PHARMACEUTICAL COMPOSITIONS CONTAINING N-PALMITOYLETHANOLAMIDE AND USE THEREOF IN THE VETERINARY FIELD

N-PALMITOYLETHANOLAMID-ENTHALTE PHARMAZEUTISCHE ZUSAMMENSETZUNGEN UND DEREN VERWENDUNG IN DER VETERINÄRMEDIZIN

COMPOSITIONS PHARMACEUTIQUES CONTENANT DU N-PALMITOYLETHANOLEAMIDE ET LEURS UTILISATIONS DANS LE DOMAINE VETERINAIRE

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
The present invention relates to pharmaceutical compositions containing N-palmitoylethanolamide (palmidrol) for use in the veterinary field, particularly for the treatment of the eosinophilic skin condition in felines which is normally known as Eosinophilic Granuloma Complex.

The eosinophilic condition in felines (Moriello K et al, 1997, Handbook of Small Animal Dermatology, pp. 205-208, Pergamon Press) has clinical signs such as erythema, pruritis and alopecia, and skin symptoms which are recognizable in the form of eosinophilic plaque (EP), eosinophilic granuloma (EG), and miliary or papulo-scabbery dermatitis, which can appear in the animal individually or simultaneously or at different times.

EP is a circumscribed area of erosion and exudation associated with clinical signs such as erythema, pruritis and auto-induced alopecia. Although they may appear anywhere on the skin surface, the lesions are located preferentially in the inguinal or perianal regions or in the medial region of the upper rear leg. The characteristic histopathology of EP shows considerable cell infiltration in the perivascular spaces, associated with epidermal hyperplasia, spongiosis and ulceration.

EG appears as an erythematous, alopecic and raised area generally located on the caudal face of the rear paws on the extremities (the claw bed and the pads), in the oral cavity, or on the chin. The characteristic histopathology of EG appears as a diffuse granulomatous dermatitis associated with areas of collagenolysis.

Miliary dermatitis is similar to EP but less extensive and with the formation of scabs.

Regardless of whether it is in the form of EP or EG, eosinophilic granuloma with lesions, is a highly recurrent condition. For this reason, animals suffering from eosinophilic granuloma, in the form either of EP or of EG, are subject throughout their lives, to intermittent or continuous treatments with antihistamines and corticosteroids the side effects of which, particularly in treatment of long duration, are known and documented.

The identification of active ingredients which can alleviate or resolve the inflammatory picture, at the same time ensuring maximum tolerability and an absence of adverse reactions, is an objective of considerable interest: in veterinary treatment.

It has now surprisingly been found that N-palmitoylethanolamide (common international name: palmidrol) is effective in the treatment of eosinophilic granuloma in cats, for both EP and EG lesions, and of tendonous keloids in horses. In the latter case in particular, a complete recovery of the animal with the possibility of a return to the competition circuit has been confirmed.

EP-A-0550008 discloses the use of NPE and related amides for treating disorders related to mast cell degranulation, e.g. keloid scars. NPE may be used in pharmaceutical compositions as powder. Suitable compositions include granulates and tablets.

EP-A-0550006 describes the use of NPE and related amides for treating disorders related to mast cell degranulation. The substance is also used in animal pathology (p. 5, line 38). NPE may be formulated in pharmaceutical compositions as powder. Suitable compositions include granulates and tablets.

WO 9618391 A discloses the use of NPE and related amides as cannabinoid agonists for treating disorders related to TNF and mast cell degranulation.


WO 9710712 A discloses that TNF is released by mast cells. Excessive TNF-a tissues levels have been implicated in autoimmune diseases and keloids (p. 8, line 6-26).

The subject of the present invention is therefore the use of n-palmitoylethanolamide, in micronized and/or co-micronized form, for the preparation of pharmaceutical compositions for veterinary use, particularly for the treatment of eosinophilic granuloma in cats, for both EP and EG lesions.

A further subject of the present invention is pharmaceutical compositions containing N-palmitoylethanolamide in micronized and/or co-micronized form.

The treatment of cats with N-palmitoylethanolamide provides for the administration of the drug in quantities of from 1 to 50 mg/kg/die for a period of between 15 and 60 days. A preferred treatment scheme provides for a daily administration of 10 mg/kg of body weight for 30 consecutive days.

