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

AGAMREE 40 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of suspension contains 40 mg of vamorolone.

Excipient with known effect

The suspension contains 1 mg sodium benzoate (E 211) in each ml.

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

AGAMREE is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.

4.2 Posology and method of administration

Treatment with AGAMREE should only be initiated by specialist physicians with experience in the management of Duchenne muscular dystrophy.

Posology

The recommended dose of vamorolone is 6 mg/kg once daily in patients weighing less than 40 kg.

In patients weighing 40 kg and above, the recommended dose of vamorolone is 240 mg (equivalent to 6 ml) once daily.

Daily dose may be down-titrated to 4 mg/kg/day or 2 mg/kg/day based on individual tolerability. Patients should be maintained at the highest tolerated dose within the dose range.

Table 1: Dosing table

	6 mg/kg/day		4 mg/kg/day		2 mg/kg/day	
Weight (kg)	**Dose in mg**	**Dose in ml**	**Dose in mg**	**Dose in ml**	**Dose in mg**	**Dose in ml**
12-13	72	1.8	48	1.2	24	0.6
14-15	84	2.1	56	1.4	28	0.7
16-17	96	2.4	64	1.6	32	0.8
18-19	108	2.7	72	1.8	36	0.9
20-21	120	3	80	2	40	1
22-23	132	3.3	88	2.2	44	1.1
24-25	144	3.6	96	2.4	48	1.2
26-27	156	3.9	104	2.6	52	1.3
28-29	168	4.2	112	2.8	56	1.4
30-31	180	4.5	120	3	60	1.5
32-33	192	4.8	128	3.2	64	1.6
34-35	204	5.1	136	3.4	68	1.7
36-37	216	5.4	144	3.6	72	1.8
38-39	228	5.7	152	3.8	76	1.9
40 kg and above	240	6	160	4	80	2

The dose of vamorolone must not be decreased abruptly if the treatment has been administered for more than one week (see section 4.4). Dose tapering should be done progressively over weeks, by steps of approximately 20% decrease from the previous dose level. The duration of each tapering step should be adjusted depending on individual tolerability.

Special populations

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh class A).

The recommended daily dose of vamorolone for patients with moderate hepatic impairment (Child-Pugh class B) is 2 mg/kg/day for patients up to 40 kg and 80 mg for patients with a body weight of 40 kg and above (see section 5.2). Patients with severe hepatic impairment (Child-Pugh class C) should not be treated with vamorolone. See sections 4.3 and 4.4.

Paediatric population
The safety and efficacy of AGAMREE in children below 4 years of age has not been established.

Method of administration

AGAMREE is for oral use. AGAMREE should be taken preferably with a meal (see section 5.2).

The oral suspension requires redispersing by shaking the bottle prior to dosing.

Only the oral syringe provided with the medicinal product should be used to measure the dose of AGAMREE in ml. After the appropriate dose is withdrawn into the oral syringe, it should be dispensed directly into the mouth.

The oral syringe should be disassembled after use, rinsed under running cold tap water and air dried. It should be stored in the box until next use. An oral syringe may be used for up to 45 days, then it should be discarded and the second oral syringe provided in the pack should be used.

Administration of AGAMREE oral suspension via enteral feeding tube
AGAMREE oral suspension may be administered through an enteral feeding tube (see section 6.6).

4.3 Contraindications

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

Severe liver impairment (Child-Pugh class C).

Use of live or live-attenuated vaccines in the 6 weeks prior to starting treatment and during the treatment (see section 4.4).

4.4 Special warnings and precautions for use

Alterations in endocrine function

Vamorolone causes alterations in endocrine function, especially with chronic use.

In addition, patients with altered thyroid function, or pheochromocytoma may be at increased risk for endocrine effects.

Risk of adrenal insufficiency

Vamorolone produces dose-dependent and reversible suppression of the hypothalamic-pituitary-adrenal axis (HPA-axis), potentially resulting in secondary adrenal insufficiency, which may persist for months after discontinuation of prolonged therapy. The degree of chronic adrenal insufficiency produced is variable among patients and depends on the dose, and duration of therapy.

Acute adrenal insufficiency (also known as adrenal crisis) can occur during a period of increased stress or if vamorolone dose is reduced or withdrawn abruptly. This condition can be fatal. Symptoms of adrenal crisis may include excess fatigue, unexpected weakness, vomiting, dizziness or confusion. The risk is reduced by gradually tapering the dose when down-titrating or withdrawing treatment (see section 4.2).

During periods of increased stress, such as acute infection, traumatic injuries or surgical procedure, patients should be monitored for signs of acute adrenal insufficiency and the regular treatment with AGAMREE should be temporarily supplemented with systemic hydrocortisone to prevent the risk of adrenal crisis. There is no data available on the effects of increasing AGAMREE dose for situations of increased stress.

The patient should be advised to carry the Patient Alert Card providing important safety information to support early recognition and treatment of adrenal crisis.

A steroid “withdrawal syndrome”, seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuation of glucocorticoids. This syndrome includes symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, and/or weight loss. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low glucocorticoid levels.

Switching from glucocorticoid treatment to AGAMREE

Patients can be switched from oral glucocorticoid treatment (such as prednisone or deflazacort) to AGAMREE without the need for treatment interruption or period of prior glucocorticoid dose reduction. Patients previously on chronic glucocorticoids should switch to AGAMREE 6 mg/kg/day to minimise the risk for adrenal crisis.

Weight gain

Vamorolone is associated with dose-dependent increase in appetite and weight gain, mainly in the first months of treatment. Age-appropriate dietary advice should be provided before and during treatment with AGAMREE in line with general recommendations for nutrition management in patients with DMD.

Considerations for use in patients with altered thyroid function

Metabolic clearance of glucocorticoids can be decreased in hypothyroid patients and increased in hyperthyroid patients. It is unknown, whether vamorolone is affected in the same way, but changes in thyroid status of the patient may necessitate a dose adjustment.

Ophthalmic effects

Glucocorticoids may induce posterior subcapsular cataracts, glaucoma with potential damage to the optic nerves, and may increase the risk of secondary ocular infections caused by bacteria, fungi, or viruses.

The risk to cause ophthalmic effects with AGAMREE is unknown.

