**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

ZTALMY 50 mg/mL oral suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral suspension contains 50 mg of ganaxolone.

Excipients with known effect

Each mL of oral suspension contains:
- 0.00068 mg benzoic acid
- 0.00023 mg benzyl alcohol
- 1.02 mg methyl parahydroxybenzoate
- 0.2 mg propyl parahydroxybenzoate

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral suspension.

White to off-white suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ZTALMY is indicated for the adjunctive treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 to 17 years of age. ZTALMY may be continued in patients 18 years of age and older.

### 4.2 Posology and method of administration

Treatment should be initiated and supervised by physicians with experience in the treatment of epilepsy.

Posology

*Children and adolescents*

ZTALMY should be titrated gradually to achieve individual clinical response and tolerability. Any patient not tolerating the dosing steps shown in the tables below, can be maintained at the lower dose for additional days before advancing to the next dose. If the next dose is still not tolerated, patients can drop back to the previous lower dose.

ZTALMY must be administered 3 times a day. It is recommended that the total daily dose is administered in 3 equal doses throughout the day. If this is not tolerated by a patient, the dose at each

dosing interval can be adjusted to manage symptoms (e.g., somnolence), provided that the total daily dose is administered.

*Patients weighing ≤ 28 kg*
The recommended maximum daily dose is 63 mg/kg/day given in three separate doses (every 8 hours). A minimum dose of 33 mg/kg/day is generally required.

The recommended titration schedule for patients weighing 28 kg or less is shown below:

| **Week** | **Dose (given 3 times a day)** | **mL/kg per single dose** | **Total daily dose** |
|---|---|---|---|
| Week 1 | 6 mg/kg | 0.12 | 18 mg/kg |
| Week 2 | 11 mg/kg | 0.22 | 33 mg/kg |
| Week 3 | 16 mg/kg | 0.32 | 48 mg/kg |
| Week 4 – ongoing | 21 mg/kg | 0.42 | 63 mg/kg |

*Patients weighing > 28 kg*
The recommended maximum daily dose is 1 800 mg per day given in three separate doses (every 8 hours). A minimum dose of 900 mg/day is generally required.

The recommended titration schedule for patients weighing more than 28 kg is shown below:

| **Week** | **Dose (given 3 times a day)** | **mL per single dose** | **Total daily dose** |
|---|---|---|---|
| Week 1 | 150 mg | 3 | 450 mg |
| Week 2 | 300 mg | 6 | 900 mg |
| Week 3 | 450 mg | 9 | 1 350 mg |
| Week 4 – ongoing | 600 mg | 12 | 1 800 mg |

*Adults*

The efficacy and safety of treatment initiation with ZTALMY in patients aged over 17 years have not yet been established. In adolescents in whom a clear treatment benefit has been demonstrated, treatment may be continued into adulthood. However, treatment initiation in adults is not recommended as efficacy and safety have not yet been established in this population (see sections 5.1 and 5.2)

*Discontinuation*

If ZTALMY must be discontinued, the dose should be decreased gradually. For patients weighing 28 kg or less, the decrease in total daily dose should be 15 mg/kg every four days. For patients weighing more than 28 kg, the decrease in total daily dose should be 450 mg every four days. ZTALMY may be stopped immediately and without down-titration in the case of an emergency, however, a down-titration is recommended to minimize the risk of increased seizure frequency and status epilepticus.

*Missed doses*

Missed doses may be taken up to 4 hours before the next scheduled dose. When the next dose is due in less than 4 hours, it is recommended to skip the dose and to continue with the next scheduled dose.

*Special populations*

*Elderly*
There is no information on the use of ZTALMY in patients with CDD who are 65 years of age and over.

*Renal impairment*
ZTALMY can be administered to patients with mild, moderate, or severe renal impairment without dose adjustment. There is no experience in patients with end-stage renal disease. It is not known if ZTALMY is dialysable (see section 5.2).

*Hepatic impairment*
Dose adjustment is not required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment (see section 4.4).

For patients with severe hepatic impairment (Child-Pugh C) the initial target dose should be one-third the recommended target dose. The dose titration should be performed as detailed in the table(s) below.

The dose in patients with severe hepatic impairment weighing 28 kg or less is shown below:

| **Week** | **Dose (given 3 times a day)** | **mL/kg per single dose** | **Total daily dose** |
|---|---|---|---|
| Week 1 | 2 mg/kg | 0.04 | 6 mg/kg |
| Week 2 | 3.7 mg/kg | 0.07 | 11 mg/kg |
| Week 3 | 5.3 mg/kg | 0.11 | 16 mg/kg |
| Week 4 – ongoing | 7 mg/kg | 0.14 | 21 mg/kg |

The dose in patients with severe hepatic impairment weighing more than 28 kg is shown below:

| **Week** | **Dose (given 3 times a day)** | **mL per single dose** | **Total daily dose** |
|---|---|---|---|
| Week 1 | 50 mg | 1 | 150 mg |
| Week 2 | 100 mg | 2 | 300 mg |
| Week 3 | 150 mg | 3 | 450 mg |
| Week 4 – ongoing | 200 mg | 4 | 600 mg |

Higher or lower doses may be considered in patients with severe hepatic impairment based on individual clinical response and tolerability.

*Paediatric population*
There is no relevant use of ZTALMY in infants below 6 months of age. The safety and efficacy of ZTALMY in children aged less than 2 years have not yet been established. No data are available.

Method of administration

Oral use only. No data are available on the feasibility of administration through an enteral feeding tube.

ZTALMY must be taken with or shortly after meals and each dose should be administered with similar types of food, if possible (see section 5.2). Do not mix with food or drinks prior to administration.

ZTALMY should only be administered using the reusable oral dosing syringes provided in each pack for a more accurate dose administration.

Each 12 mL reusable oral syringe is graduated in 0.25 mL increments (each 0.25 mL increment corresponds to 12.5 mg ganaxolone) and each 3 mL reusable oral dosing syringe is graduated in 0.1 mL increments (each 0.1 mL increment corresponds to 5 mg ganaxolone). The calculated dose should be rounded to the nearest graduated increment. If the calculated dose is 3 mL (150 mg) or less, the smaller 3 mL oral syringe should be used. If the calculated dose is more than 3 mL (150 mg) the larger 12 mL oral syringe should be used.

