

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Zenalpha 0.5 mg/ml + 10 mg/ml solution for injection for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substances:

Medetomidine hydrochloride	0.5 mg (equivalent to 0.425 mg medetomidine)
Vatinoxan hydrochloride	10 mg (equivalent to 9.2 mg vatinoxan)

Excipients:

Methyl parahydroxybenzoate (E218)	1.8 mg
Propyl parahydroxybenzoate	0.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, slightly yellow to yellow or brownish yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

To provide restraint, sedation and analgesia during conduct of non-invasive, non-painful or mildly painful procedures and examinations intended to last no more than 30 minutes.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.

Do not use in animals with cardiovascular disease, respiratory disease or impaired liver or kidney function.

Do not use in animals that are in shock or severely debilitated.

Do not use in animals that have hypoglycaemia or are at risk of developing hypoglycaemia.

Do not use as pre-anaesthetic medicine.
Do not use in cats.

4.4 Special warnings for each target species

Nervous or excited dogs with high levels of endogenous catecholamines may exhibit a reduced pharmacological response to alpha-2 adrenoceptor agonists like medetomidine (ineffectiveness). In agitated animals, the onset of sedative/analgesic effects could be slowed, or the depth and duration of effects could be diminished or non-existent. Therefore, the dog should be given the possibility to calm down before initiation of the treatment and rest quietly after administration of the product until evidence of sedation has occurred.

4.5 Special precautions for use

Special precautions for use in animals

In the absence of available data, treatment of puppies less than 4.5 months of age should be based on a benefit-risk assessment by the responsible veterinarian.

It is recommended that dogs should be fasted in accordance with currently recommended best practice (e.g. 4 – 6 hours for healthy dogs), prior to treatment with this veterinary medicinal product. Water can be given.

Animals should be frequently monitored for cardiovascular function and body temperature during sedation and recovery.

Some cardiovascular effects (e.g. bradycardia, cardiac arrhythmias such as second-degree AV block or ventricular escape complexes) may be observed after treatment.

Over the period of 15–45 minutes post treatment, blood pressure is likely to decrease by approximately 30–50 % from pre-treatment levels. Tachycardia with normal blood pressure may be observed from approximately one hour post-treatment and lasting up to six hours. Therefore, frequent monitoring of cardiovascular function should preferably be performed until tachycardia has resolved.

A decrease in body temperature of approximately 1–2°C is likely to occur after administration.

Once established, hypothermia may persist longer than sedation and analgesia. To prevent hypothermia, treated animals should be kept warm and at a constant temperature during the procedure and until fully recovered.

Medetomidine can cause apnoea and/or hypoxaemia. This effect is likely to be potentiated if used in combination with opioid medicines. Frequent monitoring of respiratory function should be performed in all cases. It is also advisable to have oxygen readily available, should hypoxaemia be detected or suspected.

Analgesia provided by the veterinary medicinal product may be shorter than the sedative effect. Additional pain management should be provided as needed. Spontaneous muscle trembling or twitching can be expected in some dogs.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Accidental exposure may cause sedation and changes in blood pressure. Caution is required during treatment administration to avoid accidental self-injection, or skin, eye or mucosal contact. Adequate restraint of the animal is recommended, as some animals may react to the injection (e.g., defence reaction).

Pregnant women should administer the veterinary medicinal product with special caution to avoid self-injection since uterine contractions and decreased foetal blood pressure may occur after accidental systemic exposure.

People with known hypersensitivity to the active substance or any of the excipients should administer the veterinary medicinal product with caution.

In case of accidental self-injection or ingestion, seek medical advice immediately and show the package leaflet to the physician but DO NOT DRIVE.

In case of skin or mucosal contact, wash the exposed skin immediately after exposure with large amounts of water and remove contaminated clothes that are in direct contact with skin. In case of eye contact, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

To the physician: The veterinary medicinal product contains medetomidine, an alpha-2 adrenoceptor agonist, in combination with vatinoxan, a peripherally selective alpha-2 adrenoceptor antagonist. Symptoms after absorption may involve clinical effects including dose-dependent sedation, respiratory depression, bradycardia, hypotension, a dry mouth, and hyperglycaemia. Ventricular arrhythmias have also been reported. Respiratory and haemodynamic symptoms should be treated symptomatically.

