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(54) Title: COMBINATION MELOXICAM AND XYLAZINE THERAPY IN ANIMALS

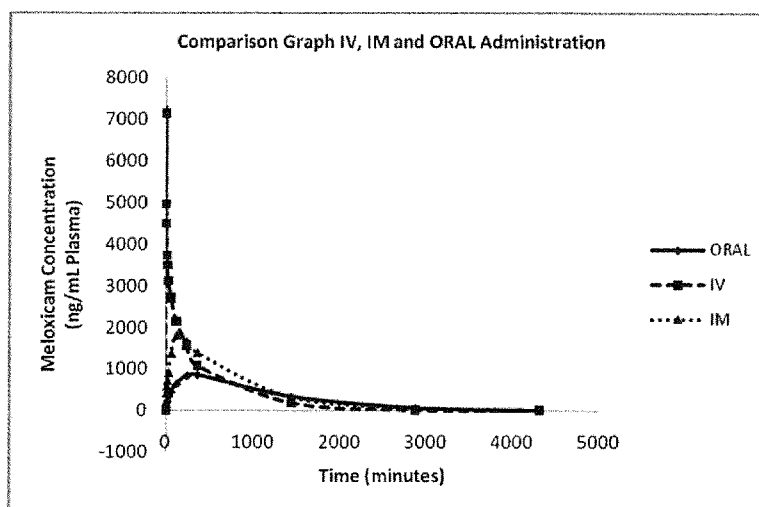


Fig. 1 Meloxicam plasma concentration vs time for 0.5mg meloxicam/kg bw dose administered via IM, IV and Oral routes in sheep

(57) Abstract: The present invention comprises both meloxicam and xylazine containing compositions and methods of their administration in the field of veterinary pharmaceuticals. A meloxicam and xylazine formulation is provided which is adapted for oral administration. A method is also provided to form a combination meloxicam and xylazine formulation from meloxicam and xylazine formulations including directions as to concentrations and dosages for sheep and cattle, the target species for the formulations.

COMBINATION OF MELOXICAM AND XYLAZINE THERAPY IN ANIMALS
TECHNICAL FIELD

The present invention is concerned with a formulation for providing potent, prolonged analgesia to livestock undergoing surgery or surgical husbandry procedures. More specifically the therapy proposed in the present invention comprises the use of a combination of an α_2 -agonist and non-steroidal anti-inflammatory agent (NSAID) absorbed systemically but administered by oral routes to achieve potent analgesia within minutes of administration and extending to in excess of 24 hours.

10 BACKGROUND ART

There are significant animal welfare issues associated with animal husbandry procedures performed on livestock (primarily, but not limited to cattle, sheep, pigs, deer) without analgesia. Pain mediation in livestock during and after surgery or surgical husbandry procedures is also desirable to reduce stress and subsequent loss of weight and condition, normally associated with an animal subjected to chronic pain without analgesia. The desirable solution is a cost-effective, efficient, once-only administration of an analgesic agent that provides rapid onset of analgesia for surgical procedures, and then extends the chronic pain relief to in excess of 24 hours.

20 Non-steroidal anti-inflammatory agents (NSAIDs), comprising several classes, are an important component of the veterinarian's armamentarium for analgesia in many species, livestock and companion animals alike. Traditional NSAIDs used in veterinary practice achieve a reduction in inflammatory response by non-selective inhibition of cyclooxygenase (COX). Cyclo-
25 oxygenase is the principle enzyme catalysing the arachadonic pathway in order to produce prostanoids. Prostanoids are a subclass of eicosanoids consisting of the prostaglandins (mediators of inflammatory and anaphylactic reactions),

the thromboxanes (mediators of vasoconstriction) and the prostacyclins (active in the resolution phase of inflammation). The prostanoids are extremely potent mediators of a diverse group of physiological processes.

There are two main isoforms of cyclo-oxygenase, COX-1 and COX-2.

