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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-083413- -00010-0000

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Act 538 PETICION Folios 3

Señora Directora
DIRECCION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 538

Referencia : Expediente No. 06.083.413
Asunto : Solicitud de Patente para **USO DE MELOXICAM PARA EL TRATAMIENTO DE ENFERMEDADES RESPIRATORIAS EN CERDOS**
Solicitante : **BOEHRINGER INGELHEIM VETMEDICA GMBH**
Clase : A61K 031/5415, A61P 011/000
Publicada en : La Gaceta No. 607 Del 31 de agosto de 2009
Fecha de Solicitud : 23 de agosto de 2006

1. Yo, LUZ CLEMENCIA DE PÁEZ, identificada como aparece al pie de mi firma, actuando como apoderada en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$470.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 69699 de 30 de diciembre de 2009.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Anexos :

- Presento así mismo sustitución del poder otorgado por el Doctor EMILIO FERRERO, a mi favor, y para lo cual solicito me sea reconocida personería para proseguir con el trámite de este asunto en favor de la sociedad solicitante.

Señora Directora,

LUZ CLEMENCIA DE PÁEZ
LUZ CLEMENCIA DE PÁEZ
T.P.A. No. 23.555

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E. S. D.

Poderdante : **BOEHRINGER INGELHEIM VETMEDICA GMBH**

Poder conferido el : 02/08/1996

Yo, EMILIO FERRERO, obrando como apoderado principal del poderdante arriba mencionado, mediante el presente escrito sustituyo el poder a mi otorgado a la doctora LUZ CLEMENCIA DE PAEZ, identificada con cédula de ciudadanía No. 35.456.344 y Tarjeta Profesional N°23.555, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil.

Señora Jefe,

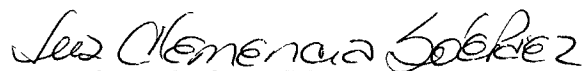


EMILIO FERRERO

T.P.A. N° 31.929

C.C. N° 438.019 de Usaquén

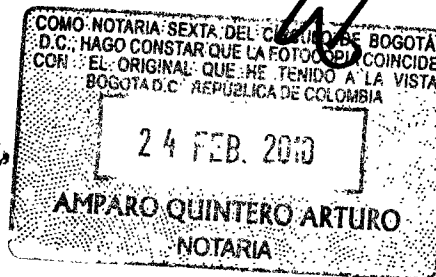
Acepto:



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
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***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILID	470,000.00
		TOTAL :	\$ 470,000.00

SON: CUATROCIENTOS SETENTA MIL PESOS

RESPONSABLE :

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117
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DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-83413

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **607** DE

FECHA **31 DE AGOSTO DE 2009** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **26 DE NOVIEMBRE DE 2009**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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- (74) Agent: **GRIFFITH HACK**; Level 3, 509 St Kilda Road, Melbourne, Victoria 3004 (AU).
- (21) International Application Number: PCT/AU02/00659
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
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(54) Title: A METHOD OF IMPROVING THE GROWTH PERFORMANCE OF AN ANIMAL

(57) Abstract: The invention broadly relates to a method of improving the growth performance of an animal. In particular the present invention relates to a method of improving the growth performance of an animal comprising the step of administering to an animal in need thereof a growth promoting amount of one or more anti-inflammatory agents.

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Title

A METHOD OF IMPROVING THE GROWTH PERFORMANCE OF AN ANIMAL

Claims

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for improving the growth performance of an animal comprising the step of administering to an animal in need thereof a growth promoting amount of one or more anti-inflammatory agents.
2. A method according to claim 1, wherein the anti-inflammatory agent is administered optionally in combination with a pharmaceutical carrier, adjuvant or vehicle.
3. A method for improving the growth performance of an animal comprising the step of administering to an animal in need thereof a composition comprising an anti-inflammatory agent in conjunction with an antibiotic, optionally in combination with a pharmaceutical carrier, adjuvant or vehicle, wherein said composition achieves a synergistic growth promoting effect.
4. A method for improving the growth performance of an animal comprising the step of administering to an animal in need thereof a compound or composition which increases or supplements endogenous anti-inflammatory agent levels, wherein growth performance is enhanced relative to the growth performance of an animal which has not been administered said compound or composition.
5. A method according to claim 4, wherein the compound or composition is administered prior to, together with, or subsequent to the administration of a growth promoting amount of one or more anti-inflammatory agents.
6. A method according to claim 4 or claim 5, wherein the compound or composition comprises an antagonist of a pro-inflammatory cytokine receptor.
7. A method according to claim 6, wherein the antagonist is of TNF- α receptor, GM-CSF receptor, IL-6 receptor, IL-1 receptor, IL-4 receptor or IL-8 receptor.
8. A method according to any one of claims 4 to 6, wherein the compound or composition comprises IL-10, 1,8- naphthosultam substituted compounds or quinoxaline compounds.
9. A method according to claim 4 or claim 5, wherein the compound or composition increases the endogenous level of anti-inflammatory agents by decreasing the amount of pro-inflammatory cytokines.
10. A method according to any one of claims 1 to 3 or 5, wherein the anti-inflammatory agent is a soluble cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragment thereof which has an anti-inflammatory effect or an anti-inflammatory agent selected from the group consisting of diclofenac, diflunisal, etodolac, flunixin, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic and tolmetin.
11. A method according to claim 10, wherein the soluble cytokine receptor or biologically active fragment thereof is selected from the group consisting of TNF α receptor, IL-6 receptor, IL-1 receptor, IL-4 receptor and IL-8 receptor or a combination thereof that are capable of improving the growth performance of an animal.
12. A method according to claim 10, wherein the soluble cytokine receptor or biologically active fragment thereof is either IL-1 receptor, IL-4 receptor, IL-8 receptor or a combination thereof.
13. A method according to claim 10, wherein the soluble cytokine receptor or biologically active fragment thereof is IL-1 receptor.
14. A method according to claim 10, wherein the cytokine receptor antagonist or biologically active fragment thereof is selected from the group consisting of IL-1ra, IL-6ra, IL-8ra and TNF- α ra.
15. A method according to claim 14, wherein the cytokine receptor antagonist or biologically active fragment thereof is IL-1ra.
16. A method according to claim 10, wherein the cytokine inhibitory factor or biologically active fragment thereof is selected from the group consisting of TNF blocking factor and TNF- α inhibitor.
17. A method according to any one of claims 1, 2, 4 to 16, further comprising the step of administering an antibiotic.
18. A method according to claim 3, wherein the step of administration the antibiotic is prior to or subsequent to the administration of the anti-inflammatory agent.
19. A method according to claim 3 or claim 17, wherein the antibiotic is selected from the group consisting of amoxycillin, penicillin, procaine, ampicillin, cloxacillin, penicillin G, benzathine, benethamine, ceftiofur, cephalonium, cefuroxime, erythromycin, tylosin, tilimicosin, oleandomycin, kitasamycin, lincomycin, spectinomycin, tetracycline, oxytetracycline, chlortetracycline, neomycin, apramycin, streptomycin, avoparcin, dimetridazole, sulfonamides (including trimethoprim and diaveridine), bacitracin, virginiamycin, monensin, salinomycin, lasalocid, narasin and olaquinox or combinations thereof.
20. A method according to claim 19, wherein the antibiotic is either lincomycin, spectinomycin or amoxicillin or combinations thereof.
21. A method according to any one of claims 1 to 20, wherein the administration is orally, topically, or parenterally.
22. A method according to claim 21, wherein parenteral administration is either by subcutaneous injection, aerosol, intravenous, intramuscular, intrathecal, intrasternal injection, infusion techniques or encapsulated cells.
23. A method according to any one of claims 1 to 22, wherein the administration is either a single dose unit or a multiple dose unit.



