swissmedic

Date: 11 February 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Agamree

International non-proprietary name:	vamorolone
Pharmaceutical form:	oral suspension
Dosage strength(s):	40 mg/mL
Route(s) of administration:	oral
Marketing authorisation holder:	Santhera Pharmaceuticals (Schweiz)
Marketing authorisation no.:	69650
Decision and decision date:	approved on 14 January 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DMD	Duchenne muscular dystrophy
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for vamorolone in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 27 February 2024.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:

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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	31 July 2024
Formal objection	28 August 2024
Response to formal objection	15 September 2024
Formal control completed	19 September 2024

List of Questions (LoQ)	18 December 2024
Response to LoQ	17 March 2025
Preliminary decision	13 June 2025
Response to preliminary decision	29 August 2025
Labelling corrections and/or other aspects	4 November 2025
Response to labelling corrections and/or other aspects	9 December 2025
Final decision	14 January 2026
Decision	approval

Based on Art. 13 TPA, Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the European Medicines Agency (EMA). This SwissPAR relates to the currently available EMA assessment report for Agamree issued by the EMA, Procedure No. EMEA/H/C/005679/0000, published 4 January 2024.

3 Medical context

Medicinal product proposed for marketing authorisation. Vamorolone is a synthetic corticosteroid analogue that acts as a glucocorticoid receptor agonist and mineralocorticoid antagonist.

Condition addressed in the indication. Duchenne muscular dystrophy (DMD) is a rapidly progressive form of muscular dystrophy that affects mainly male individuals. In the majority of patients it leads to death by young adulthood. DMD is the most common childhood muscular dystrophy. The estimated prevalence in Switzerland is around 150 to 200 affected boys and young adults.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA) (see section 2.3 Regulatory history (milestones)).

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA) (see section 2.3 Regulatory history (milestones)).

6 Clinical aspects

The evaluation of the clinical and clinical pharmacological data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information were used as a basis for the clinical evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see the appendix of this report.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Agamree was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 «Undesirable effects» for how to report adverse reactions.

AGAMREE

Composition

Active substances

Vamorolone

Excipients

Natrii benzoas (E 211), Acidum citricum monohydricum (E 330), Dinatrii phosphas (E 339), Glycerolum (E 422), Aromaticum (Aroma aurantii), Aqua purificata, Sucralosum (E 955), Xanthani gummi (E 415), Acidum hydrochloridum dilutum ad pH.
1 ml of suspension contains 1.064 mg Sodium.

Pharmaceutical form and active substance quantity per unit

Oral suspension
1 ml of suspension contains 40 mg.
White to off-white suspension.

Indications/Uses

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

Dosage/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.
In patients weighing more than 40 kg, dose reduction below the recommended starting dose (6 mg/kg/day; maximum 240 mg/day) may lead to lower systemic exposure and potentially reduced efficacy. Therefore, patients should be maintained on the highest tolerated dose whenever possible. If down-titration is required for tolerability, clinical response should be closely monitored and re-escalation to the highest tolerated dose should be considered if clinically warranted.

Table 1: Dosierungstabelle 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 Warnings and precautions). 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 Dosing Instructions

Patient with 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 «Pharmacokinetics»). Patients with severe hepatic impairment (Child-Pugh class C) should not be treated with vamorolone. See sections «Contraindications» and «Warnings and Precautions».

Children under 4 years

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 «Pharmacokinetics»).
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 Instructions for handling).

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed (see section «Composition»).
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 «Warnings and Precautions»).

Warnings and precautions

Alteration in endocrine function

Vamorolone causes alterations in endocrine function, especially with chronic use.
In addition, patients with altered thyroid function (see also "Warnings and precautions - Instructions *for use in patients with altered thyroid function*"), or pheochromocytoma (see also "Warnings and precautions – *pheochromocytoma crisis*") 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 «Posology/Administration»).

During periods of increased stress, such as acute infection, traumatic injuries or surgical procedure), patients should be monitored clinically and laboratory chemically 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.
Treatment with AGAMREE alone during periods of increased stress has not been evaluated in clinical trials and is not recommended
The patient should be advised to carry the Patient Alert Card providing important safety information to support early recognition and treatment of adrenal crisis.
During discontinuation, a steroid “withdrawal syndrome”, pathologically unrelated to adrenocortical insufficiency, may also occur any time at supraphysiological dosages during tapering off 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. Differential diagnosis and management of a steroid withdrawal syndrome should follow the currently valid recommendations.

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 acute adrenal crisis.

Cushing’s Syndrome

Cushing’s syndrome (hypercortisolism) occurs with prolonged exposure to exogenous corticosteroids, including AGAMREE with possible symptoms such as truncal obesity, buffalo hump, facial rounding, facial plethora, striae distensae, limb atrophy, edema, muscle weakness, easy and frequent bruising with thin fragile skin, atrophic skin, posterior neck fat deposition, acne, amenorrhea, hirsutism, immunodeficiencies, impaired wound healing, and psychiatric abnormalities.