## 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

Somnolence and sedation

ZTALMY causes somnolence and sedation (see sections 4.5 and 4.8).

Other Central Nervous System (CNS) depressants, including concomitantly used anti-seizure medicinal products, opioids, antidepressants, and alcohol, could potentiate the somnolence and sedation effect.

Suicidal behaviour and ideation

Suicidal behaviour and ideation have been reported in patients treated with anti-epileptic drugs (AEDs) in several indications. A meta-analysis of randomised placebo-controlled trials with AEDs has shown a small increased risk of suicidal behaviour and ideation. The mechanism of this risk is not known. The available data do not exclude the possibility of an increased risk with ganaxolone.

Patient's caregivers should be advised to monitor for signs of suicidal behaviour and ideation, or self-harm behaviour during treatment and when changes in the treatment regimen become necessary. Caregivers should be advised to seek medical advice should any signs of suicidal behaviour and ideation, or self-harm emerge.

Alcohol use

In animal models, ganaxolone has been shown to potentiate the effects of alcohol. Patients should not use alcohol during treatment (see section 4.5).

CYP3A4 inducers

Concomitant use with strong cytochrome P450 (CYP) 3A4 inducers e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin and St John's Wort should be avoided as they can reduce ganaxolone exposure (see section 4.5).

Hepatic impairment

An increase in ganaxolone exposure was seen in patients with severe hepatic impairment (Child-Pugh C) (see section 5.2). A dosage adjustment is recommended in these patients (see section 4.2).

Abuse

ZTALMY has potential for abuse (see section 5.3).

Dependence

It was not possible to assess physical dependence during clinical trials with ganaxolone; animal studies suggest that abrupt discontinuation of ganaxolone may cause withdrawal symptoms (see sections 5.1 and 5.3). It is therefore recommended that ganaxolone be tapered according to the dosage recommendations unless symptoms warrant immediate discontinuation (see section 4.2).

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per each daily dose, that is to say essentially 'sodium-free'.

This medicinal product contains 0.00068 mg benzoic acid in each mL. Benzoic acid may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

This medicinal product contains 0.00023 mg benzyl alcohol in each mL. Benzyl alcohol may cause allergic reactions. Monitor patients less than 3 years of age for respiratory symptoms. Advise patients who are pregnant or breastfeeding of the potential risk from the excipient benzyl alcohol, which might accumulate over time and cause metabolic acidosis. Use with caution in patients with hepatic or renal impairment, because of the potential risk from the excipient benzyl alcohol which may accumulate over time and cause metabolic acidosis.

This medicinal product contains 1.02 mg methyl parahydroxybenzoate and 0.2 mg propyl parahydroxybenzoate in each mL. Methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed).

## 4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 inducers

Coadministration with a strong CYP3A4 inducer will decrease ganaxolone exposure.

Concomitant use of rifampicin decreased the $AUC_{0\text{-}inf}$ of ganaxolone by approximately 57-68%. Enzyme inducing antiepileptics (e.g., carbamazepine, phenytoin, phenobarbital, and primidone) and St. John's Wort may result in similarly lower plasma exposures of ganaxolone. In patients on a stable dose of ganaxolone or in patients initiating or increasing the dose of concomitant enzyme-inducing antiepileptic medicinal products or St. John's Wort a dose increase may be necessary; however, do not exceed the maximum daily dose (see section 4.4).

CYP3A4 inhibitors

Coadministration of ganaxolone with itraconazole, a strong CYP3A4 inhibitor, increased the ganaxolone AUC by 17% in healthy subjects (the $C_{max}$ was unchanged). The changes in ganaxolone exposures when coadministered with strong, moderate, or weak CYP3A4 inhibitors are not expected to be clinically significant.

UGT inhibitors

Ganaxolone is a substrate for UGT1A3, UGT1A6, UGT1A9, and UGT2B15. No formal drug-drug interaction studies have been conducted with ganaxolone in combination with UGT inhibitors such as valproate. Dose reduction of ganaxolone and/or the UGT inhibitor may be necessary when given in combination.

Oral contraceptives

The potential interaction of ganaxolone with oral contraceptives has not been investigated.

Ethanol interaction

Concomitant use with CNS depressants (including alcohol) may increase the risk of sedation and somnolence (see section 4.4). Patients should be prohibited from drinking alcohol during treatment.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of ganaxolone in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

ZTALMY is not recommended during pregnancy and in woman of childbearing potential not using contraception.

Breast-feeding

Ganaxolone and its metabolites are excreted in human milk. Based on an average milk intake, the calculated maximum relative infant dose of ganaxolone is approximately 1% of the maternal dose. The effect of ganaxolone on breastfed newborns/infants is unknown. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue ZTALMY taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no human data on the effect of ganaxolone on fertility. Animal studies are insufficient with respect to fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

ZTALMY has a moderate to major influence on the ability to drive and use machines because it may cause somnolence, sedation and sedation-related adverse reactions, such as fatigue and ataxia, and other CNS-related events such as dizziness (see section 4.4). Patients should be advised not to drive or use machines (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials in patients with CDD include somnolence (29.4%) and pyrexia (23.5%).

Tabulated list of adverse reactions

Adverse reactions reported with ganaxolone in a clinical trials in patients with CDD with an average exposure duration of 411.5 days (N = 102) are listed in the table below by System Organ Class and frequency.

The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| System organ class | Very common | Common |
|---|---|---|
| Nervous system disorders | Somnolence | Sedation<br>Hypersomnia<br>Lethargy<br>Drooling |
| Gastrointestinal disorders | | Salivary hypersecretion |
| General disorders and administration site conditions | Pyrexia | |

Description of selected adverse reactions

*Somnolence and sedation*
ZTALMY can cause somnolence and sedation. In a placebo-controlled study for CDD, the incidence of somnolence and sedation was 31.4%, and 3.9% respectively in patients treated with ZTALMY, compared with 15.7%, and 3.9% respectively in patients treated with placebo. These adverse reactions appear early in treatment and are dose-related; symptoms may decrease with continued treatment.