Free Full-text Worldwide Patent Searching - 10,292,519 patent documents - updated Jun 8, 2010

The following documents were requested

- 1 WO 2002/096216 A1
- 2 WO 2003/103698 A1
- 3 WO 2003/051300 A2
- 4 WO 2003/081704 A2

[Back to search results](#)**WO 2002/096216 A1** (patent application)**A METHOD OF IMPROVING THE GROWTH PERFORMANCE OF AN ANIMAL**[Front Page](#) [Full Text](#) [PDF Version](#) [Patent Family & Status](#)**A METHOD OF IMPROVING THE GROWTH PERFORMANCE OF AN ANIMAL****FIELD OF THE INVENTION**

The invention broadly relates to a method of improving the growth performance of an animal . In particular the present invention relates to a method of improving the growth performance of an animal comprising the step of administering to an animal in need thereof a growth promoting amount of one or more anti-inflammatory agents.

BACKGROUND OF THE INVENTION

In the agricultural industries of many countries, commercial livestock rearing systems have become commonplace . Commercial animal husbandry techniques have been used in rearing poultry, pigs and cattle and have resulted in greatly increased production of food products derived from these animals.

The commercial raising of livestock requires maximisation of growth rate and feed conversion efficiency so as to reduce the unit cost of production. This requirement has led to the development and widespread use of so called "feed additives" .

Feed additives have two general purposes. One purpose is to enhance the performance of the animal in terms of increased growth rate and/or increased feed conversion efficiency in healthy and nutritionally unchallenged animals. The other purpose is to maintain the health of the animal during periods of trauma or "stress" that inevitably occur in the current practices of intensive rearing thereby keeping the animal disease free.

In the early 1950' s, researchers unexpectedly discovered that an antibiotic ingredient in chicken mash was a "growth factor." The finding drastically changed the livestock and poultry industries and was an economic boon for pharmaceutical companies. Feed animals are now raised under highly controlled conditions and receive specialised feed with a variety of growth promoting additives .

Routine antibiotic administration to animals has become almost universal since the discovery that the addition of small amounts of antibiotics such as penicillin, tetracycline and sulfamethasine, to animal feed increases the growth of pigs and cattle. In 1979, about 70% of the beef cattle and veal, 90% of the swine, and virtually 100% of broilers reared in the United States consumed antibiotics as part of their daily feed. This use, accounting for nearly 40% of antibiotics sold in the United States, is estimated to save consumers \$3.5 billion a year in food costs.

Animals raised under modern conditions optimised for growth promotion receive rations containing high proportions of protein, usually in the form of soybean or cottonseed meal (meat and bone or blood meal are used extensively in Australia) , and high percentages of grains such as corn or milo, a type of sorghum (wheat and barley in Australia) . Feed additives which have been used include such hormones as diethylstilbestrol, which also increases the rate of weight gain, and tranquillisers (not used widely for pigs) that prevent the effects of the stress brought on by confinement conditions from causing disease or weight loss.

Cattle ordinarily require 5 kilograms of feed to produce 1 kilogram of weight gain. Under optimal growth promoting conditions, and with enriched feed, they gain 1 kilogram with only 3 kilograms of feed. Although hormones and antibiotics have greatly increased the rate of growth of food animals, the use of such additives has not been without problems. One of the hormones that is commonly used as a growth stimulant, diethylstilbestrol or DES, has been shown to be a carcinogen and has been banned from further use in most countries .

When antibiotics are mixed in animal feed, the compounds are spread throughout the environment exposing microorganisms to the antibiotics. The constant exposure of the microorganisms to antibiotics puts biological pressure on the microorganisms to develop a resistance to the antibiotics. This can result in a microorganism that is resistant to antibiotics and causes especially severe and difficult to treat infections.

An antibiotic-resistant microorganism is potentially a serious pathogen because it is difficult to control. If the organism causes an infection in an animal or in man, the infection may not be controlled with conventional antibiotics. If the infection is serious, there may not be time to determine which antibiotics are effective against the infecting bacteria. The problem has been especially serious when antibiotic resistant organisms in meat are consumed by people who themselves take antibiotics for treatment of disease. Antibiotics inhibit many of the normal microorganisms in the respiratory and gastrointestinal tracts. This allows the resistant one to proliferate rapidly and produce more serious disease. The combination of antibiotic resistant organisms from food and ineffective antibiotic treatment of people has caused most of the deaths due to salmonella food poisoning reported in the United States in the past several years.

As a result of the increasing appearance of antibiotic resistant bacteria in feed lots and several serious epidemics caused by antibiotic resistant bacteria, there is increasing governmental pressure to ban the use of antibiotics in animal feed. In fact, the World Health Organisation and the Australian Government have specified the need to use environmentally friendly alternative methods to control infection. The imminent ban or withdrawal of various antibiotics from livestock feed and water is likely to (i) increase the incidence of infection in animals and consequently reduce growth performance (ii) further reduce the health, fertility and breeding performance of animals. Consequently, there is an immediate and increasing need for new, safe and effective growth stimulators of feed animals, as well as a reduction in disease by enhancing health. Various attempts at promoting animal growth without the use of antibiotics has been employed many using elaborate and circuitous means. These have included subcutaneous implants of hormones or complex salts having cations being made from complexes (see, for example, U.S. Pat. No. 6,197,815; U.S. Pat. No. 3,991,750; U.S. Pat. No. 4,067,994). None of these attempts have proven to be simple or effective. Accordingly, there is still a need for a method of improving the growth performance of animals, which is not reliant on the use of antibiotics or elaborate methodology.