Alterations in Cardiovascular/Renal Function

Vamorolone acts as a mineralocorticoid receptor antagonist and has not demonstrated the hypertensive or sodium-retentive effects typical of glucocorticoids. As with other corticosteroids, appropriate monitoring should nevertheless be performed during long-term therapy. Caution is advised in patients with severe cardiac or renal impairment. Monitor serum potassium, particularly if AGAMREE is co-administered with mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone).

Weight gain

Vamorolone is associated with dose-dependent increase in appetite and weight gain, mainly in the first months of treatment. Before and during treatment with AGAMREE weight should be monitored regularly and furthermore age-appropriate dietary advice should be provided in line with general recommendations for nutrition management in patients with DMD (see Undesirable effects).

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.

Pheochromocytoma Crisis

There have been reports of pheochromocytoma crisis, which can be fatal, after administration of systemic corticosteroids. In patients with suspected or identified pheochromocytoma, consider the risk of pheochromocytoma crisis prior to administering corticosteroids.

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 infection

Suppression of the inflammatory response and immune function under steriods 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.
Patients should be monitored for the development of infections. 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.

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.

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.

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.

Gastrointestinal Perforation

There is an increased risk of gastrointestinal perforation with use of corticosteroids in patients with certain gastrointestinal disorders, such as active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific ulcerative colitis. Signs of gastrointestinal perforation, such as peritoneal irritation, may be masked in patients receiving corticosteroids. Avoid AGAMREE if there is a probability of impending perforation, abscess, or other pyogenic infections; diverticulitis; fresh intestinal anastomoses; or active or latent peptic ulcer.

Kaposi’s Sarcoma

Kaposi’s sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of treatment may result in clinical improvement of Kaposi’s sarcoma.

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 «Contraindications»).

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.

Other information

This medicinal product contains 1 mg sodium benzoate in each ml which is equivalent to 100 mg/100 ml.
This medicinal product contains less than 1 mmol (23 mg) sodium per 1 ml, that is to say essentially ‘sodium-free’.

Interactions

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 other medicinal products on vamorolone

CYP3A4 Inhibitors

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.

CYP3A4 Inducers

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.

Transport-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.

Pregnancy, lactation

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) (see section «Preclinical data»).
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 «Preclinical data»).

Effects on ability to drive and use machines

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

Undesirable effects

The clinical safety experience of vamorolone was assessed using combined safety data from multiple dose clinical studies conducted in subjects with DMD. Any subject who received ≥ 1 dose of study drug and had a safety assessment available was included.
For comparative safety analysis, all treated subjects in randomized, placebo, or active control controlled multiple dose DMD studies were included in pool 1 (29 placebo, 28 vamorolone 2 mg/kg, and 26 vamorolone 6 mg/kg). The complete clinical safety data of vamorolone is provided in Pool 3, which this includes all vamorolone-treated subjects in any multiple dose DMD study (164 subjects receiving any dose; 163 subjects receiving between 2 and 6 mg/kg). Additionally, data from an open label safety study was assessed separately (7 to <18 years, not being treated with corticosteroids at

enrolment into the study enrolment, but possibly before). 6 subjects receiving 2 mg/kg vamorolone and 6 subjects receiving 6 mg/kg vamorolone).

Summary of the safety profile

The most commonly reported adverse reactions for vamorolone are reduced morning cortisol (92.6%), Cushingoid features (28.6 %), upper respiratory tract infections (20.0%), nasopharyngitis (20.1%), cough (19.5%), vomiting (17.7%), (acute) adrenal insufficiency (16.7%), pain in the extremity (15.2 %) weight increased (13.1%), headache (13.4 %), constipation (12.2%), upper abdominal pain (12.1%) irritability (10.7%) and abdominal pain (10.4%). These reactions are usually dose-dependent.

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 participating in clinical studies with vamorolone 2mg/kg/day, 4 mg/kg/day, 6 mg/kg/day or 2-6mg/kg/day (Pool 1 and Pool 3) and from an open label safety study (as described above). 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 8 < 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 reactions**	**Frequency**
Infections and parasitic diseases	Upper respiratory tract infections (20.0%)	Very common
	Nasopharyngitis (20.1%)	Very common
	Influenza	Common
	Ear infection	Common
	otitis media	Common
	Viral gastroenteritis	Common
	Enterobiasis	Common
	Pneumonia	Common
	Viral infection	Common
Diseases of the immune system	Seasonal allergy	Common
Diseases of the respiratory, thoracic cavity and mediastinum	Cough (19.5%)	Very common
	Nasal congestion	Common
Diseases of the ear and labyrinth	Earache	Common