- 5 COX-2 is induced by inflammatory stimuli in pathophysiological conditions. The most important adverse effects of inhibition of the COX-1 isoenzyme may be evident in the gastrointestinal tract (specifically, gastric ulceration and right dorsal colitis) and the kidneys (specifically, renal papillary damage). NSAIDs that selectively inhibit COX-2 rather than the COX-1 isoenzyme, thereby
10 minimising the impact on the homeostatic effect of prostanoids preferentially synthesised by COX-1, are desirable.

- Many NSAIDs can and have been used effectively on livestock, but differences in pharmacokinetic and pharmacodynamic parameters between classes of NSAIDs, specific NSAIDs and even between different formulations
15 containing the same NSAID may contribute to variances in pharmacology, onset and likelihood of pain mediation from the point of surgery extending for any particular period. It was expected that NSAID therapy alone, is unlikely to produce near-immediate pain relief and extend that relief past 24hours, desirable for the livestock industries where large volumes of animals require
20 surgical procedures, but cannot feasibly be managed in any intensive form.

- Meloxicam is of the enolic acid group of NSAIDs. It has been demonstrated to have superior COX-2 preferential inhibition when compared to other commonly used NSAIDs. The absorption, distribution, metabolism and elimination has been described in rats, humans, dogs, pigs, apes and cattle.
25 The pharmacology and pharmacokinetics of meloxicam in cattle, sheep, goats and pigs administered intramuscular, subcutaneous or intravenous injections has been described previously, but never following oral administration.

α_2 -agonists are a class of agents that produce a sedative-analgesic effect by activating α_2 -receptors located within the central nervous system. Xylazine and medetomidine are two commonly used α_2 -agonists used in veterinary practice, although the use is very limited within the livestock industry.

- 5 α_2 -agonists are principally used as sedation agents and precursors to anaesthesia, often in combination with additional anaesthetic agents. Xylazine induces dose-dependent sedation and central nervous depression. It has been reported previously that xylazine exhibits analgesic properties, similar to analgesia produced by opioids, but without the side effects. The
- 10 pharmacodynamics or pharmacokinetics or analgesic efficacy of xylazine following oral administration to livestock has not been investigated or reported.

- Currently, a therapeutic regimen comprising NSAID and α_2 -agonist could be achieved using analgesic agents administered parentally as two separate products. In a farm situation, where large numbers of livestock are involved,
- 15 this presents additional challenges such as dual administration leading to inefficient double handling of livestock, also increasing the risk of injury to animals and handlers, calculation of different dose weights and volumes by lay personnel, which renders this approach impractical in many situations.

- It is desirable that combination therapy be provided in a single
- 20 administration of two or more of the said analgesics, immediately reducing the dosage and administration issues and some occupational health and safety risks to handlers. However, when drugs of different classes are combined, there can be issues of compatibility, degradation, poor solubility, poor stability, poor or modified absorption, bioavailability, potentiating effects and suitability to
- 25 the administration route.

The majority of systemic analgesic drug delivery in livestock is administered parenterally, primarily by intra-muscular injection. Intravenous and

subcutaneous injections may also be options for certain drugs. This, more often than not, reflects a lack of availability of other dosage forms suitable for administration to various livestock species in large numbers. It is concerning, but all too common, that administration of parenteral drugs in a field setting is performed by lay personnel. This is a direct contradiction of on-farm risk mitigation strategies, and opens up avenues for litigation for both veterinarians supplying the drugs, and farm owners and contractors responsible for personnel administering the drugs. Without sufficient control over personnel administering the drug or sufficient understanding of the drug administration procedure, there is the added potential for livestock to be inadvertently overdosed or receive multiple doses that may have severe chemical residue, safety and toxicity implications.