The applicant has now surprisingly found that the administration of anti-inflammatory agents, and in particular cytokine receptor antagonists such as interleukin (IL) -1ra, increases the growth performance of animals while decreasing the amount of antibiotics. The applicant also has evidence that a similar growth performance effect can be achieved by administering soluble cytokine receptors such as TNF α receptor, IL-6 receptor, IL-4 receptor and IL-8 receptor, or cytokine blocking factors such as TNF blocking factor (Bargetzi et al, Cancer Research 53: 4010-13 (1993); Engelmann et al, Journal of Biological Chemistry 264: 11974-80 (1989)) or TNF-alpha inhibitor (Engelmann et al, Journal of Biological Chemistry 265: 1531-6 (1990); Seckinger et al, European Journal of Immunology 20: 1167-74 (1990)).

While not wishing to be bound by any particular theory or hypothesis, the applicant considers that the increases in growth performance observed in animals that have been administered anti-inflammatory agents result from the interplay of four key effects. These are:

- 1) . Anti-inflammatory effect per se;
- 2) . Immunoenhancement effect; 3) . Anti-parasitic and anti-microbial effect; and 4) . Stress reduction.

Each of these effects, either singly or together, profoundly impact upon the health and welfare of animals, which in turn affects the growth performance of animals and thereby the meat quality. For example:

1) . Anti-Inflammation

Chronic inflammation is often seen in livestock and relates to immune activation triggered by persistent infections and environmental stimuli. Inflammation plays an important role in the initiation of immune responses to infection, however, chronic immune activation, particularly by persistent infection or microbial load, can have deleterious effects on growth and development and can reduce the effectiveness of vaccination. Consequences of excessive immune activation include the production of inflammatory cytokines, fever, inappetence, amino acid resorption from muscle and redirection of nutrients away from meat production. Anti-inflammatory agents could reduce the pathology of chronic immune activation, for example, by reducing the effects of inflammatory cytokines such as IL-1, IL-6, TGF- β , IL-11, IL-18, IL-12, IL-17, LIF, IFN- γ IL-8, TNF- α and GM-CSF. Alternatively, by administering soluble cytokine receptors for these inflammatory cytokines ie IL-1 receptor, IL-8 receptor, TNF- α receptor, IL-6 receptor et al, excessive amounts of circulating inflammatory cytokines can be reduced. Cytokine receptor antagonists such as IL-1ra, IL-6ra or TNF- α ra, which competitively inhibit the binding of these pro-inflammatory cytokines to their respective membrane-expressed receptors, can be used to ameliorate the action of these cytokines.

2) . Immunoenhancement Effect a) . TH1/TH2 immune responses

The inflammatory response is inextricably tied to the body's immune system. Interplay occurs between immune cytokine regulatory networks and the other regulatory systems of the body. Immune responses to infections or antigens can acutely bias each other. The immune response can be generalised by the type of T cell response. A T helper 1 (TH1) type response is principally involved in cell mediated immunity, whilst a TH2 pattern of response is often associated with humoral immunity. TH1 and TH2 type T cell subsets have been implicated in the regulation of many immune responses defined by cytokine patterns. TH2 cells express the cytokines interleukin (IL)-4, IL-5, IL-10, and IL-13. IL-3 expression is common to both TH1 and TH2 T cells. Whereas, TH1 cells express IL-2, IFN γ , and TNF β . These TH2 cytokines influence B cell development and augment humoral responses such as the secretion of antibodies. Both types of T cells influence each other by the cytokines they secrete. For example, TH2 cytokines, such as IL-10, can suppress TH1 functions. Other cytokines can also influence TH1 or TH2 development such as TNF β , known to down regulate TH1 responses.

It is known that when there is no invading antigen, the action of Th1 cells is considered harmful to the body. Anti-inflammatory agents suppress the production of IFN- γ in Th1 cells. Also anti-inflammatory agents suppress the overproduction of Th1 cells and therefore enhance the production of Th2 (antibody-secreting) cells because these cells cross-regulate one another. This means that by administering particular anti-inflammatory agents the amount of pro-inflammatory cytokines are suppressed. Alternatively, by administering soluble cytokine receptors, cytokine receptor antagonists, or cytokine inhibitory factors of cytokines like IL-1, IL-4, IL-8, GM-CSF, IL-6 or TNF- α the overproduction of cytokines by Th1 cells may be reduced.

b) . Antibody isotype switching

Antibodies are required to eliminate or protect against infection. Mature B cells undergo the process of switching antibody class after antigenic stimulation. TH cells through physical contact and cytokines, referred to as switch factors, regulate isotype switching. Some of the cytokines known to be involved in isotype switching, either alone or in combination, are IL-4, IL-5, TNF β , IL-1, IL-2, IL-6, and IL-13. IL-4 and IL-5 synergise to enhance IgG1 responses. For example, optimal IgG1 responses also requires IL-2. IL-1 can enhance IgA production in the presence of IL-5. TNF β induces IgA production.

c) . Immune dysfunction

The genetic potential for most production traits is predetermined by birth. Many factors (stress, disease, nutrition, immunity etc.) determine whether this potential is achieved. The level and type of antigen exposure influences and establishes a 'bias' of the immune system. Most immune responses are biased towards a type that promotes immunity against bacteria and viruses or a type that promotes immunity against many parasites. While the genotype of an animal can influence this bias, the early experience by the neonate to antigens and infections can set the immune reactivity towards one or other type. This bias is altered depending on subsequent antigen exposure. Breeding programmes based on selection for production traits has appeared to be at the expense and detriment of immune competence or reactivity. This change has been further exacerbated by the persistent use of antibiotic supplements to water and feed, which has presumably resulted in an altered

genetic potential to mount effective- immune responses.

d) . Mucosal immunity

The most prevalent areas of infection in livestock are mucosal sites, primarily the gastrointestinal tract and the lungs. Thus, the mucosal immune system is the first line of defence against pathogens and disease. Cytokines, notably IL-5, IL-4, IL-6 and IL-10, play a significant role in the regulation and efficacy of immune responses in the mucosa .

