds. • Allow the bottle to sit for 60 seconds to allow most of the foam to settle. **Note:** Foaming in the bottle will reduce the amount of Ojemda for oral suspension.	
Step 11. Open the bottle by firmly pressing down on the cap and turning it to the left (counterclockwise). **Do not** throw away the cap. Firmly insert the bottle adaptor into the bottle by pushing it tightly into the top of the bottle. The top edge of the bottle adaptor should be even with the bottle top. **Do not** remove the bottle adaptor after it is inserted into the bottle.	

Step 12. Check the dose in millilitres (ml) as prescribed by your doctor. Pick up the oral dosing syringe again. Each mark on the oral dosing syringe is equal to 1 ml. Draw air into the oral dosing syringe by pulling the plunger out to the prescribed dose. For example, if the prescribed dose is 12 ml, you would draw the oral dosing syringe by pulling the plunger out to the 12 ml mark.	
Step 13. Insert the tip of the oral dosing syringe into the bottle adaptor. • The tip of the oral dosing syringe should fit snugly into the hole of the bottle adaptor. • Keep the oral dosing syringe attached to the bottle. 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.	
Step 14. Inject the air from the oral dosing syringe into the bottle. Hold the oral dosing syringe in place and turn the bottle upside down. To measure the 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.	
Step 15. While the syringe is still 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 **Step 15** until you see that few or no air bubbles remain or if you draw up the wrong dose in the oral dosing syringe. **Note:** Only use up to 12 ml of Ojemda from each prepared bottle. • If the prescribed dose is more than 12 ml (300 mg), split the dose as equally as possible between each prepared bottle. • For example, if the dose is 13 ml, draw 6 ml from the first prepared bottle, and 7 ml from the second prepared bottle.	
Step 16: Leave the tip of the oral dosing syringe in the bottle adaptor and carefully turn the bottle upright. Put the bottle onto your flat work surface again. Slowly remove the oral dosing syringe tip from the bottle adaptor by gently pulling straight up. **Do not** hold the oral dosing syringe by the plunger because the plunger may come out.	

Step 17: Check again to be sure the top of the plunger of the oral dosing syringe is at your prescribed ml dose mark. If you do not have the correct prescribed ml dose, repeat **Steps 15 to 17.**
If you are giving a dose of Ojemda **by mouth, continue to Step 18**.
If you are giving a dose of Ojemda through a feeding tube, go to **Section B**.
Ojemda **must be given within 15 minutes** after prepared for use.

Step 18. Your child should sit upright to take or give a dose of Ojemda. Place the tip of the oral dosing syringe towards the inside of the cheek inside the mouth.
• Slowly push the medicine into the mouth by pressing down on the plunger.
• **Do not** forcefully push the plunger. This may cause choking.
• Allow the child to swallow while given Ojemda. Your child may drink liquids right away after swallowing Ojemda.
• Be sure to give the entire dose of Ojemda.
• If 2 bottles of Ojemda are required to prepare your prescribed dose, repeat **Section A, Steps 1 to 18** for the second bottle.
• Throw away the prepared Ojemda oral suspension if it is not given within 15 minutes.



Step 19: See **Section C** for instructions on "**How to throw away used, expired or unused bottles of Ojemda, and oral dosing syringes"**

SECTION B: ADMINISTRATION VIA A FEEDING TUBE

Before giving a dose of Ojemda **for oral suspension** through a feeding tube, read the following information and talk to child's doctor before continuing to **STEP 20**:
• Ojemda may be given through a feeding tube, as directed by the doctor.
• Only use a feeding tube **with a minimum size of 12 French.**
• Always use the 20 ml oral dosing syringe (included in the box) to prepare each dose of Ojemda in the bottle.
• Always use a 20 ml ENFit syringe and an ENFit adaptor (neither included in the box) to measure and give each dose of Ojemda through the feeding tube.

Step 20. Flush the feeding tube according to the manufacturer's instructions before giving a dose of Ojemda.

Step 21:
Follow **Steps 1 to 11** in **Section A** to prepare Ojemda using the 20 ml oral dosing syringe.
Then, follow **Steps 12 to 17** in **Section A** to draw up your child's dose of Ojemda using the ENFit syringe and ENFit adaptor.

Step 22: Connect the 20 ml ENFit syringe containing Ojemda to the feeding tube.

Step 23: Apply steady pressure to the plunger to give the entire dose of Ojemda through the feeding tube.

Step 24: Flush the feeding tube after giving each dose of Ojemda according to the manufacturer's instructions. If 2 bottles are required, **repeat Step 21** and give the remainder of the dose right away.

Step 25: Go to **Section C** for instructions on "**How to throw away used, expired or unused bottles of Ojemda, and oral dosing syringes"**

Section C: How to throw away used, expired or unused bottles of Ojemda, and oral dosing syringes

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.