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 limited clinical trial experience regarding overdose. Adverse events of the central nervous system (e.g., somnolence, sedation) have been reported to be dose dependent.

In the event of overdose, the patient should be observed and appropriate symptomatic treatment given, including monitoring of vital signs.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics, ATC code: N03AX27.

Mechanism of action

Ganaxolone is a methyl analogue of the endogenous neurosteroid allopregnanolone. Ganaxolone is a neuroactive steroid that positively and allosterically modulates gamma-aminobutyric acid type A ($GABA_A$) receptors in the CNS by interacting with a recognition site that is distinct from other allosteric $GABA_A$ receptor modulators.

The precise mechanism by which ganaxolone exerts its therapeutic effects in the treatment of seizures associated with CDD is unknown, but its anticonvulsant effects are thought to result from this modulation of $GABA_A$ receptor function providing constant, or tonic, modulation of GABA-mediated inhibitory neurotransmission.

Clinical efficacy and safety

The efficacy to treat seizures associated with CDD in patients 2 years and older was established in a single, double-blind, randomised, placebo-controlled study in patients aged 2 to 19 years (Study 1042-CDD-3001).

Patients enrolled in Study 1042-CDD-3001 had a molecular confirmation of pathogenic or likely pathogenic CDKL5 variant, their seizures were inadequately controlled by at least 2 previous concomitant AED medicinal products, and they had a minimum of 16 seizures of primary seizure type per 28 days in each 1-month period during the 2-month period prior to screening.

Totally, 101 patients were enrolled into the study (51 placebo and 50 study drug). Patients were mostly female (79.2%; consistent with the demographics of CDD) and aged between 2 and 19 years (mean [standard deviation (SD)]: 7.26 [4.55]) with the majority being paediatric (children 2 to 11 years [82.2%], adolescents [16.8%]), concomitant AEDs s were given to 96% patients. The mean (SD) number of concomitant AEDs used by subjects was 2.2 (1.14) in the placebo group and 2.6 (1.40) in the ganaxolone group. The most frequent (≥ 10 patients) concomitant AEDs were valproate, levetiracetam, clobazam and vigabatrin.

The primary efficacy endpoint was the percentage change from baseline in 28-day frequency of major motor seizures during the 17-week double blind treatment phase. Major motor seizures include bilateral tonic, bilateral clonic, atonic, generalized tonic-clonic and focal to bilateral tonic-clonic seizures. At baseline, the mean (SD) number of major motor seizures over 28-days was 104.8 (173.53) for placebo and 117.2 (138.62) for ganaxolone.

At the end of the 13-week maintenance phase, there was a statistically significant difference in the median percent change from baseline in major motor seizure frequency for patients treated with ganaxolone compared to patients receiving placebo (see Table 1).

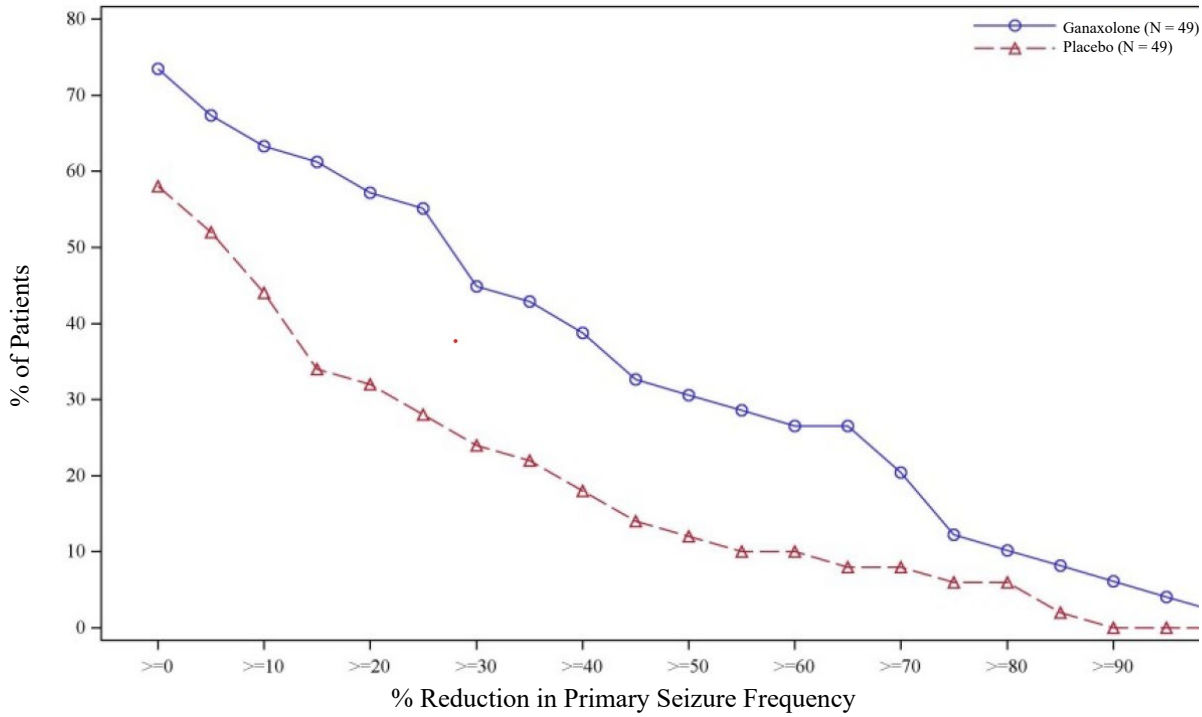
**Table 1 Study 1042-CDD-3001 Change in frequency of major motor seizures per 28 days in the 13-week maintenance phase**

| | **Placebo** | **Ganaxolone** |
|---|---|---|
| 28-Day seizure frequency for primary seizure types, N | 51 | 49 |
| 13-Week Maintenance, Median Percent change (95% CI) | -6.49 (-26.77, 38.46) | -29.39 (-65.78, 1.30) |
| Wilcoxon Test p-value | | 0.0097 |
| Response Rate, N | 50 | 49 |
| n (%) | 6 (12.0) | 15 (30.6) |
| Difference (95% CI) | | 18.6 (2.0, 34.9) |
| p-value[a] | | 0.0283 |

CI=95% confidence interval.
[a] Response is defined as at least 50% reduction from baseline in 28-day Seizure Primary Seizures Frequency. P-value is based on Fisher's Exact test.