IL-5 and IL-6 act upon B-1 and B-2 subpopulations of lymphocytes in the mucosal immune system. Deficiencies in either the production of IL-5 or IL-6, or their receptors result in significantly impaired production of IgA, the antibody isotype responsible for protective responses in the mucosa. Similarly, IL-5, IL-6 and the chemokine MIP-1 alpha have the capacity to increase IgA responses to mucosal vaccines. IL-4 has an immunoregulatory role in mucosal tissues, primarily by enhancing TH2 responses, and thus, enhancing antibody production. IL-4 is considered essential to the development of mucosal immune responses in the lung, via the involvement of TH2 pathways. Both IL-4 and IL-5 operate in concert in the lung, with IL-4 committing naive T cells to a TH2 phenotype which upon subsequent activation secrete IL-5, resulting in eosinophil accumulation. Furthermore, IL-4 and IL-10 play a role in mucosal tolerance, and thus, help regulate and dampen allergic type responses in the gut and reduce the susceptibility of animals to chronic inflammatory conditions of the gut.

3) . Anti-Parasitic and Anti-Microbial Effect a) . Anti -parasitic effect

Acquired immune responses against pathogens generally fall into one of two types, cell mediated (TH1) or antibody mediated (TH2) , and this is controlled by cytokines . Cytokines involved in TH2 responses are attractive therapeutic targets, as they could protect against ectoparasites and gastrointestinal worms and suppress inflammation induced by TH1 cytokines. TH2 cytokines induce eosinophilia, IgE synthesis, and mucus production that enhance protection against worms and other gut parasites. b) . Anti -microbial effects

Microbial infections remain a world-wide problem in terms of economic impacts and health, despite advances in nutrition, vaccines, chemicals and antibiotics. The immune response to microbial pathogens incorporates two systems of recognition. The first line of defence is innate immunity and this is followed, if required, by the ensuing adaptive response (cell mediated and antibody responses) . By decreasing the inflammation with anti- inflammatory agents including phenylbutazone, flunixin meglumine and ketoprofen or intravenous DMSO there is an improvement in the blood flow to the affected tissue, which in turn assists in the innate immunity to help overcome the infection. This process may be assisted by using vasodilation drugs such as acetylpromazine, phenoxymethamine, isoxsuprine, pentoxifylline, aspirin and heparin. An alternative approach is to administer the soluble cytokine receptors of known inflammatory cytokines such as IL-1, TNF- α , IL-6 and IL-8.

4) . Stress Reduction

Many conditions within a commercial environment contribute to a reduction in feed intake, growth rate and carcass quality. Despite extensive research efforts to evaluate the mechanisms by which stressors affect performance in many species, the long-standing problems within the livestock industries have not been alleviated. Stress, particularly early and sustained stress, results in immune dysfunction, Hypothalamic-Pituitary-

Adrenalcortical (HPA) activity and an imbalance of chemicals in the brain. The nervous and immune systems are integrated and form an interdependent neuroimmune network. Depression, physical or emotional stresses activate the endocrine system altering immunological function, which in turn elicits physiological and chemical changes in the brain. Likewise, immunological stress in the form of infection activates the neuro-endocrine system via cytokines and other soluble mediators to induce stress responses which in turn impair productivity. Cytokines mediate interactions between the immune, endocrine and central nervous systems. Previously believed to be immunosuppressive, there is mounting evidence that stress induces a shift in TH1/TH2 immune responses resulting in immune dysregulation rather than immunosuppression. The potential for cytokines to affect homeostatic pathways creates a need to evaluate the activities of the immune system.

SUMMARY OF THE INVENTION

In its broadest aspect the present invention provides a method for improving the growth performance of an animal comprising the step of administering to an animal in need thereof a growth promoting amount of one or more anti-inflammatory agents.

The anti-inflammatory agents preferably increase or supplements the animals own anti-inflammatory systems. The present invention also provides a method for improving the growth performance of an animal comprising the step of administering to an animal in need thereof a compound or composition which increases or supplements endogenous anti-inflammatory agent levels, wherein growth performance is enhanced relative to the growth performance of an animal which has not been administered said compound or composition.

Preferably, the compound or composition is administered prior to, together with, or subsequent to the administration of a growth promoting amount of one or more anti-inflammatory agents.

More preferably the compound or composition comprises antagonists of pro-inflammatory cytokine receptors. Even more preferably, the compound or composition comprises antagonists of TNF- α receptor, GM- CSF receptor, IL-6 receptor, IL-1 receptor, IL-4 receptor or IL-8 receptor. Most preferably the compound or composition comprises IL-10, 1, 8-naphthosultam substituted compounds or quinoxaline compounds.

Alternatively, the compound or composition increases the endogenous level of anti-inflammatory agents by decreasing the amount of pro-inflammatory cytokines. Accordingly, the compound or composition comprises agents capable of increasing the amount of circulating, soluble cytokine receptors to pro-inflammatory cytokines. The present invention also provides a method for improving the growth performance of an animal comprising the step of administering to an animal in need thereof a composition comprising an anti-inflammatory agent in conjunction with an antibiotic, optionally in combination with a pharmaceutical carrier, adjuvant or vehicle, wherein said composition achieves a synergistic growth promoting effect .

Preferably, the anti-inflammatory agent is any soluble cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragment thereof which has an anti-inflammatory effect or an anti- inflammatory agent selected from the group consisting of diclofenac, diflunisal, etodolac, flunixin, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic and tolmetin. Preferably, the soluble cytokine receptor or biologically active fragment thereof is selected from the group consisting of TNF α receptor, IL-6

receptor, IL-1 receptor, IL-4 receptor and IL-8 receptor or a combination thereof that are capable of improving the growth performance of an animal. More preferably, the soluble cytokine receptor or biologically active fragment thereof is IL-1 receptor. Preferably, the cytokine receptor antagonist or biologically active fragment thereof is selected from the group consisting of IL-1ra, IL-6ra, IL-8ra and TNF- α ra. More preferably, the cytokine receptor antagonist or biologically active fragment thereof is IL-1ra.

Preferably, the cytokine inhibitory factor or biologically active fragment thereof is selected from the group consisting of TNF blocking factor and TNF- α inhibitor.