Increased risk of infections

Suppression of the inflammatory response and immune function may increase the susceptibility to infections and their severity. Activation of latent infections or exacerbation of intercurrent infections could occur. The clinical presentation may often be atypical and serious infections may be masked and may reach an advanced stage before being recognised.
These infections may be severe and at times fatal.

While no increased incidence or severity of infections was observed with vamorolone in the clinical studies, limited long-term experience does not allow to exclude an increased risk for infections.

The development of infections should be monitored. Diagnostic and therapeutic strategies should be applied in patients with symptoms of infection while on chronic treatment with vamorolone. Supplementation with hydrocortisone should be considered in patients presenting with moderate or severe infections, who are treated with vamorolone.

Diabetes mellitus

Long-term therapy with corticosteroids can increase the risk for diabetes mellitus.

No clinically relevant changes in glucose metabolism have been observed in vamorolone clinical studies, long-term data is limited. Blood glucose should be monitored at regular intervals in patients chronically treated with vamorolone.

Vaccination

Response to live or live attenuated vaccines can be altered in patients treated with glucocorticoids. The risk with AGAMREE is unknown.

Live attenuated or live vaccines should be administered at least 6 weeks prior to starting AGAMREE treatment.

For patients without a history of chicken pox or vaccination, vaccination against varicella zoster virus should be initiated before treatment with AGAMREE.

Thromboembolic events

Observational studies with glucocorticoids have shown an increased risk of thromboembolism (including venous thromboembolism) particularly with higher cumulative doses of glucocorticoids.

The risk with AGAMREE is unknown. AGAMREE should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

Anaphylaxis

Rare instances of anaphylaxis have occurred in patients receiving glucocorticoid therapy.

Vamorolone shares structural similarities with glucocorticoids and should be used with caution when treating patients with known hypersensitivity to glucocorticoids.

Hepatic impairment

Vamorolone has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and must not be used in these patients (see section 4.3).

Concomitant use with other medicinal products

UGT substrates
The potential for drug-drug-interactions involving UGTs has not been fully evaluated, therefore all inhibitors of UGTs should be avoided as concomitant medication and should be used with caution if medically required.

Excipients

Sodium benzoate
This medicinal product contains 1 mg sodium benzoate in each 1 ml which is equivalent to 100 mg/100 ml.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 7.5 ml, that is to say essentially `sodium-free`.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Vamorolone acts as an antagonist at the mineralocorticoid receptor. The use of vamorolone in combination with mineralocorticoid receptor antagonist may increase the risk of hyperkalaemia. No cases of hyperkalaemia have been observed in patients using vamorolone alone or in combination with eplerenone or spironolactone. Monitoring potassium levels one month after starting a combination between vamorolone and a mineralocorticoid receptor antagonist is recommended. In case of hyperkalaemia, a reduction of the dose of the mineralocorticoid receptor antagonist should be considered.

Pharmacokinetic interactions

Effect of other medicinal products on vamorolone
Concomitant administration with the strong CYP3A4 inhibitor itraconazole led to an increase of the vamorolone area under the plasma concentration time curve of 1.45-fold in healthy subjects. The recommended dose of vamorolone when administered with strong CYP3A4 inhibitors (e.g telithromycin, clarithromycin, voriconazole, grapefruit juice) is 4 mg/kg/day.

Strong CYP3A4 inducers or strong PXR inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) may decrease plasma concentrations of vamorolone and lead to lack of efficacy, therefore alternative treatments that are not strong inducers of CYP3A4 activity should be considered. Concomitant treatment with a moderate PXR or CYP3A4 inducer should be used in caution as the plasma concentration of vamorolone may be decreased relevantly.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available data from the use of vamorolone in pregnant women. Animal reproductive toxicity studies with vamorolone have shown reproductive toxicity (see section°5.3). Glucocorticoids have been associated with various types of malformations (palate cleft, skeletal malformations) in animal studies.

AGAMREE should not be used during pregnancy unless the clinical condition of the women requires treatment with vamorolone.

Women of childbearing potential have to use effective contraception during treatment with AGAMREE.

Breast-feeding

There are no data on the excretion of vamorolone or its metabolites in human milk. A risk to the newborns / infants cannot be excluded. Breast-feeding should be discontinued during treatment with AGAMREE.

Fertility

There are no clinical data on the effects of vamorolone on fertility.

Long-term vamorolone treatment inhibited male and female fertility in dogs (see section 5.3).

4.7 Effects on ability to drive and use machines

AGAMREE has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions for vamorolone 6 mg/kg/day are Cushingoid features (28.6%), vomiting (14.3%), weight increased (10.7%) and irritability (10.7%). These reactions are dose-dependent, usually reported in the first months of treatment and tend to decline or stabilise over time with continuous treatment.

Vamorolone leads to the suppression of the hypothalamic-pituitary-adrenal axis, which correlates with dose and the duration of treatment. Acute adrenal insufficiency (adrenal crisis) is a serious effect that can occur during a period of increased stress or if the vamorolone dose is reduced or withdrawn abruptly (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions are listed below according to MedDRA system organ class and frequency. The table contains adverse reactions in patients treated in the placebo-controlled study for patients treated with vamorolone 6 mg/kg/day (Pool 1). 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), very rare (< 1/10 000) (including isolated cases), not known (cannot be estimated from the available data).

Table 2: Adverse reactions

System Organ Class (SOC)	Adverse reaction (Preferred term)	Frequency
Endocrine disorders	Cushingoid	Very common
Metabolism and nutrition disorders	Weight increased Increased appetite	Very common
Psychiatric disorders	Irritability	Very common
Gastrointestinal disorders	Vomiting Abdominal pain Abdominal pain upper Diarrhoea	Very common Common Common Common
Nervous system disorders	Headache	Common

Description of selected adverse reactions

Cushingoid features
Cushingoid features (hypercortisolism) was the most frequently reported adverse reaction with vamorolone 6 mg/kg/day (28.6%). The frequency of cushingoid features was lower in the vamorolone 2 mg/kg/day group (6.7%). In the clinical study, cushingoid features were reported as mild to moderate "weight gain in the face", or "rounded face". The majority of the patients presented with Cushingoid features in the first 6 months of treatment (28.6% in Month 0 to 6 vs 3.6% in Month 6 to 12 in vamorolone 6 mg/kg/day) and did not result in discontinuation of treatment.