The following examples explain the invention and the preferred method of implementing it without, however, being limiting thereof.
Example A - Effect of oral treatment with N-palmitoylethanolamide in eosinophilic skin condition in cats

Method

Included in the investigation were 15 cats of European race with short hair, of which 9 were female and 6 were male, with ages of between 7 and 123 months. All of the animals had symptoms of the eosinophilic condition, such as, pruritis, alopecia and erythema, and the skin manifestations associated therewith and, more precisely, 6 subjects had EP, 5 had EG and 4 had milary dermatitis (scabs). A numerical evaluation relating to the intensity and location of the signs and symptoms was assigned to each individual animal in accordance with the P.A.S.I. (psoriasis area severity index) “score” (Marks R. et al., 1989, Arch. Dermatol., 125: 235-240). The improvements in the clinical signs and in the associated lesions were evaluated on the 15th and 30th days of treatment. The treatment consisted of a preparation in accordance with Example 3 of the pharmaceutical preparations given below, containing 120 mg of micronized N-palmitoylethanolamide. The active ingredient was administered in a proportion of 10 mg/kg/die for 30 days.

Table 1 below summarizes the results of the test (PEA = N-palmitoylethanolamide):

<table>
<thead>
<tr>
<th></th>
<th>improved</th>
<th>unchanged</th>
<th>worsened</th>
<th>improved</th>
<th>unchanged</th>
<th>worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>not treated</strong></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>T15</td>
<td>0</td>
<td>70</td>
<td>30</td>
<td>0</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>T30</td>
<td>14.3</td>
<td>85.7</td>
<td>0</td>
<td>30</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td><strong>treated with</strong></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>composition of Example 3</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>T15</td>
<td>67</td>
<td>33</td>
<td>0</td>
<td>30</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td>T30</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td><strong>treated with</strong></td>
<td></td>
<td></td>
<td></td>
<td>14.6</td>
<td>85.4</td>
<td>0</td>
</tr>
<tr>
<td>Non-micronized</td>
<td></td>
<td></td>
<td></td>
<td>14.6</td>
<td>85.4</td>
<td>0</td>
</tr>
<tr>
<td>PEA (10 mg/kg/die)</td>
<td></td>
<td></td>
<td></td>
<td>14.6</td>
<td>85.4</td>
<td>0</td>
</tr>
<tr>
<td>T15</td>
<td>8.2</td>
<td>91.8</td>
<td>0</td>
<td>30</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td>T30</td>
<td>52</td>
<td>48</td>
<td>0</td>
<td>30</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td><strong>treated with</strong></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>cortisones</td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>T15</td>
<td>28</td>
<td>72</td>
<td>0</td>
<td>40</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>T30</td>
<td>65</td>
<td>35</td>
<td>0</td>
<td>64.8</td>
<td>35.2</td>
<td>0</td>
</tr>
</tbody>
</table>

It is clear from the results given above that N-palmitoylethanolamide in micronized form or comicronized with an excipient, can advantageously be used in the treatment of eosinophilic granuloma in cats, for both EP and EG lesions, both when these conditions are acute and when they are chronic.

The treatment of the cat with N-palmitoylethanolamide, gave results comparable to treatment with cortisones, with the substantial advantage that it does not have the serious side effects typical of these drugs.

The use of N-palmitoylethanolamide in micronized and/or co-micronized form (for example, with lactose) is particularly advantageous in bringing about the positive outcome of the treatment.

Clearly, the use of N-palmitoylethanolamide, in micronized and/or co-micronized form, for the treatment of eosinophilic granuloma in cats, for lesions in both EP and EG forms, may be extended to all animals which have conditions of the same type.
PREPARATION OF N-PALMITOYLETHANOLAMIDE (PEA)

PEA is a known compound and can be prepared in accordance with the synthesis method described in EP 0 550 008.

The micronization of PEA and its co-micronization with excipients were performed with compressed-air turbine micronizing apparatus. This apparatus is known and is not therefore described in greater detail.

The product obtained was subjected to analysis of the particles with Mastersizer, µ version apparatus from Malvern Instruments Co. UK. The final fineness of the PEA particles produced can be summarized as follows:

<table>
<thead>
<tr>
<th>particle size</th>
<th>quantity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 14 µ</td>
<td>traces</td>
</tr>
<tr>
<td>&lt; 10 µ</td>
<td>96% approx.</td>
</tr>
<tr>
<td>&lt; 6 µ</td>
<td>80%</td>
</tr>
</tbody>
</table>

It should be noted that this result of the micronization method obtained with PEA is surprising since it is unusual for a molecule of a lipid nature to produce particles with a mean fineness much less than 10 µ. The extreme fineness of the particles can be translated into improved absorption of the drug.

EXAMPLES OF PHARMACEUTICAL PREPARATIONS

Example 1 - tablets for cats
Each tablet, divisible from 350 g, contained: micronized N-palmitoylethanolamide 120 mg, maize starch 30 mg, lactose 115 mg, carboxymethyl cellulose 15 mg, microcrystalline cellulose 60 mg, magnesium stearate 10 mg.