In one particular embodiment, the anti-inflammatory agents of the present invention are formulated into a growth enhancing composition by combining one or more anti-inflammatory agents together with one or more pharmaceutical carriers, adjuvants or vehicles. More preferably, a growth enhancing composition is formulated by combining one or more soluble cytokine receptors, cytokine receptor antagonists, cytokine inhibitory factors or biologically active fragments thereof with either one or more other anti-inflammatory agents or pharmaceutical carriers, adjuvants or vehicles. Any known pharmaceutical carrier, adjuvant or vehicle may be used as long as it does not adversely affect the growth promoting effects of the anti-inflammatory agent(s). Accordingly, in a second aspect the present invention provides a growth promoting composition comprising one or more anti-inflammatory agents together with one or more pharmaceutical carriers, adjuvants or vehicles. Preferably, the composition comprises anti-inflammatory agents selected from the group consisting of soluble cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragment thereof, diclofenac, diflunisal, etodolac, flunixin, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic and tolmetin. More preferably, the composition comprises one or more soluble cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragments thereof and one or more different soluble cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragments thereof or one or more anti-inflammatory agent. Most preferably, the composition comprises one soluble cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragment thereof and one different anti-inflammatory agent or a pharmaceutical carrier, adjuvant or vehicle. Compositions comprising antibiotics assist in limiting the microbial load in an animal, thereby assisting the anti-inflammatory agent to improve growth performance in the animal. Particularly preferred antibiotics are those already in use in conventional animal production environments. However, in particular, the preferred antibiotic is selected from the group consisting of amoxycillin, ampicillin, apramycin, avoparcin, bacitracin, benethamine, benzathine, ceftiofur, cefuroxime, cephalonium, chlortetracycline, cloxacillin, dimetridazole, erythromycin, kitasamycin, lasalocid, lincomycin, monensin, narasin, neomycin, oleandomycin, oxytetracycline, olaquinox, penicillin, penicillin G, procaine, spectinomycin, streptomycin, tetracycline, tilmicosin, trimethoprim, tylosin, salinomycin, sulfonamides (including and diaveridine) and virginiamycin or combinations thereof. Most preferably, the antibiotic is amoxycillin, lincomycin or spectinomycin.

Depending upon the activity of the anti-inflammatory agent, manner of administration, age and body weight of the animal, different doses of anti-inflammatory agent can be used. Under certain circumstances, however, higher or lower doses may be appropriate. The administration of the dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administrations of subdivided doses at specific intervals. It will be understood, however, that the specific dose level for any particular animal will depend upon a variety of factors including the activity of the specific anti-inflammatory agent employed, the age, body weight, general health, sex, diet, time of administration, and route of administration, rate of excretion and anti-inflammatory agent or antibiotic combination. However, generally the preferred route of administration is selected from the group consisting of oral, topical and parenteral administration.

Parenteral administration includes subcutaneous injections, aerosol, intravenous, intramuscular, intrathecal injection, infusion techniques or encapsulated cells. The anti-inflammatory agents or compositions of the invention may also be administered as an additive to animal water and/or feed.

The growth performance of an animal may be determined by any known measure including increased growth rate, increased efficiency of feed use, increased final weight, increased dressed weight or decreased fat content. It will be further appreciated by those skilled in the art that the improved growth performance of an animal may result from immunoenhancement, anti-parasitic or anti-microbial effect, anti-inflammatory effect or stress reduction. More preferably, the immunoenhancement will result from a TH1/TH2 immune response, antibody isotype switching, hematopoiesis, improvement in immune function, mucosal immunity, beneficial effects on homeostatic processes such as appetite, endocrine or neural-endocrine processes.

It will be appreciated by those skilled in the art that the methods and compositions disclosed herein may be useful for any animal for which improving the growth performance is a desirable outcome. However, the present invention is particularly useful for feed animals i.e. those animals that are routinely farmed for meat production. Preferably, the animal is a higher artiodactyl or bird. Artiodactyls include cattle, pigs, sheep, camels, goats and horses. Birds include chickens, turkeys, geese, and ducks. More preferably, the present invention relates to animals selected from the group consisting of cattle, pigs, sheep, camels, goats, horses and chickens. Most preferably, the animals are cattle, pigs, or sheep.

In a third aspect, the anti-inflammatory agent is administered to an animal as a nucleic acid molecule encoding said anti-inflammatory agent such that upon expression of said nucleic acid molecule in the animal a growth promoting amount of the anti-inflammatory agent is produced. Thus, the present invention provides a method for improving the growth performance of an animal comprising the step of administering to an animal in need thereof a nucleic acid molecule encoding one or more anti-inflammatory agents, wherein the expression of said nucleic acid molecule produces an effective growth promoting amount of one or more anti-inflammatory agents. The nucleic acid molecule may be DNA, cDNA, RNA, or a hybrid molecule thereof. It will be clearly understood that the term nucleic acid molecule encompasses a full-length molecule or a biologically active fragment thereof. Preferably the nucleic acid molecule is a DNA molecule encoding a soluble cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragment thereof. Most preferably, the DNA encodes a cytokine receptor selected from the group consisting of TNF α receptor, IL-6 receptor, IL-1 receptor, IL-4 receptor and IL-8 receptor or a combination thereof, or a cytokine receptor antagonist selected from the group consisting of IL-1ra, IL-6ra and TNF- α ra.

The nucleic acid molecule may integrate into the animal genome, or may exist as an extrachromosomal element.

The nucleic acid molecule may be administered by any known method; however, it is preferably injected subcutaneously, intravenously, or intramuscularly or administered as an aerosol.

The amount of nucleic acid that is administered will depend upon the route and site of administration as well as the particular cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragment thereof encoded by the nucleic acid molecule. As described herein, introducing an amount of 200 μ g of a nucleic acid molecule encoding a cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragment thereof is sufficient to improve growth performance in an animal. Thus, preferably the amount of about 200 μ g to 1,000 μ g of a nucleic acid molecule encoding a cytokine receptor, cytokine receptor antagonist, cytokine inhibitory factor or biologically active fragment thereof is preferably introduced into an animal.

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Frequently used carriers, adjuvants or vehicles include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatine, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial, anti-oxidants, chelating agents and inert gases. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington's *Pharmaceutical Sciences*, 15th ed. Easton: Mack Publishing Co., 1405-1412, 1461-1487 (1975) and The National Formulary XIV., 14th ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. The pH and exact concentration of the various components of the pharmaceutical composition are adjusted according to routine skills in the art. See Goodman and Gilman's *The Pharmacological Basis for Therapeutics* (7th ed.). The pharmaceutical compositions according to the invention may be administered locally or systemically in a growth promoting amount. Amounts effective for this use will, of course, depend on the anti-inflammatory agent and the weight and general state of the animal. Typically, dosages used in *vi tro* may provide useful guidance in the amounts useful for *in si tu* administration of the compositions. Various considerations are J ω t t H μ>



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Novel galenic formulations of meloxicam for oral administration

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FP AUSTRALIA.

1 8 OCT 1999

15 hydrated form when stored under normal ambient conditions.