Behaviour problems
Behaviour problems were reported in the first 6 months of treatment at a higher frequency with vamorolone 6 mg/kg/day (21.4%) than with vamorolone 2 mg/kg/day (16.7%) or placebo (13.8%), due to an increased frequency of events described as mild irritability (10.7% in 6 mg/kg/day, no patient in 2 mg/kg/day or placebo). The majority of behaviour problems occurred in the first 3 months of treatment and resolved without treatment discontinuation. Between month 6 and month 12, the frequency of behaviour problems decreased in both vamorolone doses (10.7% for vamorolone 6 mg/kg/day and 7.1% for vamorolone 2 mg/kg/day).

Weight gain
Vamorolone is associated with increase in appetite and weight. The majority of the events of weight gain in the vamorolone 6 mg/kg/day group were reported in the first 6 months of treatment (17.9% in month 0 to 6 vs 0% in months 6 to 12). Weight gain was similar between vamorolone 2 mg/kg/day (3.3%) and placebo (6.9%). Age-appropriate dietary advice should be provided before and during treatment with AGAMREE in line with general recommendations for nutrition management in patients with DMD (see section 4.4).

Withdrawal signs and symptoms

Abruptly reducing or withdrawing the daily dose of vamorolone following prolonged treatment for more than one week can lead to adrenal crisis (see sections 4.2 and 4.4).

Paediatric population

The adverse events in paediatric patients with DMD treated with vamorolone were similar in frequency and type in patients 4 years of age and older.

The type and frequency of adverse events in patients older than 7 years were consistent with those seen in 4 to 7-year old patients. There is no available information on the effects of vamorolone on pubertal development.

A higher frequency of behaviour problems was observed in patients <5 years compared to patients ≥5 years when treated with vamorolone 2-6 mg/kg/day.

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

Treatment of acute overdose is by immediate supportive and symptomatic therapy. Gastric lavage or emesis can be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB18

Mechanism of action

Vamorolone is a dissociative corticosteroid that selectively binds to the glucocorticoid receptor, which triggers anti-inflammatory effects via inhibition of NF-kB mediated gene transcripts, but leads to less transcriptional activation of other genes. In addition, vamorolone inhibits the activation of the mineralocorticoid receptor by aldosterone. Due to its specific structure, vamorolone is likely not a substrate for 11ß-hydroxysteroid dehydrogenases and is therefore not subject to local tissue amplification. The precise mechanism by which vamorolone exerts its therapeutic effects in patients with DMD is unknown.

Pharmacodynamic effects

Vamorolone produced a dose-dependent decrease in morning cortisol levels in the clinical studies. A dose-dependent increase in haemoglobin, haematocrit values, erythrocytes, leukocyte counts and lymphocyte counts was observed with in clinical studies with vamorolone. No relevant changes in mean neutrophil counts or immature granulocytes were observed. High density lipoprotein (HDL) cholesterol and triglycerides values increased in a dose-dependent manner. There was no relevant effect on glucose metabolism up to 30 months of treatment.

Unlike corticosteroids, vamorolone did not result in a reduction of bone metabolism as measured by bone turnover markers, nor in a significant reduction in lumbar vertebral bone mineralisation parameters by Dual-Energy X-Ray Absorptiometry (DXA) after 48 weeks in the clinical studies. The risk for bone fractures in patients with DMD treated with vamorolone has not been established.

Clinical efficacy and safety

The efficacy of AGAMREE for the treatment of DMD was evaluated in Study 1, a multi-centre, randomised, double-blind, parallel-group, placebo- and active-controlled study of 24 weeks duration followed by a double-blind extension phase. The study population consisted of 121 male paediatric patients 4 to < 7 years of age at time of enrolment in the study who were corticosteroid naïve and ambulatory, with a confirmed diagnosis of DMD.

Study 1 randomised 121 patients to one of the following treatments: vamorolone 6 mg/kg/day (n = 30), vamorolone 2 mg/kg/day (n = 30), active comparator prednisone 0.75 mg/kg/day (n = 31), or placebo (n = 30). After 24 weeks (Period 1, primary efficacy analysis), patients who had been

receiving prednisone or placebo were re-assigned according to an initially defined randomisation scheme to either vamorolone 6 mg/kg/day or 2 mg/kg/day for an additional 20 weeks of treatment (Period 2).

In Study 1, efficacy was evaluated by assessing the change from Baseline to Week 24 in Time to Stand Test (TTSTAND) velocity for vamorolone 6 mg/kg/day compared to placebo. A pre-specified hierarchical analysis of relevant secondary endpoints consisted of change from baseline in TTSTAND velocity for the vamorolone 2 mg/kg/day vs placebo group, change from baseline in 6 Minute Walk Test (6MWT) distance for vamorolone 6 mg/kg/day followed by 2 mg/kg/day vs placebo.