The cumulative response curve shows that ganaxolone produced greater reductions than placebo in seizure frequency at all response rates (see Figure 1).

**Figure 1 Study 1042-CDD-3001 Cumulative Responder Curves of 28-Day Seizure Frequency for Primary Seizure Types - 13-Week Maintenance Phase, Intent-to-Treat Population**




Open-label data

CDD patients who participated in the double-blind phase of 1042-CDD-3001 could continue the study and participate in an open-label extension phase. The primary objective of the open-label extension phase was long-term safety and tolerability of ganaxolone. To enter the open-label extension phase, patients underwent a blinded cross-titration to a maximum daily dose of 63 mg/kg/day in patients <28 kg or 1800 mg/day in patients who were at least 28 kg. Data are reported for 88 patients who participated in the open-label extension phase and received ganaxolone for up to 4.25 years. A total of 63.6% of patients discontinued study participation during the open-label extension phase, predominantly due to withdrawal by subject/parent (17.0%), lack of efficacy (18.2%) and adverse events (11.4%).

Adult population

The CDD population in Study 1042-CDD-3001 predominantly consisted of paediatric patients. Two patients were 19 years old at the time of study enrolment (one randomised to placebo, one to ganaxolone). Seven patients turned 18 years of age during the open-label extension phase of the study. For these patients (n=9), the median percent change in major motor seizure frequency from baseline to their last 3 months in the open-label phase was -32.1% (range -86.2% to 72.7%).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ZTALMY in one or more subsets of the paediatric population in CDKL5 deficiency disorder (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

Ganaxolone is rapidly absorbed, with a time to maximum observed plasma concentration ($T_{max}$) of 2.0 to 3.0 hours at steady state (Css). Css is achieved within 2 to 3 days. Ganaxolone undergoes first-pass metabolism, the absolute bioavailability of ganaxolone suspension is approximately 13%.

Paediatric patients aged 2 to < 6 years (median body weight 14.8 kg), aged 6 to < 12 years (median body weight 22.6 kg), and aged 12 to < 18 years (median body weight 36.1 kg) had a $C_{max}$ of 247, 269, and 293 ng/mL and $AUC_{0-24}$ of 3903, 3998, and 4106 ng*h/mL, respectively, when given a dose of 21 mg/kg with a maximum of 600 mg three times a day. $C_{max}$ and $AUC_{0-24}$ in adult patients was 292 ng/mL and 4100 ng*h/mL, respectively.

Co-administration of ganaxolone with a high-fat meal increased $C_{max}$ by 2-fold and AUC by 3-fold when compared to fasted levels. The effect of different types of food is not known.

Distribution

Ganaxolone is extensively distributed throughout the body and its volume of distribution is approximately 580 L. Ganaxolone is approximately 99% protein bound in serum.

Biotransformation

Ganaxolone is extensively metabolized in humans, and over 50 Phase 1 and Phase 2 metabolites have been detected. The ganaxolone metabolite pattern at steady state has been characterised and is qualitatively similar to the pattern after a single dose but with increased proportion in the form of sulfated metabolites. The sulfated metabolites have a long elimination half-life. Ganaxolone is metabolised by CYP3A4 and CYP3A5; CYP2B6, CYP2C19, CYP2D6, UGT1A3, UGT1A6, UGT1A9, UGT2B7, and UGTB15.

Elimination

The half-life ($t_{½}$) for ganaxolone at steady state was 7.8 to 10.1 hours. Following a single oral dose of 300 mg [$^{14}$C]-ganaxolone to healthy male subjects, 55% of the total radioactivity was recovered in feces (2% as unchanged ganaxolone) and 18% of the total radioactivity dose was recovered in urine. Metabolites of ganaxolone may have a longer $t_{½}$ than ganaxolone, up to 230 hours.

Ganaxolone is excreted in breast milk, concentrations were approximately 4-fold higher than in plasma (see section 4.6).

Dose proportionality and accumulation

The pharmacokinetics of ganaxolone are generally linear between 200 mg and 600 mg (or their paediatric equivalent). When dosing three times a day, $C_{max}$ and $AUC_{tau}$ accumulation ratios are 1.5-fold and 1.7-fold, respectively.

Special populations

*Effect of age, sex, race*

Population pharmacokinetic analyses demonstrated that there were no clinically relevant effects of age, sex, or race on exposure to ganaxolone. CL, V, and maximum absorbed dose all follow an allometric relationship with weight. No clinically relevant effects were observed in children with body weight below 28 kg due to weight-based dosing. Population pharmacokinetic simulations indicate that the ganaxolone exposure in adults was reversely correlated with body weight. The clinical relevance is

currently unknown as the efficacy and safety have only been demonstrated for CDD paediatric patients with a low body weight.

*Paediatric population*

The observed pharmacokinetic exposures in patients in study 1042-CDD-3001 were comparable across the age groups 2 to less than 6 years of age (mean weight 14.8 kg, n=45), 6 to less than 12 years of age (mean weight 22.6 kg, n=28), and 12 to less than 18 years of age (mean weight 36.1 kg, n=16), and greater than 18 years of age (mean weight 35.1 kg, n=2). There are no pharmacokinetic data in children less than 2 years of age.

*Renal impairment*

The pharmacokinetics of ganaxolone were not significantly altered in patients with severe renal impairment. Following oral administration of a single 300 mg dose in subjects with severe renal impairment (creatinine clearance between 15 and 30 mL/min), the $AUC_{0\text{-}inf}$ of ganaxolone decreased 8% and $C_{max}$ decreased 11% as compared to that in subjects with normal renal function (creatinine clearance ≥90 mL/min as estimated by Cockcroft-Gault). Patients with end-stage renal disease were not studied.