Surprisingly, it has been found that meloxicam from the salts formed with bases becomes available for absorption substantially faster after administration and in greater

20 quantities than neutral meloxicam in spite of the low solubility at low pH levels which correspond to the environment of the stomach. The rise in the plasma levels after oral administration of the salts of meloxicam takes place considerably faster than when pure meloxicam is

25 used. The high degree and rapidity of the rise in plasma levels which can be achieved with meloxicam salts, particularly the meloxicam-meglumin salt, could not have been expected by anyone skilled in the art, taking into account the properties of the NSAID salts known from the

30 prior art. The increased solubility obtained by using a meloxicam salt surprisingly occurs *in vivo* even at low pH

values. This makes it possible for large amounts of the active substance to be dissolved even immediately after administration and thus become available for absorption by

35 the body.

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Example 7 together with Figure 4 shows that after oral administration of a meloxicam salt formulation the plasma level rises considerably faster than after the administration of a conventional capsule formulation of

5 the neutral active substance. Just 15 min after administration of the meloxicam-meglumin salt formulation according to the invention, a plasma level of 286 ng/ml is achieved, which virtually corresponds to the minimum plasma concentration in the steady-state, whilst 30 min

10 after administration of the comparative formulation, still no appreciable plasma level (42 ng/ml) can be detected. Moreover, with the formulation according to the invention, after barely 2 hours a maximum plasma level of 812 ng/ml is obtained, which is twice as great as the minimum

15 steady-state plasma level achieved with the comparative formulation (the maximum plasma level was determined on the basis of variability in time, not from the average curve in Fig. 4, but from the underlying individual curves). Thus, a rapid onset of activity as well as a

20 particularly high activity can be expected in the first 23 hours after taking a formulation according to the invention, particularly a meloxicam-meglumin salt formulation, which is important for relieving acute pain. With the comparative formulation, on the other hand, no

25 marked plasma level peak is achieved, but rather the plasma level rises more or less continuously until it reaches a plateau in the steady state.

The AUC_{0-∞} (AUC: area under the plasma concentration-time

30 curve, 0-∞: from time 0 of the administration to

infinity; measurement of resorption) of the conventional capsule formulation according to Figure 4 is 14.1 pg h/mL, that of the meloxicam-meglumin salt formulation is 15.0 pg h/mL; the two are to be regarded as equivalent with regard

35 to this parameter.

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Other approaches to solving the problem of the present invention, e.g. the formation of inclusion compounds of meloxicam with β -cyclodextrin, did not produce sufficiently high plasma concentrations within a short period.

5 Similarly, compression of a mixture of the two individual components meloxicam and meglumin did not solve the problem of the present invention.

The invention therefore relates to an orally administered,

10 solid pharmaceutical form of meloxicam, from which the active substance is rapidly released and absorbed, for pain therapy, wherein meloxicam is present in the form of a salt with an inorganic or organic base, optionally together with conventional excipients and/or carriers, in a rapidly

15 decomposing tablet produced by direct tableting.

Such a

tablet could be used for pain therapy, particularly for treating acute rheumatic attacks and for fighting acute

pain.

Suitable salts include, for example, the sodium,

potassium or ammonium salt, the meglumin salt, the Tris

20 salt or the salt of a basic amino acid such as L-lysine or L-arginine. The meloxicam-meglumin salt and the meloxicam sodium salt are preferred, the meloxicam-meglumin salt is particularly preferred, e.g. the meloxicam-meglumin salt dihydrate or especially the meloxicam-meglumin salt

monohydrate.

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Examples of excipients or carriers include microcrystalline cellulose, lactose, crosslinked polyvinylpyrrolidone, magnesium stearate, dicalcium phosphate and various

30 starches.

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It is advantageous if the pharmaceutical preparation has a very short decomposition time in order to ensure rapid release of active substance after oral administration. As a rule the release of active substance can only proceed to

5 a greater extent after breakdown.

It has been found that a

sufficiently short breakdown time can be achieved if the active substance is made into tablets directly with suitable excipients such as lactose, dicalcium phosphate, cellulose and suitable breakdown adjuvants such as

10 crosslinked polyvinylpyrrolidone or sodium starch, i.e. the corresponding powder mixtures are compressed directly into tablets without any intermediate granulation of the powder -

before compression, as would normally be carried out.

This

has the advantage of being a simpler and cheaper method of 15 production.

In another embodiment of the invention there is provided a process for preparing an orally administered solid pharmaceutical preparation of meloxicam, which has a

20 short decomposition time and from which the active substance is released and absorbed rapidly, for pain therapy, particularly for treating acute rheumatic attacks and for relieving acute pain,

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characterised in that an optionally pulverised meloxicam salt of an inorganic or organic base is intimately mixed with suitable pulverised excipients and/or carriers and compressed directly into tablets with no granulation of

5 the powder before the compressing. The abovementioned meloxicam salts might be used, for example, the meglumin and the sodium salt of meloxicam being preferred. The meloxicam-meglumin salt is particularly preferred, for example the meloxicam-meglumin salt dihydrate or more

10 particularly the meloxicam-meglumin salt monohydrate.

As already mentioned hereinbefore, the polymorphism and hygroscopy of the meloxicam-meglumin salt particularly led one to expect considerable difficulties in using the

15 active substance in this form to achieve the objective of the invention, since only a reproducibly manufactured, uniform and stable modification can be used in a pharmaceutical formulation. Surprisingly, this condition can be met with the meloxicam-meglumin salt if, during

20 crystallisation of the salt from a mixture of a watermiscible organic solvent and water, seed crystals consisting of crystalline meloxicam-meglumin salt monohydrate, preferably seed crystals of a meloxicammeglumin salt monohydrate form previously crystallised

25 from acetone/water, are added to the mixture. A product is then obtained, reproducibly and uniformly, which corresponds to the crystalline form of the seed crystals used.

30 From the crystalline meloxicam-meglumin salt monohydrate thus obtained, the crystalline meloxicam-meglumin salt dihydrate can be obtained by treating the monohydrate at high humidity.

35 As a result of the slight tendency to spontaneous crystallisation and the strong tendency to form different

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polymorphic forms it is advisable to seed the solution with crystals of the desired monohydrate form in the last step of the production of the solid meloxicam-meglumin salt for pharmaceutical use. If desired, the dihydrate form can then

5 be obtained from the monohydrate form as mentioned above.

The synthesis plan is shown in Figure 2.

In a further embodiment of the invention is the crystalline meloxicam-meglumin salt monohydrate and a process for

10 preparing it, wherein meloxicam and meglumin are heated in a mixture of a water-miscible organic solvent and water and meloxicam~meglumin salt monohydrate- seed-crystals-are added to the mixture for crystallisation, and an orally administered, solid pharmaceutical preparation containing

15 meloxicam in the form of the crystalline meloxicam-meglumin salt monohydrate.

Examples of organic solvents include acetone, methanol, ethanol, n-propanol, l-propanol, tetrahydrofuran or dioxane, 20 preferably acetone, ethanol, tetrahydrofuran and dioxane .