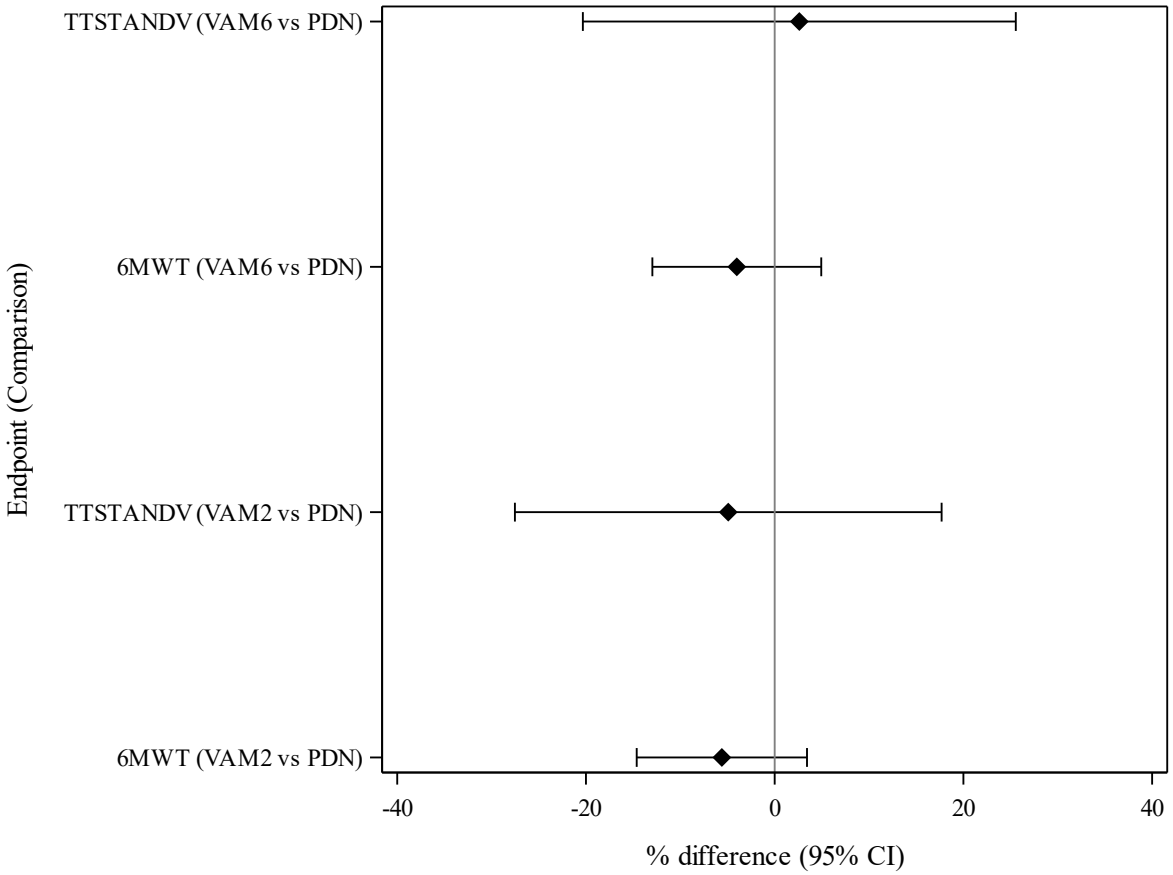
Treatment with vamorolone 6 mg/kg/day and 2 mg/kg/day resulted in a statistically significant improvement in change in TTSTAND velocity and change in 6MWT distance between baseline and Week 24 compared to placebo (see table 2). Study 1 was not designed to maintain the overall Type I error rate for comparisons of each vamorolone group versus prednisone, therefore a global assessment of treatment differences across endpoints, expressed in percentual change from baseline with 95% confidence intervals is presented in Figure 1 for these endpoints.

Table 3: Analysis of change from baseline with vamorolone 6 mg/kg/day or vamorolone 2 mg/kg/day compared to placebo at Week 24 (Study 1)

TTSTAND velocity (rises/s) / TTSTAND in Seconds (s/rise)	**Placebo**	**Vam 2 mg/kg/day**	**Vam 6 mg/kg/day**	**Pred 0.75 mg/kg/day**
Baseline mean rises/s Baseline mean s/rise	0.20 5.555	0.18 6.07	0.19 5.97	0.22 4.92
Mean change at 24 weeks Rises /s Improvement in s/rise	 -0.012 -0.62	 0.031 0.31	 0.046 1.05	 0.066 1.24
Difference versus placebo* Rises /s s/rise	-	0.043 (0.007 ; 0.079) 0.927 (0.042 ; 1.895)	0.059 (0.022 ; 0.095) 1.67 (0.684 ; 2.658)	 not given not given
p-value	-	0.020	0.002	not given
6MWT distance (meters)	**Placebo**	**Vam 2 mg/kg/day**	**Vam 6 mg/kg/day**	**Pred 0.75 mg/kg/day**
Baseline mean (m)	354.5	316.1	312.5	343.3
Mean change at 24 weeks	-11.4	+25.0	+24.6	+44.1
Difference versus placebo*	-	36.3 (8.3 ; 64.4)	35.9 (8.0 ; 63.9)	not given
p-value	-	0.011	0.012	not given

Mean changes and differences are model-based least-squares means (LSM) and mean differences.
Positive numbers indicate improvement as compared with the baseline value. *Differences in LSM presented with 95% CI

Figure 1 Comparisons between vamorolone and prednisone in timed tests for motor function, analysed as percentual changes from baseline (mITT-1 population)



Test data are standardised by using the percentual change from baseline as the endpoint. The percentile changes are calculated as (value at visit – baseline value) / baseline value x 100%. VAM: Vamorolone, PDN: Prednisone
All the percent- change values from the two endpoints are entered to a single statistical model (MMRM)

For vamorolone 6 mg/kg/day, the improvements in all tested measurements of lower limb function seen at 24 weeks were largely maintained for 48 weeks of treatment, while results across the efficacy outcome measures for the vamorolone 2 mg/kg/day dose were rather inconsistent with declines in relevant functional outcome parameters at Week 48, i.e. TTSTAND velocity and 6MWT, reaching clinically significant differences compared to vamorolone 6 mg/kg/day but only minimal decrease in the NSAA score.

Patients who switched during Study 1 from prednisone 0.75 mg/kg/day in Period 1 to vamorolone 6 mg/kg/day in Period 2 appeared to retain the benefit in terms of these motor function endpoints, while declines were observed in patients that switched to vamorolone 2 mg/kg/day.

At baseline, children in vamorolone groups were smaller in height (median -0.74 SD and -1.04 SD in height z-score for 2 mg/kg/day and 6 mg/kg/day groups, respectively) than children on placebo (-0.54 SD) or prednisone 0.75 mg/kg/day (-0.56 SD). The change in height percentile and height Z-score was similar in children treated with vamorolone or placebo over 24 weeks while they decreased with prednisone. The height percentiles and Z-scores did not decrease with vamorolone over the 48-week study period in Study 1. Switching from prednisone after 24 weeks in Period 1 to vamorolone in Period 2 led to an increase in mean and median height z-score up to Week 48.

5.2 Pharmacokinetic properties

Absorption

Vamorolone is well absorbed and distributes quickly into tissues. After oral administration with food, the median T_{max} is about 2 hours (range 0.5 to 5 hours).

Effect of food
Co-administration of vamorolone with a meal reduced C_{max} by up to 8% and delayed T_{max} by 1 hour, relative to administration under fasting conditions. The overall systemic absorption as measured by AUC was increased by up to 14% when vamorolone was taken with food. In the Chinese adult population, AUC_{inf} and C_{max} increased by 24 % and 25 % respectively and the median T_{max} was delayed by 3 hours with a high fat meal. It is unlikely that this food effect will pose a safety concern. Although food does not significantly alter the overall bioavailability of vamorolone, consistent co-administration with food may reduce variability in bioavailability.