4.6 Adverse reactions (frequency and seriousness)

Hypothermia, bradycardia and tachycardia were very commonly observed in safety and clinical studies. Diarrhoea/colitis and muscle tremor were commonly observed. Vomiting/nausea and involuntary defaecation were uncommonly observed. Cardiac arrhythmias, such as second-degree AV block and ventricular escape complexes, were seen very commonly in laboratory safety studies. Injected sclera were observed very rarely in laboratory safety studies.

All of the above adverse reactions were transient/resolved without treatment, although external warming was provided where required in cases of hypothermia.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy or lactation

The safety of the veterinary medicinal product has not been established in dogs during pregnancy or lactation or in dogs intended for breeding. No data are available on the use of vatinoxan in breeding animals. Published data in laboratory animals do not show direct reproductive or developmental toxicity of medetomidine. The use of the veterinary medicinal product is therefore not recommended in pregnant or lactating animals.

4.8 Interaction with other medicinal products and other forms of interaction

The use of other central nervous system depressants and/or vasodilating medicines are expected to potentiate the effects of the veterinary medicinal product and an appropriate dose reduction should be made after benefit-risk assessment by the veterinarian.

Due to the rapid recovery from sedation expected with the veterinary medicinal product, routine administration of atipamezole is not indicated after the veterinary medicinal product. The intramuscular administration of atipamezole (30 minutes after the administration of the veterinary medicinal product) has been investigated in a study involving a limited number of animals. As tachycardia was observed in 50% of the animals following the administration of atipamezole, close monitoring of the heart rate during recovery is therefore advised in those cases where administration of atipamezole is deemed clinically necessary.

4.9 Amounts to be administered and administration route

For intramuscular use.

The dose is based on body surface area. The dose will result in administration of 1 mg medetomidine and 20 mg vatinoxan per square metre of body surface area (m²).

Calculate the dose using 1 mg/m² medetomidine or use the dosing table below. Note that the mg/kg dosage decreases as body weight increases.

Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

To ensure a correct dosage, bodyweight should be determined as accurately as possible.

Table 1. Dose volume based on bodyweight

Dog bodyweight	Dose volume
kg	ml
3.5 to 4	0.4
4.1 to 5	0.6
5.1 to 7	0.7
7.1 to 10	0.8
10.1 to 13	1.0
13.1 to 15	1.2

15.1 to 20	1.4
20.1 to 25	1.6
25.1 to 30	1.8
30.1 to 33	2.0
33.1 to 37	2.2
37.1 to 45	2.4
45.1 to 50	2.6
50.1 to 55	2.8
55.1 to 60	3.0
60.1 to 65	3.2
65.1 to 70	3.4
70.1 to 80	3.6
>80	3.8

Re-administration of the veterinary medicinal product during the same procedure has not been evaluated and therefore the veterinary medicinal product should not be re-administered during the same procedure.

The number of permissible stopper broachings is limited to a maximum of 15.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

The veterinary medicinal product given 3 and 5 times the recommended dose, showed a slightly prolonged sedation and greater degree of reduction in mean arterial pressure and rectal temperature. Overdose can increase incidence of sinus tachycardia during recovery.

Atipamezole can be administered to reverse the central nervous system effects and most of the cardiovascular effects of medetomidine, excluding hypotension. Appropriate cardiopulmonary support should be initiated if required.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Psycholeptics, hypnotics and sedatives.
ATC vet code: QN05CM99

5.1 Pharmacodynamic properties

Medetomidine is a potent and selective alpha-2 adrenoceptor agonist that inhibits the release of noradrenaline from noradrenergic neurons and produces sedation and analgesia. These effects are dose dependent in depth and duration. Medetomidine is a racemic mixture containing the active enantiomer dexmedetomidine and the inactive enantiomer levomedetomidine. Within the central nervous system, sympathetic neurotransmission is inhibited and the level of consciousness decreases. Respiratory rate and body temperature can also decrease. In the periphery, medetomidine stimulates alpha-2 adrenoceptors within vascular smooth muscle which induces vasoconstriction and hypertension, resulting in decreased

heart rate and cardiac output. Dexmedetomidine also induces a number of other alpha-2 adrenoceptor mediated effects, which include piloerection, depression of motor and secretory functions of the gastrointestinal tract, diuresis and hyperglycaemia.