Acetone and ethanol are particularly preferred, especially acetone .

In the mixture, organic solvent and water may be used in a

25 ratio by volume of 10:1 to 100:1, preferably in a ratio of 20:1 to 50:1 or most preferably in a ratio of 35:1 to 45:1, a ratio of about 40:1 being particularly suitable when acetone is used .

30 Meloxicam and meglumin may for example be used in a molar ratio of 1:1.5 to 1.5:1, preferably in a molar ratio of 1:1.2 to 1.2:1, but particularly in an equimolar ratio.

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Appropriately, the mixture may be heated with the addition of activated charcoal which is removed again before the addition of the seed crystals.

5

The amount of seed crystals added depends on the solvent system used and the quantity of mixture. For example, to a batch A = 12.5 kg meloxicam, mixture B = 5 to 50 g of meloxicam-meglumin salt monohydrate seed crystals (ratio by

10 weight of A : B = 125

0.05 - 0.5) are added, whilst if the

solvent acetone/water is used the amount added is from 5 to

30 g, but particularly with a ratio "of acetone

water

40:1 it is particularly appropriate to add 10 to 15 g of seed crystals. It is readily possible for the skilled man to determine the proper quantity of seed crystals for a given batch size and a given solvent system.

After the addition of the seed crystals the mixture is cooled to 10 to 30 °C, but preferably to a temperature of

20 about 20 °C. Preferably, the mixture is then refluxed again and then slowly cooled to a temperature 10 and 30°C, preferably 15 to 25°C, but most usefully about 20 °C. A fine crystalline crystal suspension of the desired meloxicam-meglumin salt monohydrate is obtained which is

25 worked up in the usual way. The powder X-ray reflexes of the particularly preferred meloxicam meglumin salt monohydrate modification are contained in Table 2 which follows .

30 Another embodiment of the invention is crystalline meloxicam-meglumin salt dihydrate and a process for preparing it, in which crystalline meloxicam-meglumin salt

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meloxicam meglumin salt
 calculated as meloxicam 7.5 mg
 microcrystalline cellulose 205.5 mg
 15 lactose 205.5 mg
 polyvinylpyrrolidone
 (crosslinked) 22.5 mg
 magnesium stearate 4.5 mg 20 Preparation:

The active substance (ground or not ground) is intimately mixed with the excipients specified in the recipe and compressed directly to form tablets.

25

Example 5: directly

Meloxicam sodium salt tablets, compressed

Recipe for meloxicam sodium salt tablets:

30

meloxicam sodium salt
 calculated as meloxicam 7.5 mg
 microcrystalline cellulose 209.5 mg
 lactose 205.5 mg
 polyvinylpyrrolidone
 (crosslinked) 22.5 mg
 magnesium stearate 4.5 mg 35

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Preparation:

The active substance (ground or not ground), prepared for example according to the data in EP-A-O 002 482, is

5 intimately mixed with the excipients specified in the recipe and compressed directly to form tablets.

Example 6: ~n vitro release:

meloxicam (neutral)/directly compressed versus

10 meloxicam (neutral)/granulated/compressed

When the release profiles of two tablets are compared with each other, one formulation having been produced by compressing a powder mixture whilst the other has been

15 prepared by compressing previously granulated powder, it is apparent that the meloxicam is released more quickly from the tablet prepared by compressing of the powder mixture (Figure 3). The release was measured over the investigation period by spectral-photometric determination

20 of the active substance at its extinction peak.

Recipe for meloxicam tablets: (directly compressed from powder)

25

meloxicam

microcrystalline cellulose lactose polyvinylpyrrolidone

(crosslinked) magnesium stearate

7.5 mg 210.0 mg 205.0 mg

22.5 mg 4.5 mg

30

Recipe for meloxicam tablets: (compressed from granules) meloxicam 7.5 mg microcrystalline cellulose 210.0 mg

35 lactose 205.0 mg

polyvinylpyrrolidone

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(crosslinked) magnesium stearate

22.5 mg 4.5 mg

Example 7: Human trials for verifying the advantages

5 of the pharmaceutical composition according to the invention over a conventional preparation.

The following formulations were tested on 18 test subjects in a single dose in a cross-over trial:

7.5 $\Delta = 490 \rightarrow 100\%$
 209.5 $7.5 \rightarrow x$
 205.5 1.5%
 22.5
 4.5

10

Recipe for meloxicam meglumin salt tablets (directly compressed) :

15

meloxicam meglumin salt
calculated as meloxicam 7.5 mg
microcrystalline cellulose 205.5 mg
lactose 205.5 mg
polyvinylpyrrolidone
(crosslinked) 22.5 mg
magnesium stearate 4.5 mg 20

25

Recipe for meloxicam (granulated) capsules: meloxicam

sodium citrate

microcrystalline cellulose lactose

polyvinylpyrrolidone (soluble) silicon dioxide (highly dispersed) polyvinylpyrrolidone (crosslinked) magnesium stearate

7.5 mg
15.0 mg
102.0 mg
23.5 mg
10.5 mg
3.5 mg
16.3 mg
1.7 mg 30

Figure 4 shows the averages of the plasma levels obtained. It is apparent that the differences found in the dissolution processes in vitro are also seen in the blood

35 levels in humans after oral administration. when the rapidly released form with the salt of meloxicam was used,

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the plasma levels rose faster, leading to an increase in the maximum plasma levels and a shortening of the time taken to achieve these levels.

5

With an onset of activity correlated to the plasma level a formulation of this kind will give a faster acting analgesic effect.

Throughout this specification and the claims which follow, 10 unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will

be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art

forms part of the common general knowledge in Australia .

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Orally administered, solid pharmaceutical form of meloxicam, from which the active substance is rapidly

5 released and absorbed, for pain therapy, wherein meloxicam is present in the form of a salt with an inorganic or organic base, optionally together with conventional excipients and/or carriers, in a rapidly decomposing tablet produced by direct tableting.

10

2. Pharmaceutical form according to claim 1 wherein the meloxicam salt is the sodium, potassium or ammonium salt, the meglumin salt, the Tris salt or the salt of a basic amino acid.

15

3. Pharmaceutical form according to claim 2, wherein the meloxicam salt is the sodium or meglumin salt.

4. Process for preparing an orally administered solid

20 pharmaceutical preparation of meloxicam, wherein an optionally pulverised meloxicam salt of an inorganic or organic base is intimately mixed with conventional powdered excipients and/or carriers and compressed directly into tablets with no granulation of the powder .

25

5.