Distribution

The apparent volume of distribution of vamorolone for a DMD patient with a body weight of 20 kg taking vamorolone is 28.5 L based on the population PK analysis. Protein binding is 88.1% in vitro. The blood to plasma ratio is approximately 0.87.

Biotransformation

Vamorolone is metabolised via multiple Phase I and Phase II pathways, such as glucuronidation, hydroxylation, and reduction. The main plasma and urine metabolites are formed through direct glucuronidation as well as hydrogenation with subsequent glucuronidation. The involvement of specific UGT and CYP enzymes in the metabolism of vamorolone has not been conclusively demonstrated.

Elimination

The major route of elimination is by metabolism with subsequent excretion of metabolites into urine and faeces. Vamorolone clearance for a DMD patient with a body weight of 20 kg taking vamorolone is 58 L/h based on the population PK analysis. The terminal elimination half-life of vamorolone in children with DMD is approximately 2 hours.

Approximately 30% of vamorolone dose is excreted in faeces (15.4% unchanged) and 57% of vamorolone dose is excreted in urine as metabolites (< 1% unchanged). The major metabolites in urine are glucuronides.

Linearity/non-linearity

The PK are linear and vamorolone exposure increases proportionally with either single or multiple doses. Vamorolone does not accumulate with repeated administration.

Special populations

Hepatic impairment

The effect of moderate hepatic impairment (Child-Pugh class B) of vamorolone was studied in humans. Vamorolone Cmax and AUC0inf values were approximately 1.7- and 2.6-fold higher in subjects with moderate hepatic impairment compared to age, weight and sex matched healthy adults. AGAMREE dose should be reduced in patients with moderate hepatic impairment to 2 mg/kg/day for patients up to 40 kg and to 80 mg for patients with a body weight of 40 kg and above

Based on the available data, the increase in vamorolone exposure is proportional to the severity of hepatic dysfunction. Patients with mild hepatic impairment (Child-Pugh class A) are not expected to have a significant increase in exposure and therefore no dose adjustment is recommended.
There is no experience with vamorolone in patients with severe hepatic impairment (Child-Pugh class C) and vamorolone should not be administered to these patients (see section 4.3).

Renal impairment
There is no clinical experience in patients with renal impairment. Vamorolone is not excreted unchanged via the kidney, and increases in exposure due to renal impairment are considered unlikely.

Transporter-mediated interactions
Vamorolone is not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, MATE1, or BSEP. Vamorolone shows weak inhibition of OAT3 and MATE2-K transporters *in vitro*. Vamorolone is not a substrate of P-gp, BCRP, OATP1A2, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, MATE2-K or BSEP.

Paediatric population
At steady state, the geometric mean C_{max} and the geometric mean AUC of vamorolone in children (ages 4-7 years) were estimated by Population PK to 1200 ng/ml (CV%=26.8) and 3650 ng/ml.h respectively after administration of 6 mg/kg vamorolone daily.

5.3 Preclinical safety data

Repeat-dose toxicity
Repeated vamorolone administration resulted in transient increases of triglycerides and cholesterol as well as liver enzymes in mice and dogs. Focal hepatic inflammation/necrosis observed in both species might have developed secondary to the hepatocellular hypertrophy and vacuolation containing glycogen and lipid accumulations that likely reflect the stimulation of gluconeogenesis.

Long-term vamorolone dosing also caused adrenal cortex atrophy in mice and dogs, which are ascribable to the known suppression of the hypothalamic-pituitary-adrenal axis by glucocorticoid agents.

The primary anti-inflammatory activity of vamorolone further accounted for mild to moderate lymphocyte depletion in spleen, thymus and lymph nodes of both species. The adverse liver and adrenal gland findings and the lymphoid changes in mice and dogs developed with no safety margins to the MRHD based on AUC.

Genotoxicity and carcinogenicity

Vamorolone did not exert any genotoxic potential in the standard test battery. Carcinogenicity studies have not been conducted with vamorolone, but the absence of pre-neoplastic lesions in long-term toxicity studies and experience with other glucocorticoid agents do not suggest a particular carcinogenic hazard.

Reproductive and developmental toxicity

No standard reproductive and developmental toxicity studies have been performed. An exploratory embryo-foetal developmental study with vamorolone in mice showed higher foetal and litter incidences of cleft palate at exposures similar to the human exposure at the MRHD indicative of a teratogenic effect of vamorolone. Vamorolone did not adversely affect the development of sperm and reproductive tissues in the chronic toxicity study in mice. Following chronic dosing in dogs, incompletely reversible spermatocyte/spermatid degenerations were observed in testes leading to oligospermia and germ cell debris in epididymides. Furthermore, the prostate glands were reduced and contained less secretory product.

In female animals, long-term repeated dosing in dogs additionally resulted in partially reversible bilateral absence of *corpora lutea* in the ovaries. The inhibition of male and female fertility is attributable to the known interference of long-term glucocorticoid treatment with the hypothalamus-pituitary-gonadal axis and developed without AUC-based safety margin to humans at the MRHD.

Juvenile toxicity

The main target organs of vamorolone in male and female juvenile mice overlap with those of adult mice such as adrenal cortical atrophy and vamorolone-related adverse hepatocellular degeneration/necrosis.

Vamorolone-related effects exclusively observed in juvenile mice were non-adverse tibia and body lengths reductions in male and female animals and were attributed to the induction of slower growths. In addition, acinar cell hypertrophy of mandibular salivary glands were detected in female animals. Whereas growth retardation is a well known effect associated with glucocorticoid treatment of children, the relevance of the salivary gland findings for children is unknown. At the no observed adverse effect level (NOAEL) for general toxicity in male and female juvenile mice, no safety margin with respect to human exposure at the MRHD exists.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (monohydrate) (E 330)
Disodium phosphate (E 339)
Glycerol (E 422)
Orange flavour
Purified water
Sodium benzoate (E 211)
Sucralose (E 955)
Xanthan gum (E 415)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before opening

3 years.

After first opening

3 months.
Store in a refrigerator (2 °C – 8 °C) in upright position

6.4 Special precautions for storage

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

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber coloured glass bottle containing 100 ml oral suspension with a polypropylene tamper evident child resistant closure with low density polyethylene liner.

Each pack contains one bottle, one press-in bottle adapter (low density polyethylene) and two identical oral syringes (low density polyethylene) graduated from 0 to 8 ml by increments of 0.1 ml.