Endocrine disorders	Cushingoide Gesichtszüge (Pseudo-Cushing-Syndrom) (28.6%) Reduced morning cortisol (92.6%) (Acute) adrenal insufficiency (16.7%)	Very common Very common Very common
Metabolism and nutrition disorders	Weight increased (13.1%) Increased appetite Increased triglycerides in the blood	Very common Common Common
Skeletal muscle, connective tissue and bone diseases	Pain in the extremity (15.2%) Muscle cramps Osteopenia Arthralgia	Very common Common Common Common
Psychiatric disorders	Irritability (10.7%) Agitation Behavioural problems	Very common Common Common
Gastrointestinal disorders	Vomiting (17.7%) Constipation (12.2%) Pain in the upper abdomen (12.1%) Diarrhoea (12.8%) Abdominal pain (10.4%) Nausea Toothache	Very common Very common Very common Very common Very common Common Common
Nervous system disorders	Headache (13.4%)	Very common
Diseases of the kidneys and urinary tract	Chromaturia	Common
General diseases and administration site complaints	Fatigue Influenza-like disease Chest pain	Common Common Common

Description of selected adverse reactions and additional information

Adrenal suppression and acute adrenal insufficiency (adrenal crisis, adrenal crisis)

Vamorolone results in suppression of the hypothalamic-pituitary-adrenocortical axis, which correlates with dose and duration of treatment. Acute adrenal insufficiency (adrenal crisis) is a serious side effect that can occur during periods of increased stress or when the dose of vamorolone is abruptly reduced or discontinued (see "Warnings and precautions").

Reduced morning cortisol

Vamorolone causes a dose-dependent reduction in morning cortisol levels, reflecting suppression of the HPA-axis. After 24 weeks of treatment in the active-controlled pivotal Study 1 (see “clinical efficacy”), decreased morning cortisol was reported in up to 92.6% of patients receiving vamorolone 6 mg/kg/day and 26.1% of patients receiving 2 mg/kg/day.

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%) (see «Warnings and Precautions»).

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 «Posology/Administration» and Warnings and Precautions»).

Children and adolescents

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 aged 4 to <5 years compared to patients ≥5 years when treated with vamorolone 2-6 mg/kg/day.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

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.

Pharmacodynamics

Vamorolone, like all chronic exogenous glucocorticoid therapy, 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.
In the clinical studies, there was no reliable evidence after 48 weeks of treatment to indicate a reduction of bone metabolism as measured by bone turnover markers, nor in a significant reduction in lumbar vertebral bone mineralisation parameters measured by Dual-Energy X-Ray Absorptiometry (DXA). However, these results relate to a small group of test subjects.
The risk for bone fractures in patients with DMD treated with vamorolone is not known.
After 24-weeks of treatment in Study 1 the prednisolone group showed a decrease in height (percentile and Z-score) whereas changes for vamorolone and placebo were similar. Furthermore, height percentiles and Z-scores did not decrease with vamorolone over the 48-week study period and for those patients who switched from prednisone after 24 weeks in Period 1 to vamorolone in Period 2 there was an increase in mean and median height z-score up to Week 48.

Clinical efficacy

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 3). Study 1 was not designed to maintain the overall Type I error rate for comparisons of each vamorolone group versus prednisone.

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/rises)	**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 in 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

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.

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.

Pharmacokinetics

Absorption

Vamorolon wird gut resorbiert und verteilt sich schnell in die Gewebe. Nach oraler Anwendung zusammen mit Nahrung beträgt die mediane tmax etwa 2 Stunden (tmax-Bereich 0,5 bis 5 Stunden).

Effect of food

Co-administration of vamorolone with a meal reduced Cmax by up to 8% and delayed Tmax 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.

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.

Metabolism

Vamorolon wird über mehrere Phase-I- und Phase-II-Wege metabolisiert, wie z. B. Glucuronidierung, Hydroxylierung und Reduktion. Die wichtigsten Plasma- und Urinmetaboliten werden durch direkte Glucuronidierung sowie durch Hydrierung mit anschließender Glucuronidierung gebildet. Die Beteiligung bestimmter UGT- und CYP-Enzyme an der Metabolisierung von Vamorolon wurde nicht schlüssig nachgewiesen.

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.

Kinetics in specific patient groups

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.

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 «Contraindications»).

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.

Children and adolescents

At steady state, the geometric mean Cmax 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.

Preclinical 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.
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.
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.

Reproductive 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 hypothalamo-pituitary-gonadal axis and developed without AUC-based safety margin to humans at the MRH.

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. 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.

Other information

Incompatibilities

Not applicable.

Shelf life

The medicinal product may only be used up to the date marked “EXP” on the packaging.

Shelf life after opening

Use opened bottle within 3 months. Any residual quantity should be properly disposed of after 3 months.

Special precautions for storage

Before opening: Do not store above 25°C.
After opening: Store in a refrigerator (2 °C – 8 °C) in upright position.
Keep out of reach of children.

Instructions for handling

Shake before use.
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.
Any unused medicinal product or waste material should be disposed of properly.

Authorisation number

69650 (Swissmedic)

Packs

1 pack with 1 bottle of 100 ml and 2 graduated application syringes with a scale of 0 to 8 ml in steps of 0.1 ml [A].

Marketing authorisation holder

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