*Hepatic impairment*

The influence of hepatic impairment on the pharmacokinetics of ganaxolone was studied following a single oral dose of 300 mg. No clinically significant effects on the exposures of ganaxolone were observed following administration in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. Patients with severe (Child-Pugh C) hepatic impairment had an approximately 5.8-fold increase in $AUC_{0\text{-}inf}$ as compared to those with normal hepatic function (see section 4.2).

Drug interaction studies

*In vitro assessment of drug interactions*

*In vitro* studies with ganaxolone demonstrated that no other pharmacokinetic interactions are expected. Ganaxolone is not an inhibitor or an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. *In vitro*, ganaxolone did not inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7. Ganaxolone does not inhibit BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP. Ganaxolone is not a substrate for BCRP, P-gp, OCT1, OCT2, OATP1B1 or OATP1B3.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology repeated dose toxicity, and genotoxicity.

Repeated dose toxicity

Primary effects in animals were central nervous system clinical observations (e.g., sedation), which were dose-limiting and attributed to exaggerated pharmacology.

In the 12-month repeat-dose toxicology study in dogs, a dose-dependent increase in heart rate at ≥ 3 mg/kg/day (similar to clinical exposure levels) was observed and there were incidences of sinus tachycardia at higher doses. There were no changes in QTc intervals, blood pressure parameters, or histopathologic correlates.

Carcinogenicity/ genotoxicity

Carcinogenicity studies have not been conducted with ganaxolone in rats. Ganaxolone is not considered genotoxic.

Ganaxolone was not tumorigenic or carcinogenic in a 6-month carcinogenicity study in transgenic mice at up to the highest nonclinical dose level of 1 000 mg/kg/day. The plasma (AUC) exposure of ganaxolone at the high dose was lower than the AUC exposure in adult patients at the maximum recommended human dose of 1 800 mg (~0.3-fold clinical AUC). The carcinogenic potential of ganaxolone remains uncertain due to the low exposure in transgenic mice.

Reproductive and developmental toxicity

The reproductive and developmental toxicity studies are of limited value since exposure levels were far below clinically relevant levels.

In the fertility and early embryonic development study in rats, alterations in oestrous cyclicity occurred.

In the combined embryo-foetal development and pre- and post-natal development study in rats, gestation length was slightly lengthened and slight delays in offspring growth and related developmental milestones occurred.

Studies in lactating rats indicate that ganaxolone and its metabolites are excreted in milk with concentrations generally higher in milk compared with plasma.

It is not known if ganaxolone crosses the placenta.

Juvenile toxicity

Histological changes in juvenile rats were similar to those in adult rats on an AUC exposure basis. Sedation occurred at lower exposures in adults than in juvenile animals. Decreased bodyweight gain and a delay in sexual maturation occurred in juvenile males and females, with no effects on oestrous cyclicity or any fertility or reproductive parameters. Exposure levels in juvenile animals were similar to or lower than the clinical exposure levels.

Ganaxolone administration caused a dose-dependent increase in neurodegeneration in multiple brain regions, consistent with findings from other GABA modulators. There were no functional, neurobehavioural consequences of this effect in the 13-week juvenile study. Exposure levels in juvenile animals were similar to or lower than the clinical exposure levels.

Abuse

Ganaxolone shares an internal/subjective interoceptive cue with benzodiazepines and dose-dependently supported self-administration in a rodent model of reward, suggesting ganaxolone has reinforcing characteristics similar to benzodiazepines.

Dependence

Animal studies suggest that abrupt discontinuation of ganaxolone may cause withdrawal symptoms.

Studies with metabolites

Based on *in vitro* data, a potential hormonal effect of metabolite M2 at clinical exposures cannot be excluded. In repeat-dose toxicity studies with direct administration of M2, for up to 6-month duration, changes in the prostate gland (decreased weight, small size, decreased secretion, and atrophy) and/or

seminal vesicles (small size, decreased secretion, and atrophy) were observed in male rats at around clinical exposure levels (0.6 to 2.4-fold), and the clinical relevance remains unknown.

In a 9-week oral M2 study in juvenile rats, signs of precocious puberty in females, adverse effects on female reproductive organs including decreased corpora lutea and follicular cysts in the ovary, and oestrous cycle disruption; in males changes in seminal vesicles (i.e. decreased weight, small appearance, atrophy), delayed male sexual maturation, and lower mean epididymis and prostate gland weight were observed at below or around clinical exposure levels (0.3 to 2-fold clinical AUC). The risk to humans for these effects is unknown.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Hypromellose (E464)
Polyvinyl alcohol (E1203)
Sodium lauryl sulfate (E487)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Citric acid, anhydrous (E330)
Sodium citrate dihydrate (E331)
Artificial cherry flavour (including propylene glycol [E1520] and benzyl alcohol [E1519])
Sucralose (E955)
Simethicone emulsion (simethicone, polysorbate 65, methylcellulose, polyethylene glycolmonostearate, glycerol monostearate, xanthan gum, benzoic acid [E210], sorbic acid, and purified water)
Purified water

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

Use within 30 days of first opening the bottle.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

### 6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with a polypropylene (PP) child resistant (CR) cap lined with an induction foil liner packed into a carton along with calibrated reusable oral dosing syringes (HDPE plunger and polypropylene barrel), and a bottle adaptor(s) (low-density polyethylene).

Each carton contains either:
- one 110 mL-bottle with two 3 mL oral dosing syringes, two 12 mL oral dosing syringes, and one bottle adaptor, or
- five 110 mL-bottles with five 12 mL oral dosing syringes, and five bottle adaptors.

Each 12 mL syringe is graduated in 0.25 mL increments and each 3 mL syringe is graduated in 0.1 mL increments.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material (including any used/unused bottle adaptors and reusable oral dosing syringes) should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Immedica Pharma AB
113 63 Stockholm
Sweden

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1743/001
EU/1/23/1743/002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 July 2023

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

**A. MANUFACTURER(S) 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**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Immedica Pharma AB
Solnavägen 3H
113 63 Stockholm
Sweden

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dunkalk, A91 P9KD
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## 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 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## 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.

# ANNEX III

# LABELLING AND PACKAGE LEAFLET

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

ZTALMY 50 mg/mL oral suspension
ganaxolone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 50 mg of ganaxolone.