6.6 Special precautions for disposal and other handling

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

Each oral syringe supplied with AGAMREE may be used for up to 45 days.

Use with an enteral feeding tube:
AGAMREE can be administered through an enteral feeding tube (12 – 24 fr) without modification or dilution of the usual prescribed dose. AGAMREE should not be mixed with the feeding formula or other products. Flushing the enteral feeding tube with a minimum of 20 ml of water before and after administration of AGAMREE should be performed.

7. MARKETING AUTHORISATION HOLDER

Santhera Pharmaceuticals (Deutschland) GmbH
Marie-Curie Strasse 8
D-79539 Lörrach
GERMANY
office@santhera.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1776/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 December 2023

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(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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Santhera Pharmaceuticals (Deutschland) GmbH
Marie-Curie-Strasse 8
D-79539 Lörrach
GERMANY

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.

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.

- **Additional Risk Minimisation Measures**

Patient Alert Card

This patient is on long term treatment with AGAMREE (vamorolone), a dissociative corticosteroid for the chronic treatment of Duchenne Muscular Dystrophy, and therefore is physically dependent on daily steroid therapy as a critical medicine.

If this patient is unwell (excess fatigue, unexpected weakness, vomiting, diarrhea, dizziness or confusion), acute adrenal insufficiency or crisis must be taken into consideration.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

AGAMREE 40 mg/ml oral suspension
vamorolone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral suspension contains 40 mg of vamorolone.

3. LIST OF EXCIPIENTS

Contains sodium benzoate (E 211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension

1 bottle of 100 ml of oral suspension.
1 press-in-bottle adapter.
Two 8 ml oral syringes.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well before use.
Read the package leaflet before use.
Oral 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
After first opening, store bottle upright in a refrigerator.
Discard any remaining suspension within 3 months after first opening.

Date of 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

Santhera Pharmaceuticals (Deutschland) GmbH
Marie-Curie-Straße 8
D-79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1776/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AGAMREE

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

AGAMREE 40 mg/ml oral suspension
vamorolone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral suspension contains 40 mg of vamorolone.

3. LIST OF EXCIPIENTS

Contains sodium benzoate (E 211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension

100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well before use.
Read the package leaflet before use.
Oral 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
After first opening, store bottle upright in a refrigerator.
Discard any remaining suspension within 3 months 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

Santhera Pharmaceuticals (Deutschland) GmbH
Marie-Curie-Straße 8
D-79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1776/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

AGAMREE 40 mg/ml oral suspension
vamorolone

▼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 start taking this medicine because it contains important information for you.
- 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.
- 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 AGAMREE is and what it is used for
2. What you need to know before you take AGAMREE
3. How to take AGAMREE
4. Possible side effects
5. How to store AGAMREE
6. Contents of the pack and other information

1. What AGAMREE is and what it is used for

AGAMREE is a steroidal anti-inflammatory medicine that contains the active substance vamorolone.

AGAMREE is used to treat patients aged 4 years and older with Duchenne muscular dystrophy (DMD). DMD is a genetic condition caused by defects in the dystrophin gene, which normally makes a protein that keeps muscles healthy and strong. In patients with DMD, this protein is not generated and the body is unable to grow new muscle cells or replace damaged muscle. This causes the muscles of the body to become weaker over time.

AGAMREE is used to stabilize or improve muscle strength in patients with DMD.

2. What you need to know before you take AGAMREE

Do not take AGAMREE
- if you are allergic to vamorolone or any of the other ingredients of this medicine (listed in section 6)
- if you have a severe liver problem
- if you plan to have or have had any vaccination with live or live attenuated vaccines (such as Measles, Mumps, Rubella or Chickenpox) in the last 6 weeks. Talk to your doctor if you are already being treated with AGAMREE and planning such vaccination.

Warnings and precautions
Talk to your doctor before using AGAMREE

Alterations in endocrine function: adrenal insufficiency

AGAMREE reduces the amount that your body can produce of a hormone called cortisol. This is called adrenal insufficiency.

- you should not reduce the amount of AGAMREE or stop taking AGAMREE without talking to your doctor; if you abruptly reduce or stop taking AGAMREE for a few days, you may develop symptoms of acute adrenal insufficiency such as excess fatigue, dizziness or confusion, which may be life-threatening; your doctor may have to monitor your treatment more closely if you change the dose.
- if you are under unusual stress (such as acute infection, traumatic injuries or a major surgical procedure), you may need to take an additional steroidal medicine to prevent acute adrenal insufficiency. Discuss with your doctor what to do in case of unusual stress before starting AGAMREE
- if you are being treated with another corticosteroid such as prednisone, you will be able to switch to AGAMREE from one day to the other, but your doctor will advise you on the dose of AGAMREE that you should take.
- if you have a type of tumor in your adrenal glands called pheochromocytoma, your doctor may have to monitor your treatment more closely

IMPORTANT: The AGAMREE pack includes a Patient Alert Card which contains important safety information about adrenal crisis. Keep this card with you at all times.

Weight gain

- AGAMREE may increase your appetite and therefore your weight, mainly in the first months of treatment; your doctor or nurse will give you dietary advice before and during treatment.

Patients with altered thyroid function

- if you have hypothyroidism (an underactive thyroid) or hyperthyroidism (an overactive thyroid), your doctor may have to monitor your treatment more closely, or change your dose.

Ophthalmic effects

- if you or somebody in your family has glaucoma (increased pressure in the eye), your doctor may have to monitor your treatment more closely

Increased risk of infections

AGAMREE may reduce your natural resistance to infections.

- if you have a lowered immune response (due to an immunodeficiency syndrome, a disease or due to other medicines that suppress the immune system), your doctor may have to monitor your treatment more closely
- if you experience an infection while on treatment with AGAMREE, your doctor may have to monitor you more closely and you may require treatment with an additional steroidal medicine

Diabetes mellitus

- AGAMREE use over years may increase the probability that you develop diabetes mellitus (a sugar related disease); you doctor may check your sugar levels regularly.

Vaccination

- if you plan to receive a vaccination with live attenuated or live vaccines, this should occur at least 6 weeks prior to starting AGAMREE treatment.
- if you have never had chickenpox or have not been vaccinated against chickenpox, you may discuss vaccination with your doctor before starting AGAMREE.