Example 2 - oily gel for cats
100 g contained:
- N-palmitoylethanolamide co-micronized with lactose 2.5 g, lactose co-micronized with N-palmitoylethanolamide 1.5 g, soya lecithin 82.5 g, geleol 12.0 g, vitamin E acetate 0.5 g.

Example 3 - Gel for use on oral mucosae in cats
100 g contained:
- micronized N-palmitoylethanolamide hyaluronic acid, sodium salt (titrated in bio-binding epitope) 300 mg, carbomer 200 mg, methyl paraoxybenzoate 280 mg, ethyl paraoxybenzoate 200 mg, fish flavouring 800 mg, sorbitol 20 g, demineralized water to make up to 100 g.

In general, a composition for administration to cats contains from 20 mg to 4 g of PEA per 100 g of composition.
[0029] Clearly, other pharmaceutical compositions containing a pharmacologically effective dose of N-palmitoylethanolamide together with pharmacologically acceptable excipients may be provided. These compositions may be in the form of capsules, tablets, powders and pellets, and also in gastroresistant formulations for oral administration and may also be produced with the use of preliminary microencapsulation, liposomization or micellization techniques. For topical routes, including the transdermal route, formulations in suppositories, micro-enemas, creams, ointments, sprays, gels, foams, dressings of various thicknesses and patches may be used. All possible pharmaceutical forms indicated for the various administration routes may also be formulated with excipients or by technological processes suitable for producing fast-release or slow-release medicaments.

Claims

1. Use of N-palmitoylethanolamide for the preparation of a pharmaceutical composition for the treatment of eosinophilic granuloma in Felines, for lesions in both EP and EG forms, this condition being manifested in both acute and chronic form, in which the N-palmitoylethanolamide is present in micronized form or is co-micronized with an excipient.

2. Use according to claim 1, in which the Feline is the cat.

3. A pharmaceutical composition containing N-palmitoylethanolamide in micronized form or co-micronized with an excipient, together with pharmaceutically acceptable excipients.

4. A pharmaceutical composition according to claim 3, containing from 20 mg to 4 g of N-palmitoylethanolamide per 100 g of composition, for use in the cat.

5. A pharmaceutical composition according to claim 3 or to claim 4, in the form of an oral powder, oral granules, tablets or gel.

6. Process for the preparation of a pharmaceutical composition comprising N-palmitoylethanolamide together with pharmaceutically acceptable excipient, said process comprising the step of micronizing or co-micronizing said N-palmitoylethanolamide with an excipient.

Patentansprüche


2. Verwendung nach Anspruch 1, wobei das Katzentier eine Hauskatze ist.

3. Pharmazeutische Zusammensetzung, die N-Palmitoylethanolamid in feinstgemahlener Form oder in einer zusammen mit einem Exzipienten feinstgemahlenen Form zusammen mit pharmazeutisch akzeptablen Exzipienenten enthält.

4. Pharmazeutische Zusammensetzung nach Anspruch 3, die 20 mg bis 4 g N-Palmitoylethanolamid auf 100 g Zusammensetzung enthält, für die Verwendung bei der Hauskatze.

5. Pharmazeutische Zusammensetzung nach Anspruch 3 oder 4 in Form eines Oralpulvers, eines Oralgranulats, von Tabletten oder eines Gels.

Revendications

1. Utilisation de N-palmitoyléthanolamide pour la préparation d'une composition pharmaceutique destinée au traitement du granulome eosinophile chez les félin, pour des lésions à la fois de forme EP et EG, cette condition étant manifestée à la fois sous forme aiguë et chronique, et dans laquelle le N-palmitoyléthanolamide est présent sous forme micronisée ou bien est co-micronisée avec un excipient.

2. Utilisation selon la revendication 1, dans laquelle le félin est le chat.

3. Composition pharmaceutique contenant du N-palmitoyléthanolamide sous forme micronisée ou bien co-micronisée avec un excipient, en association avec des excipients pharmaceutiquement acceptables.

4. Composition pharmaceutique selon la revendication 3, contenant de 20 mg à 4 g de N-palmitoyléthanolamide pour 100 g de composition, pour une utilisation chez le chat.

5. Composition pharmaceutique selon la revendication 3 ou selon la revendication 4, sous la forme d'une poudre pour voie orale, de granules pour voie orale, de tablettes ou de gel.

6. Procédé pour la préparation d'une composition pharmaceutique comprenant du N-palmitoyléthanolamide en association avec un excipient pharmaceutiquement acceptable, ledit procédé comprenant une étape de micronisation ou de co-micronisation dudit N-palmitoyléthanolamide avec un excipient.