## 3. LIST OF EXCIPIENTS

Also contains: methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), artificial cherry flavour (including benzyl alcohol [E1519]), simethicone emulsion (including benzoic acid [E210]). See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
1 bottle pack:
1 × 110 mL bottle
2 × 12 mL reusable oral dosing syringes
2 × 3 mL reusable oral dosing syringes
1 bottle adaptor

5 bottle pack:
5 × 110 mL bottles
5 × 12 mL reusable oral dosing syringes
5 bottle adaptors

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Shake well 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

Discard unused portion 30 days after first opening.

## 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

Immedica Pharma AB
113 63 Stockholm
Sweden

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1743/001
EU/1/23/1743/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ZTALMY

## 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

ZTALMY 50 mg/mL oral suspension
ganaxolone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 50 mg of ganaxolone.

## 3. LIST OF EXCIPIENTS

Also contains: E218, E216, E1519, E210. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
110 mL

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use. Oral use
Shake well 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
Discard 30 days after first opening.
Discard by: ___/___/___

## 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

Immedica Pharma AB

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1743/001
EU/1/23/1743/002

## 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**

**ZTALMY 50 mg/mL oral suspension**
ganaxolone

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

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

**What is in this leaflet**


1. What ZTALMY is and what it is used for
2. What you or your child need to know before taking ZTALMY
3. How to take ZTALMY
4. Possible side effects
5. How to store ZTALMY
6. Contents of the pack and other information


## 1. What ZTALMY is and what it is used for

ZTALMY contains the active substance ganaxolone, a neuroactive steroid that works by attaching to specific receptors and stops the brain from having epileptic seizures.

ZTALMY is used to treat a rare epileptic seizure disorder called 'cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder' (CDD) in patients 2 to 17 years of age. If ZTALMY is helping to treat your seizures, it can still continue to be used when you or your child turns 18.

ZTALMY is used in combination with other anti-epileptic medicines.

This medicine will reduce the number of daily epileptic seizures you or your child may experience.

## 2. What you or your child need to know before taking ZTALMY

**Do not take ZTALMY**
- if you are allergic to ganaxolone or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor or pharmacist before taking ZTALMY if:

- **you or your child feel drowsy**
  ZTALMY can cause drowsiness or sleepiness, or the feeling of being overly calm and relaxed (i.e. feeling sedated). Talk to your doctor or pharmacist before taking ZTALMY if you have any concerns about these effects or if you are taking central nervous system depressants such as other medicines to treat seizures, opioids, antidepressants or alcohol, as these can increase the sleepiness and sedative effects of ZTALMY.

- **you or your child have had thoughts about harming or killing yourself**
  If you notice unusual changes in your mood or behaviour or have thoughts of harming or killing yourself, **contact your doctor straightaway**.
  If you are caring for a child with CDD, look out for any unusual changes in their mood or behaviour or anything they say that could mean they are thinking about self-harming or killing themselves. **If you notice any of these, contact your doctor straightaway.**

- **you or your child have a history of alcohol or drug addiction**
  ZTALMY has the potential to be abused or used for the wrong purpose. Talk to your doctor or pharmacist before taking ZTALMY if you have a medical history of alcohol or drug abuse.

- **you or your child have severe liver problems**
  Your doctor will monitor you closely during treatment and may reduce your dose of ZTALMY.

**Children and adolescents**
ZTALMY must not be given to children under the age of 2 years since there is no information on use in children below this age.

**Other medicines and ZTALMY**
Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take any other medicines. Taking ZTALMY with certain other medicines may cause side effects, affect how other medicines work or affect how ZTALMY works.
Do not start or stop taking other medicines without talking to your doctor or pharmacist first.

Tell your doctor if you or your child are taking any of the following medicines, as your dose of ZTALMY may need to be adjusted:

- Valproate-containing medicines, which are used to treat epilepsy, they may require your dose of ZTALMY to be lower;
  Medicines that may reduce how ZTALMY works may require your dose of ZTALMY to be higher:
- Other antiepileptic or anticonvulsant medicines such as carbamazepine, phenytoin, phenobarbital and primidone;
- Antibiotics such as rifampicin;
- St. John's Wort (*Hypericum perforatum*), a herbal remedy used for mild depression.

The interaction between this medicine and oral contraceptives has not been investigated. Talk to your doctor if you are taking oral contraceptives.

**ZTALMY with alcohol**
Alcohol should not be consumed as it can increase the sleepiness and sedative effects of ZTALMY.

**Pregnancy**
If you are pregnant or think you may be pregnant, ask your doctor or pharmacist for advice before taking this medicine.

ZTALMY is not recommended if you are pregnant or a women of child-bearing potential and not using contraception.

**Breast-feeding**
Do not use ZTALMY whilst breast-feeding unless your doctor decides the benefits of taking ZTALMY outweighs any potential risks.

**Driving and using machines**
ZTALMY can make you feel drowsy/sleepy. If affected, do not drive, ride a bicycle or operate a machine until you feel more alert.

**ZTALMY contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per each mL, that is to say, it is essentially 'sodium-free'.

**ZTALMY contains benzoic acid**
This medicine contains 0.00068 mg benzoic acid in each mL. Benzoic acid may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

**ZTALMY contains benzyl alcohol**
This medicine contains 0.00023 mg benzyl alcohol in each mL. Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children. Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor. Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist. Increased risk due to accumulation in young children. Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called 'metabolic acidosis').

**ZTALMY contains methyl parahydroxybenzoate and propyl parahydroxybenzoate**
This medicine contains 1.02 mg methyl parahydroxybenzoate and 0.2 mg propyl parahydroxybenzoate in each mL which may cause allergic reactions (possibly delayed).

## 3. How to take ZTALMY

ZTALMY is given under supervision of a doctor experienced in the treatment of epilepsy. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

It is an oral suspension (a liquid to be swallowed). Your doctor or pharmacist will tell you how much (in mL) of the oral suspension to take each day, and how many times a day you should take it.

**Your doctor will calculate the dose according to your body weight.** You may start on a low dose that your doctor gradually increases over time.

If you have severe hepatic impairment, your doctor will start you on a lower dose and follow a different titration schedule.