Thromboembolic events

- if you have had thromboembolic events (a blood clot inside your body) or a disease that increase your risk to have blood clotting, your doctor may have to monitor your treatment more closely.

Hepatic impairment

- if you have liver disease, your doctor may have to change your dose.

Children
Do not give AGAMREE to children under the age of 4 years as it has not been tested in this group of patients.

Other medicines and AGAMREE
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines:
- Medicines used to treat seizures and neuropathic pain, such as carbamazepine or phenytoin as these can influence the effect of the medicine
- Medicines used to treat fungal infections (including candidiasis and aspergillosis) known as triazoles, such as itraconazole and voriconazole, as these can influence the effect of the medicine
- Antibiotics known as macrolides (such as clarithromycin) or "ketolides" (such as telithromycin), as these can influence the effect of the medicine
- Antibiotics knowns as rifamycins, such as rifampicin, as these can influence the effect of the medicine
- Spironolactone or eplerenone, known as potassium-sparing diuretic treatments (treatments that increase urine production), which may be used to lower blood pressure and protect cardiovascular function as they may some similar effects as AGAMREE; your doctor may have to monitor your potassium levels and change the dose of these medicines
- St John's wort (*Hypericum perforatum*), a herbal medicine used to treat depression and emotional disorders, as these can influence the effect of the medicine

If you need to receive a vaccine, seek your doctor's advice first (see section 2: 'Do not take AGAMREE'). You should not receive certain types of vaccine (live or live-attenuated vaccines) from up to 6 weeks before starting treatment with AGAMREE, as in this combination, these vaccines could trigger the infection that they are supposed to prevent.

AGAMREE with food and drink
Avoid grapefruit and grapefruit juice during treatment with AGAMREE, as these can influence the effect of the medicine.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you are pregnant, you should not use AGAMREE unless clearly indicated by your doctor.

If you are a women who could become pregnant, you have to use effective contraception during treatment with AGAMREE.

Animal studies have shown that long-term treatment with AGAMREE may impair male and female fertility.

Driving and using machines
Discuss with you doctor whether your illness allows you to drive vehicles, including a bicycle, and use machines safely. AGAMREE is not expected to affect the ability to drive, cycle or use machines.

AGAMREE contains sodium benzoate and sodium
AGAMREE contains 1 mg sodium benzoate (E211) in each ml.
AGAMREE contains less than 23 mg of sodium per 7.5 ml and is essentially 'sodium-free'.

3. How to take AGAMREE

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

The recommended dose of AGAMREE depends on your body weight and your age.

If you are 4 years or older and your weight is less than 40 kg, the dose is usually 6 mg per kg body weight, taken once a day.

If you are 4 years or older and your weight is 40 kg or more, the dose of is usually 240 mg, taken once a day.

If you get certain side effects while you are taking AGAMREE (see section 4), your doctor may lower your dose or stop treatment temporarily or permanently. Your doctor may reduce your dose if you suffer from liver disease.

This medicine is taken by mouth. AGAMREE should be taken preferably with a meal (see section 2 "AGAMREE with food and drink").

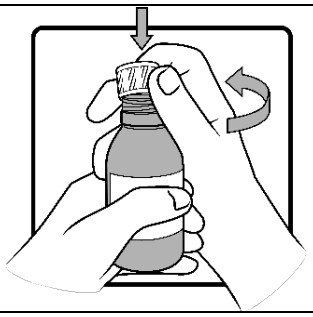
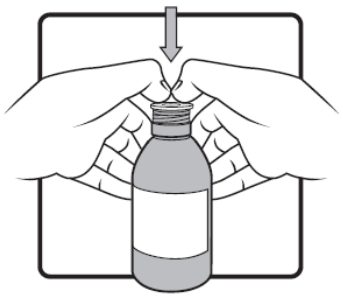
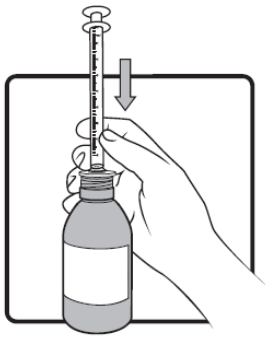
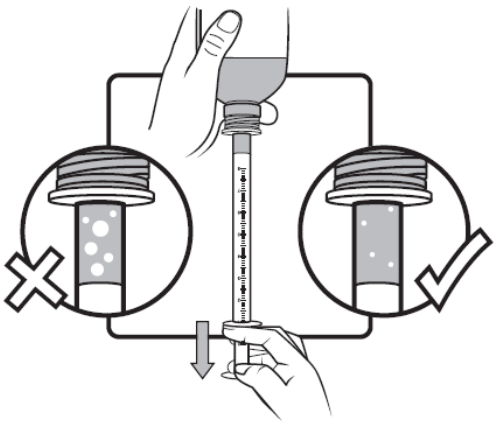
To withdraw the medicine, use one of the oral syringes included in the pack. Use only these oral syringes when measuring out your dose. Your doctor will tell you how much you need to withdraw with the syringe for your daily dose.

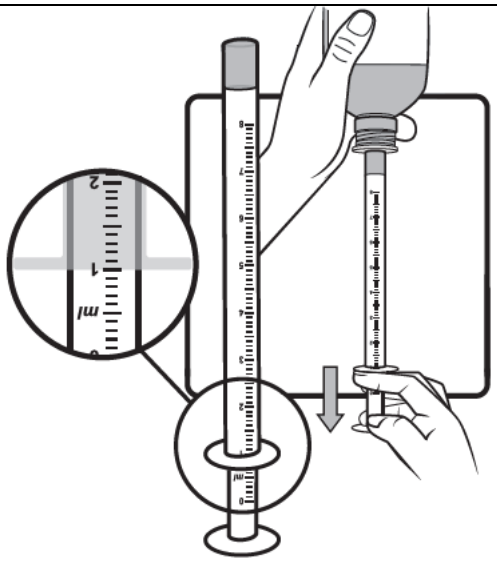
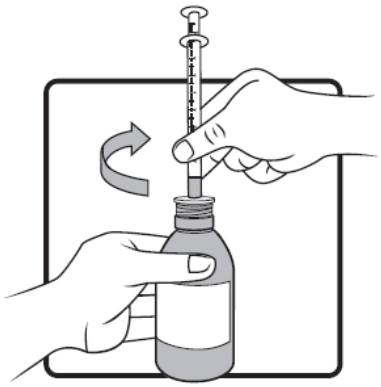
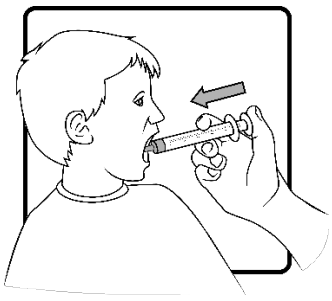
Caregivers should provide assistance with the administration of AGAMREE, particularly with regards to the use of oral syringes to measure and administer the prescribed dose.

