SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AGAMREE

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.

Patient Safety Information Card
The marketing of AGAMREE is subject to a risk management plan (RMP) including a 'patient safety information card'. The patient safety information card' emphasizes important support early recognition and treatment of adrenal crisis. Please explain to the patient the need to review the card before starting treatment.

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 can be taken with or without 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.

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 have not been conducted with vamorolone. Glucocorticoids were associated in animal studies to various types of malformations (palate cleft, skeletal malformations), however the relevance in humans is unknown.

AGAMREE should not be used during pregnancy unless the clinical condition of the woman 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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.

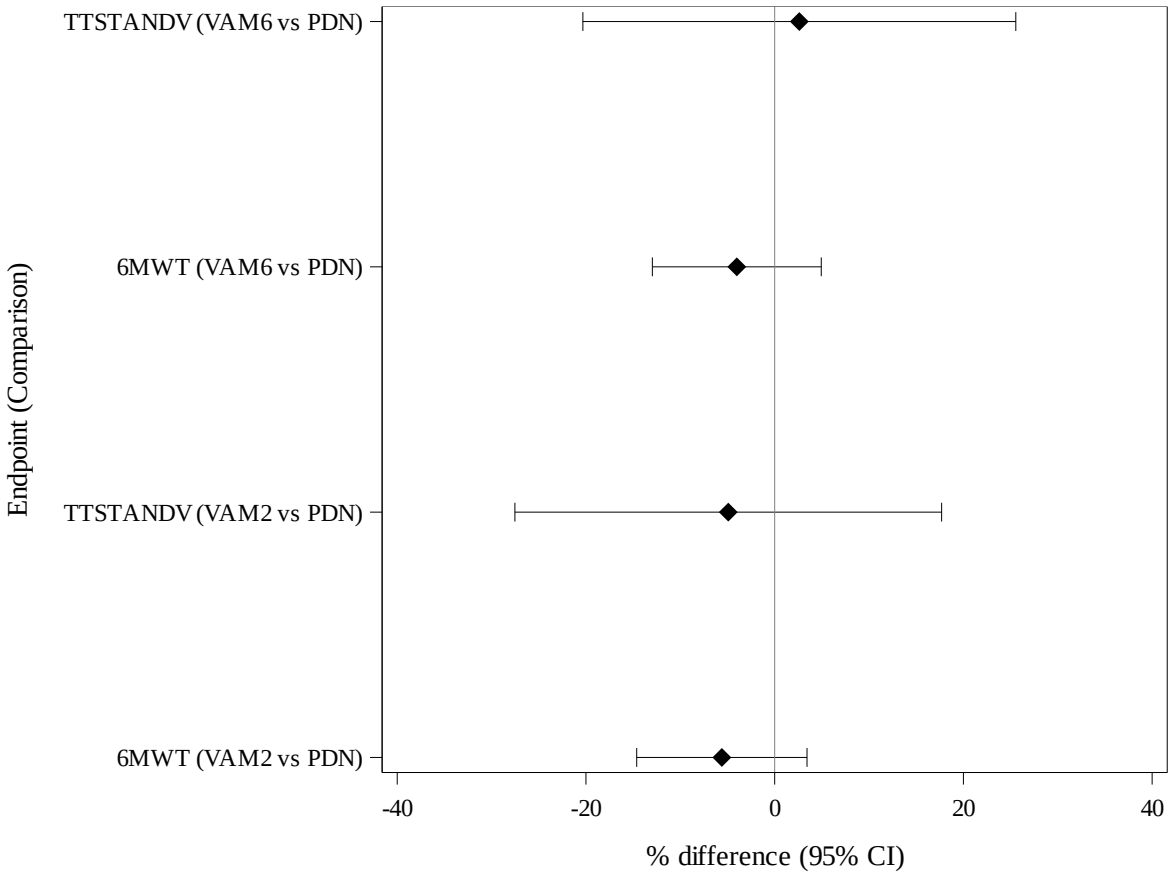
Treatment with vamorolone 6 mg/kg/day and 2 mg/kg/day resulted in a statistically significant improvement in change in TTSTAND velocity and change in 6MWT distance between baseline and Week 24 compared to placebo (see table 2). Study 1 was not designed to maintain the overall Type I error rate for comparisons 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. The observed differences in absorption do not lead to clinically relevant differences in exposure and therefore vamorolone can be administered either with or without food.

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. 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

Glycerol
Xanthan gum
Disodium phosphate
Citric acid (monohydrate)
Sucralose
Sodium benzoate
Orange flavour
Hydrochloric acid (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before opening

Store below 25°C.
Store the medical product upright.
The expiry date of the product is indicated on the packaging materials.
After first opening

3 months.
Store in a refrigerator (2 °C – 8 °C) in upright position.
Each oral syringe supplied with AGAMREE may be used for up to 45 days.

6.4 Special precautions for storage

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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 (4mg).

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.

7. MANUFACTURER

Santhera Pharmaceuticals (Switzerland) Ltd.,
Hohenrainstrasse, Pratteln, Switzerland.

8. MARKETING AUTHORISATION NUMBER(S)

179-10-38103-99

9. LICENSE HOLDER

Megapharm Ltd.,
Hatidahr st. 15, Ra'anana, Israel

10. APPROVED IN APRIL 2025