Patient weighing **less than or equal** to 28 kg

You or your child will gradually have your dose increased over 4 weeks until you receive the recommended maximum daily dose of 63 mg/kg/day given in three separate doses every 8 hours.

Patient weighing **more than** 28 kg

You or your child will gradually have your dose increased over 4 weeks until you receive the recommended maximum daily dose of 1 800 mg/day given in three separate doses every 8 hours.

It is recommended that you take 3 equal doses throughout the day. However, ZTALMY can make you feel sleepy, and your doctor may decide you should be given a lower dose during the daytime and a higher dose in the evening to avoid any sleepy effects during the daytime.

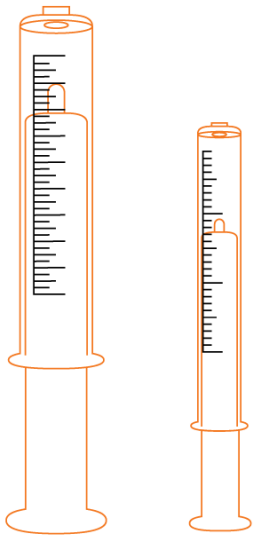
Talk to your doctor if you are unsure of your dose or if you think it may need to be changed.

How to take ZTALMY
- Take the medicine with or shortly after meals

- If possible, try to take with similar types of food (e.g. similar fat content) so you get the same effect each time
- Do not mix ZTALMY with food or drink
- To ensure an accurate dose, please use the reusable oral dosing syringes provided in each pack.

Instructions for use

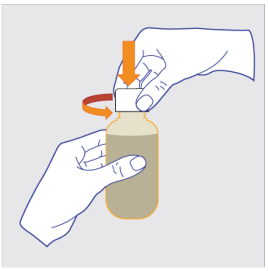
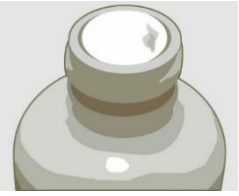
Each single-bottle pack is supplied with:

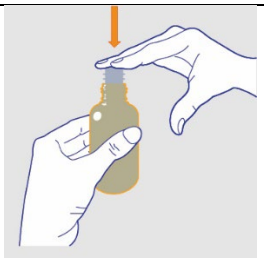
| | |
|---|---|
| One bottle of oral suspension closed with a child resistant cap | |
| Two 12 mL and two 3 mL reusable oral dosing syringes |  |
| One bottle adaptor | |

ZTALMY is also supplied in a pack with five bottles of oral suspension, five 12 mL reusable oral dosing syringes and five bottle adaptors. Please note that the pack containing five bottles of ZTALMY does not include a 3 mL reusable oral dosing syringe.

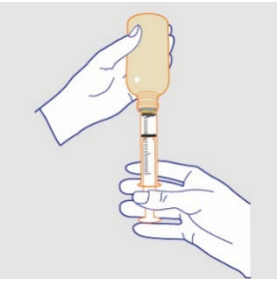
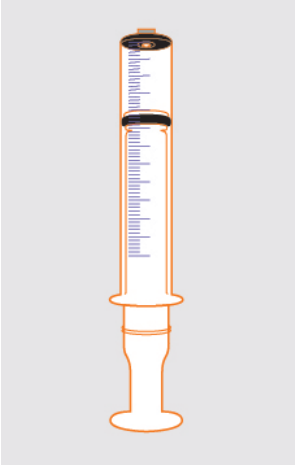
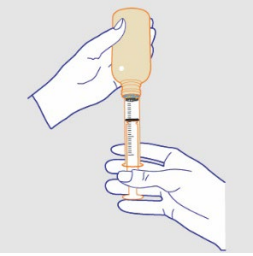
- Ask your doctor, pharmacist or nurse if you are not sure how to prepare or take the prescribed dose of ZTALMY.
- You will receive 12 mL and 3 mL reusable oral dosing syringes in the single-bottle pack. If your dose is 3 mL or less, use the smaller 3 mL syringes to take your medicine. If your dose is more than 3 mL use the larger 12 mL syringes to take your dose.
- Always use the correct reusable oral dosing syringe provided with ZTALMY to make sure you measure the right amount of ZTALMY. Do not use a household spoon. Do not mix ZTALMY with food or drink to administer.
- Each 3 mL dosing syringe may be used for 16 consecutive days. After 16 days, throw away the used dosing syringe and use the spare syringe contained in the carton.
- Use ZTALMY within 30 days of first opening the bottle. There is space on the bottle label for you to write down the date for discarding the bottle after opening so you do not forget.
- After 30 days, discard any ZTALMY that has not been used, and use a new bottle.

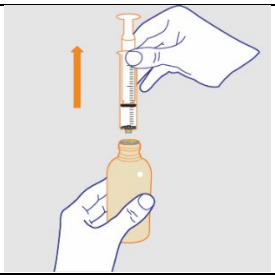
Preparing the bottle:

| | |
|---|---|
| 1. Hold the bottle in your hand and shake it up and down well for 1 minute.<br><br>Always shake the bottle well for 1 minute then let the bottle stand for 1 minute so that any foam that builds up during shaking can settle before measuring and giving **each dose** of ZTALMY. This helps you measure the correct amount of medicine.<br><br>**NOTE:** This step is for each dose of the medicine. | |
| 2. Remove the child-resistant cap on the bottle by pushing the cap down whilst turning the cap to the left (anti-clockwise). |  |
| 3. Puncture and peel off the induction seal from the bottle.<br><br>**NOTE:** This step is only for the first use of the bottle. |  |
| 4. Hold the bottle tight with one hand while pushing the bottle adaptor firmly into the neck of the bottle with the other hand, and make sure it is fully inserted. The adaptor could come off and cause choking if it is not fully inserted. | |