Shake the bottle well before withdrawing with the syringe. Withdraw your dose into the oral syringe, then immediately and slowly empty the syringe directly into your mouth. Please read the instructions below for more information about how to measure and take the dose correctly. Check with your doctor or pharmacist if you are unsure how to use the oral syringe.

After taking your prescribed dose, disassemble the oral syringe, rinse the syringe and plunger under running cold tap water and air dry. Store the cleaned oral syringe in the pack until next use. An oral syringe should only be used for up to 45 days. After this time, discard it and use the second oral syringe provided in the pack. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

HOW TO PREPARE YOUR DOSE OF AGAMREE ORAL SUSPENSION

	Before taking/giving AGAMREE	
Step 1	Make sure the child-resistant bottle cap is tightly secured and shake the bottle well.	
Step 2	Remove the child-resistant bottle cap by pushing it firmly down and turning it counter clockwise.	
Step 3	Firmly insert the bottle adapter into the bottle. This is to be done the first time that you open the bottle. The adapter must thereafter stay in the bottle. If you drop the bottle adapter, clean it under cold running water and air dry for at least 2 hours.	
	Preparing a dose of AGAMREE	
Step 4	Hold the bottle upright. Before inserting the tip of the oral syringe into the bottle adapter, push the plunger completely down toward the tip of the oral syringe. Insert the tip firmly into the opening of the bottle adapter	
Step 5	Hold the oral syringe in place and carefully turn the bottle upside down. Pull the plunger out slowly until the desired amount of medicine is withdrawn into the oral syringe. If there are large air bubbles in the oral syringe (as seen on the figure on the left) or if you have drawn up the wrong dose of AGAMREE, insert the syringe tip firmly into the bottle adapter while the bottle is in an upright position. Push the plunger all the way down so that	

	AGAMREE flows back into the bottle and repeat Steps 4 through 6.	
Step 6	Check your dose in millilitres (ml) as prescribed by your doctor. Find the gradation to read the dose in millilitres (ml) on the plunger as shown in the picture on the right. On the depicted scale, each line corresponds to 0.1 ml. In the example, a dose of 1 ml is shown. Do not take more than the prescribed daily dose.	
Step 7	Turn the entire bottle right side up and remove the oral syringe carefully from the bottle. Do not hold the oral syringe by the plunger, because the plunger may come out.	
	Giving AGAMREE	
Step 8	Do not mix the medicine with any liquid before giving. The patient must sit upright when taking the medicine. Empty the syringe directly into the mouth. . Gently press the plunger to empty the syringe. Do not forcefully push on the plunger. To avoid the risk of choking, do not squirt the medicine to the back of the mouth or throat.	

	After giving AGAMREE	
Step 9	Close the bottle with the child-resistant cap after each use.	
Step 10	Disassemble the oral syringe, rinse under running cold water and air dry prior to next use. Each oral syringe supplied with AGAMREE may be used for up to 45 days.	

Enteral feeding tube
AGAMREE can be administered via an enteral feeding tube, following the instructions present in the enteral feeding tube kit. The usual prescribed dose of AGAMREE should be used, no dilution is required. Do not mix with the feeding formula or other products. The tube must be flushed before and after administration of AGAMREE, using the syringe provided in the enteral feeding tube kit. A minimum of 20 ml of water should be used to flush the tube.

If you take more AGAMREE than you should
If you take too much AGAMREE, contact your doctor or a hospital for advice. Show the AGAMREE package and this leaflet. Medical treatment may be necessary.

If you forget to take AGAMREE
Do not take any more AGAMREE and do not repeat the dose.
Take your next dose as normal.
Talk to your health care professional if you are concerned.

If you stop taking AGAMREE
Take AGAMREE for as long as your doctor tells you to. Talk to your doctor before stopping AGAMREE treatment, as your dose needs to be gradually reduced to avoid undesirable side effects.

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.

Treatment with AGAMREE leads to adrenal insufficiency. Talk to your doctor before starting AGAMREE (refer to Section 2 for more information).

The following side effects have been reported with AGAMREE at a very common frequency (may affect more than 1 in 10 people):

- More rounded, swollen aspect of the face (Cushingoid)
- Increase of body weight (weight increased)
- Increased appetite
- Irritability
- Vomiting

The following side effets have been reported at a common frequency (may affect up to 1 in 10 people):

- Belly pain (abdominal pain)
- Pain in the upper belly (abdominal pain upper)
- Diarrhoea
- Headache

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 AGAMREE

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.
After you first open AGAMREE, store the bottle upright in a refrigerator (2 °C – 8 °C). The medicine can be kept in the refrigerator for up to 3 months.

Discard any unused medicine within 3 months after first opening the bottle.

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 AGAMREE contains
The active substance is vamorolone. Each ml of suspension contains 40 mg of vamorolone.

The other ingredients are: citric acid (monohydrate) (E 330), disodium phosphate (E 339), glycerol (E422), orange flavour, purified water, sodium benzoate (E 211) (see section 2, "AGAMREE contains sodium benzoate"), sucralose (E 955), xanthan gum (E 415) and hydrochloric acid (for pH adjustment). See section 2 "AGAMREE contains sodium benzoate and sodium".

What AGAMREE looks like and contents of the pack
AGAMREE is a white to off-white oral suspension. It comes in an amber coloured glass bottle with a polypropylene tamper evident child-resistant closure with low density polyethylene liner. The bottle contains 100 ml of oral suspension. Each pack contains one bottle, a bottle adapter and two identical oral syringes for dosing. The oral syringes are graduated from 0 to 8 ml by increments of 0.1 ml.

Marketing Authorisation Holder and Manufacturer
Santhera Pharmaceuticals (Deutschland) GmbH
Marie-Curie-Straße 8
D-79539 Lörrach
Germany

This leaflet was last revised in

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