Process according to claim 4 wherein the meloxicam salt

is the sodium, potassium or ammonium salt, the meglumin salt, the Tris salt or the salt of a basic amino acid.

30 6.

Process according to claim 5, wherein the meloxicam

salt is the sodium or meglumin salt.

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29.53 3.02 10
30.18 2.96 8
31.19 2.87 4
36.01 2.49 9
36.16 2.48 8
37.73 2.38 8
38.64 2.33 6
39.78 2.26 8

8. Process for preparing the crystalline meloxicam-

meglumine salt monohydrate according to claim 7, wherein

5 meloxicam and meglumine are heated in a mixture of a watermiscible organic solvent and water, and meloxicam-meglumine salt monohydrate seed crystals are added to the mixture for crystallisation.

10 9.

Process according to claim 8 wherein acetone, methanol,

ethanol, n-propanol, I-propanol, tetrahydrofuran or dioxane is used as the organic solvent.

10. Process according to claim 9, wherein acetone or 15 ethanol is used as the organic solvent.

11. Process according to claim 8, wherein in the mixture organic solvent and water are used in a ratio by volume of 10:1 to 100:1.

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12. Process according to claim 11, wherein in the mixture organic solvent and water are used in a ratio by volume of

20:1 to 50:1.

13. Process according to claim 12, wherein in the mixture organic solvent and water are used in a ratio by volume of

35:1 to 45:1.

14. Process according to claim 8, wherein meloxicam and 10 meglumine are used in a molar ratio of 1:1.5 to 1.5:1.

15. Process according to claim 14, wherein meloxicam and meglumine are used in a molar ratio of 1:1.2 to 1.2:1.

15 16. Process according to claim 8, wherein in a mixture of A = 12.5 kg meloxicam, mixture B = 5 to 50 g of meloxicammeglumine salt monohydrate seed crystals are added or, in a different quantity of mixture, seed crystals are added in a corresponding ratio by weight of A : B = 125 : 0.05 - 0.5.

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17. Process for preparing crystalline meloxicam-meglumine salt dihydrate, wherein crystalline meloxicam-meglumine salt monohydrate is treated at high humidity.

25 18. Process according to claim 17, wherein crystalline meloxicam-meglumine salt monohydrate is treated at high humidity by storing it for at least one day at a relative humidity of at least 75%.

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado:
Luz Clemencia DE PAEZ

ASUNTO:	Radicación No.	06 08 3413
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	
	Folios	NO 8194

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Documentos estudiados:

Descripción:	Folios 35 a 51 como se radicó inicialmente
Reivindicaciones:	Folios 52 a 53 como se radicó inicialmente
	Folio 110 modificadas en fase nacional.
Prioridad:	EP 04004054.5 (23/02/2004)

Objeto de la Invención

Título de la invención: "Uso de meloxicam para el tratamiento de enfermedades respiratorias en cerdos"

Problema Técnico Planteado: "Proveer una medicación para la prevención o el tratamiento de enfermedades respiratorias en cerdos"

Solución: "Proveer un método para tratar o prevenir enfermedades respiratorias en cerdos que comprende administrar una cantidad eficaz de meloxicam a los cerdos que lo necesitan"

IPC: A61K 31/31/5415; A61P 11/00

Se acepta el nuevo capítulo reivindicatorio radicado el 27-06-2008.

Análisis de la Solicitud de Patente

Título

El título no es conciso con el objeto reclamado en el último capítulo reivindicatorio presentado, el cual es una composición que contiene meloxicam.

Además el título es alusivo a la reclamación de un segundo uso del meloxicam. Teniendo en cuenta que los usos y los segundos usos no son materia patentable en Colombia se requiere al solicitante para que modifique el título.

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación 23/02/2004 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO02/096216	<i>A method of improving the growth performance of an animal</i>	05.12.2002
D2	AU762322C	<i>Novel galenic formulations of meloxicam for oral administration</i>	07.10.1999

Análisis de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La nueva reivindicación 1 dice: *“Una composición farmacéutica que comprende meloxicam o una sal farmacéuticamente aceptable y por lo menos un antibiótico seleccionado del grupo consistente en B- lactamas, quinolonas, tetraciclinas, sulfonamidas.”*

D1 revela un método para mejorar el crecimiento de un animal (portada), que consiste en administrar una composición con un agente antiinflamatorio en conjunción con un antibiótico en combinación con un portador o vehículo (folio 119. Reiv. 3; folio 122, resumen). D1 enseña como antiinflamatorio meloxicam y como antibióticos presenta tetraciclina, penicilina, amoxicilina, cefuroxima, sulfonamidas. (folio 123), adicionalmente, muestra que o vehículos pueden ser lactosa, manitol, otros azúcares, gelatina y almidón entre otros.

La solicitud se diferencia de D1 en que el meloxicam puede ser una sal en la anterioridad.

El Efecto Técnico que logra la diferencia es obtener una composición que contenga meloxicam y antibióticos para ser usada en cerdos.

El Problema Técnico Objetivo de esta solicitud es proveer una composición que contenga meloxicam para cerdos.

D2 muestra composiciones que comprenden principalmente meloxicam en forma de sales, más particularmente muestra la sal meloxicam – meglumina(folio 126, p.8, lín. 15-30; folio 127, p. 10, 10-25); y lactosa, celulosa microcristalina, polivinilpirrolidona y otros como excipientes y vehículos (folio 127, p. 10, 25-30) para la elaboración de granulados. D1 enseña una relación molar 1:1.5 a 1.5: 1 o de 1:1.2 a 1.2:1 de meloxicam y meglumina (folio 133, reiv. 14, p. 29, lín. 10-25). D1 enseña una formulación en el ejemplo 5 en el que el porcentaje de meloxicam es 1,5%.

El experto habría sido sugerido por D2 para la inclusión de una sal de meloxicam en la composición presentada por D1 que incluía antibióticos y un antiinflamatorio;

lo cual daría como resultado la composición reclamada por la presente reivindicación 1.

Las características presentadas por las demás reivindicaciones ya habían sido sugeridas por D2, dado que este documento muestra composiciones farmacéuticas que contienen los excipientes que se reclaman en la presente solicitud, así como también la razón molar entre el meloxicam y la meglumina.

Se observa que no hay un efecto inesperado o sorprendente logrado por la presente materia reclamada.

Se concluye que las realizaciones de la materia reclamada por la reivindicación 1 y las reivindicaciones 2-7 pueden carecer de nivel inventivo.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO02/096216	1-7	Nivel inventivo
D2	AU762322C	1-7	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

5 JUN. 2010

CONCEPTO TECNICO NUMERO: 1535	EXAMINADOR TÉCNICO Código:202092
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