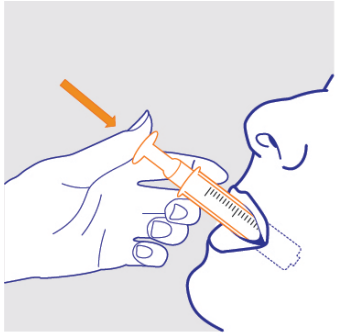
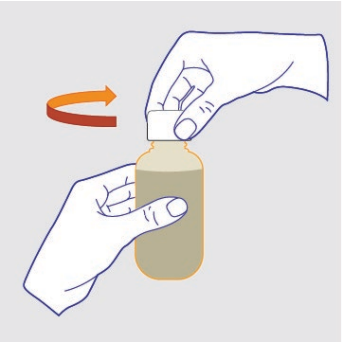
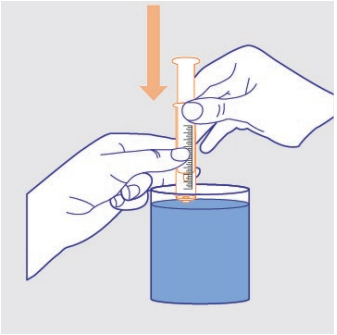
| | |
|---|---|
| **NOTE: Do not** remove the press-in bottle adapter from the bottle after it is inserted. |  |

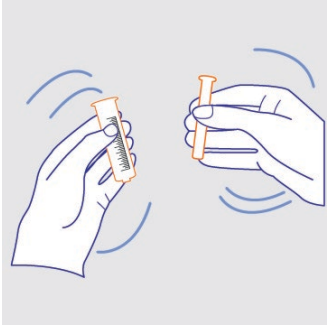
Preparing the dose:

| | |
|---|---|
| 5. Insert the tip of the correct reusable oral dosing syringe fully into the bottle adaptor, and with the oral syringe in place, turn the bottle upside down.<br><br>It is important that you use the correct reusable oral dosing syringe to measure your dose:<br>• If your dose is 3 mL (150 mg) or less, you should use the smaller 3 mL syringe.<br>• If your dose is more than 3 mL (150 mg), you should use the larger 12 mL syringe. |  |
| 6. Slowly pull back the plunger of the syringe, so the volume (number of mL) of oral suspension needed is drawn into the syringe. Line up the end of the plunger with the volume marking required, as shown opposite.<br><br>If there is an air bubble in the syringe, push the liquid back into the bottle whilst keeping the bottle upside down, and repeat Step 6 until the bubble has gone. |  |
| 7. Turn the bottle the right side up, and carefully remove the oral syringe from the adaptor. |  |

| | |
|---|---|
| |  |

Taking or giving ZTALMY:

| | |
|---|---|
| 8. Place the tip of the oral syringe inside the cheek, and gently push the plunger to release the medicine. Do not push the plunger forcefully or direct the medicine to the back of the mouth or throat. |  |
| 9. Screw the child resistant cap back on the bottle tightly, by turning the cap to the right (clockwise). You do not need to remove the bottle adaptor; the cap will fit over it. |  |
| 10. Wash the oral syringe immediately after use. Remove the plunger from the barrel of the syringe, and rinse both parts using room temperature tap water.<br><br>**Warning:**<br>**Do not use bleach or any other harsh cleaning solutions.**<br>**Do not wash the oral syringe in a dishwasher.** |  |

| | |
|---|---|
| 11. Shake off any water from both syringe parts and allow them to air-dry separately until the next use. Make sure both parts are completely dry before placing the plunger back into the syringe barrel for the next use. If both parts are not completely dry before the next dose, use the appropriate spare syringe provided in the pack.<br><br>When using the 12 mL syringe accompanying each bottle, do not throw away the reusable oral syringes until the bottle is empty. When using the 3 mL syringe, discard after 16 days. |  |
| 12. Repeat steps 1-3 and 6-12 for each next dose. | |

**If you take more ZTALMY than you should**
If you accidentally take more ZTALMY than you should, tell a doctor or pharmacist immediately, or contact your nearest hospital casualty department, and take the medicine with you. You may feel drowsy or sleepy from taking too much medicine.

**If you forget to take ZTALMY**
If you forget to take a dose, the missed dose may be taken up to 4 hours before the next scheduled dose. When the next dose is due in less than 4 hours, it is recommended to skip the dose and continue with the next scheduled dose.

**If you stop taking ZTALMY**
Do not reduce the dose or stop taking ZTALMY without first talking to your doctor. Stopping this treatment abruptly could increase your seizures. The doctor will explain how to gradually stop taking ZTALMY.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

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

You may get the following side effects with this medicine. **Tell the doctor** if you have any of the following:

**Very common** (may affect more than 1 in 10 people):
- feeling drowsy or sleepy;
- fever.

**Common** (may affect more than 1 in 100 people):
- feeling overly calm or relaxed;
- feeling excessively tired during the day or sleeping longer than usual at night;
- lack of energy;
- drooling;
- producing more saliva than usual.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. 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 ZTALMY

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 carton and the bottle label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Discard any unused medicine 30 days after first opening.

Do not throw away any medicines in the 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 ZTALMY contains**
- The active substance is ganaxolone. Each mL of oral suspension contains 50 mg of ganaxolone.

- The other ingredients are: hypromellose (E464), polyvinyl alcohol (E1203), sodium lauryl sulfate (E487), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), citric acid anhydrous (E330), sodium citrate dihydrate (E331), artificial cherry flavour (including propylene glycol [E1520] and benzyl alcohol [E1519]), sucralose (E955), simethicone emulsion (simethicone, polysorbate 65, methylcellulose, polyethylene, glycolmonostearate, glycerol monostearate, xanthan gum, benzoic acid [E210], sorbic acid and purified water), purified water (see also section 2 'ZTALMY contains sodium'; 'ZTALMY contains benzoic acid', 'ZTALMY contains benzyl alcohol', and 'ZTALMY contains methyl parahydroxybenzoate and propyl parahydroxybenzoate').

**What ZTALMY looks like and contents of the pack**
ZTALMY is a white to off-white oral suspension. It comes in a plastic bottle which has a plastic child-resistant cap. Each bottle contains 110 mL of oral suspension.

ZTALMY is supplied in packs of either:
- one bottle of oral suspension, two 12 mL and two 3 mL oral dosing syringes, and one bottle adaptor; or
- five bottles of oral suspension, five 12 mL oral dosing syringes, and five bottle adaptors.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**
Immedica Pharma AB
113 63 Stockholm
Sweden

**Manufacturer**
Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dunkalk, A91 P9KD
Ireland

**This leaflet was last revised in:**

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