Vatinoxan is a peripherally selective alpha-2 adrenoceptor antagonist which poorly penetrates the central nervous system. Vatinoxan is administered as the active (RS) diastereomer. By limiting its effects to peripheral organ systems, vatinoxan will prevent or attenuate the cardiovascular and other effects of dexmedetomidine outside the central nervous system when administered simultaneously with the alpha-2 adrenoceptor agonist. The central effects of dexmedetomidine remain unaltered, although vatinoxan will reduce the duration of sedation and analgesia induced by dexmedetomidine, predominantly by increasing the clearance of the latter via improving the cardiovascular function. Vatinoxan stimulates insulin release and counteracts medetomidine's hyperglycaemic effects.

The safety and efficacy of the veterinary medicinal product was tested in a multi-centre clinical study, using 223 client-owned dogs. Dogs requiring a non-invasive, non-painful or mildly painful procedure or examination were treated with either the recommended dose of the veterinary medicinal product (test group), or dexmedetomidine (control group). Procedures included: radiographic examination or diagnostic imaging, ear examination and treatment, eye examination and treatment, anal sac treatment, dermatological examination and procedures, orthopaedic examination, dental examination and biopsy, fine needle aspiration/superficial biopsy, drain seroma or abscess, nail trimming, coat grooming and venous blood draw. One hundred and ten dogs received the test product. In this group, sedation sufficient to perform the procedure occurred on average in 14 minutes. Although duration of clinically-useful sedation varies substantially between individuals and intended procedure, 73% of test group cases had at least 30 minutes duration of sedation and the procedure was completed successfully in 94.5% of cases. Test group mean heart rate remained within the normal range (60–140 beats per minute) at all times after administration; however, 22% of dogs displayed tachycardia at some time point(s) after treatment (range 140–240 beats per minute). In the dexmedetomidine-treated control group, the average time to onset of sedation was 18 minutes and sedation lasted for at least 30 minutes in 80% of dogs. The procedure was completed successfully in 90.1% of control group cases.

5.2 Pharmacokinetic particulars

After intramuscular administration of a pilot formulation of medetomidine (1 mg/m²) + vatinoxan (30 mg/m²), both medetomidine and vatinoxan were rapidly and highly absorbed from the injection site. Maximal plasma concentration was reached at 12.6 ± 4.7 (mean ± standard deviation) minutes and 17.5 ± 7.4 minutes for dexmedetomidine (the active enantiomer of medetomidine) and vatinoxan, respectively. Vatinoxan increased the volume of distribution and the clearance of dexmedetomidine. Thus, the clearance of dexmedetomidine was increased two-fold when given in combination with vatinoxan. The same phenomena were also seen with intravenous administration.

Concentrations of dexmedetomidine and vatinoxan in cerebrospinal fluid (CSF) were measured after intravenous administration of the final formulation of the veterinary medicinal product. Plasma unbound fraction : CSF ratio was approximately 50:1 for vatinoxan and 1:1 for dexmedetomidine.

Medetomidine plasma protein binding is high (85–90%). Medetomidine is mainly oxidised in the liver, a smaller amount undergoes methylation in the kidneys, and excretion is mainly via urine. Vatinoxan plasma protein binding is approximately 70%. Low levels are detectable in the central nervous system. Vatinoxan is metabolised to a very limited extent in the dog. Only a small amount (<5%) of vatinoxan dose has been found to be excreted via the urine. This suggests that vatinoxan is most likely eliminated in the faeces, although no data are available to confirm this.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Citric acid monohydrate
Methylparahydroxybenzoate (E218)
Propylparahydroxybenzoate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid, concentrated (for pH adjustment)
Water for injections

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 3 months.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

Clear type I glass vials closed with coated bromobutyl rubber stopper with an aluminium seal and a flip-top cap.

Cardboard box with 1 vial of 10 ml
Cardboard box with 5 boxes of 1 vial of 10 ml
Cardboard box with 10 boxes of 1 vial of 10 ml

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vetcare Oy
P.O. Box 99
24101 Salo
Finland

8. MARKETING AUTHORISATION NUMBER

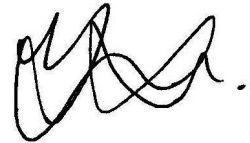
Vm 42810/5000

9. DATE OF FIRST AUTHORISATION

22 December 2021

10. DATE OF REVISION OF THE TEXT

December 2021

A handwritten signature in black ink, consisting of several loops and a final horizontal stroke.

Approved: 22 December 2021