A method to reduce the risks of administration for users and target species is desirable. With this in mind, it is reasoned that the risks associated with systemic drug delivery to various livestock species by injection can be significantly reduced by delivering the analgesic agents by oral administration, where certain drugs can be effectively absorbed from the gastrointestinal tract following ingestion, or absorbed through the oral mucosa lining the oral cavity. Oral mucosal absorption (oral transmucosal) is primarily through, but not limited to, the cheek (buccal) or floor of the mouth (sub-lingual) because these regions are most permeable. The oral cavity is highly vascularised, and drugs absorbed through the oral mucosa enter systemic circulation, effectively bypassing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, oral mucosal absorption can lead to rapid onset of action, something desirable where analgesia is required for surgical husbandry procedures in the field, where the time between administration and surgery can be optimized.

Furthermore, doses of the formulations detailed in the present invention can be administered efficiently and comfortably to livestock, thereby dramatically reducing the occurrence of injection site lesions, stock losses from secondary infection, and the risk of injury to personnel handling livestock.

- 5 It is an object of the invention to provide a combination of two or more analgesic agents in combination therapy for the treatment of pain, more specifically an NSAID and α_2 -agonist, more specifically meloxicam and xylazine or meloxicam.

DISCLOSURE OF INVENTION

- 10 According to one aspect of the invention, there is provided a pharmaceutical composition comprising a NSAID or a salt or derivative thereof, in combination with an α_2 -agonist or a salt or a derivative thereof, pharmaceutically acceptable carrier, as well as any one or more of a number of desired excipients.

- 15 Preferably the NSAID is meloxicam.

More preferably the α_2 -agonist is xylazine.

Still more preferably the composition is formulated for oral administration.

- 20 Preferably the meloxicam is present as a milled solid and the resultant composition is a liquid suspension or gel.

Alternatively and more preferably, the meloxicam is dissolved and the resultant composition is a solution or gel.

- 25 In a further aspect of the invention, there is provided a method of using a pharmaceutical composition comprising orally administering to a subject animal, a pharmaceutical composition comprising a NSAID or a salt or derivative thereof, in combination with an α_2 -agonist or a salt or a derivative

thereof, pharmaceutically acceptable carrier, as well as any one or more of a number of desired excipients.

More preferably the method includes the administration of a pharmaceutical composition that is comprised of both meloxicam and xylazine.

5 Still more preferably the subjects of the present method are sheep or cattle.

Even more preferably the method comprises administering to a sheep orally between 0.1 mg/kg - 0.2 mg/kg of xylazine and 1.0 mg/kg of meloxicam.

Alternatively the method comprises administering to cattle orally 0.1
10 mg/kg - 0.2 mg/kg of xylazine and 0.5 mg/kg of meloxicam.

Preferably administering the composition orally involves administration via the oral transmucosal route.

Preferably the meloxicam containing formulation is formulated as a gel containing dissolved meloxicam.

15 Preferably, the co-administration includes the step of mixing the meloxicam containing formulation and xylazine containing formulations before administering the mixture.

Preferably the mixture is formed by mixing the constituent formulations in ratios such that the resulting mixture has a concentration of meloxicam at
20 between 9.52mg/ml-9.8mg/ml meloxicam and between 0.95 to 0.49mg/ml of xylazine.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 Meloxicam plasma concentration vs time for 0.5mg meloxicam/kg body weight ("bw") dose administered via IM, IV and Oral routes in sheep
25 assayed in Example 4.

Fig. 2 Closer view of IM, Oral curves in Fig. 1.

Fig. 3 Xylazine plasma concentration vs time for 0.2mg xylazine/kg bw dose administered via IM, IV and Oral routes in sheep assayed in Example 4.

Fig. 4 Closer view of IM, Oral curves in Fig. 3.

Fig. 5 Meloxicam plasma concentrations assayed in Example 5.

5 MODES FOR CARRYING OUT THE INVENTION

For the purposes of the present specification, the use of the word gel is to be taken as a description of a liquid formulation or a formulation that is substantially liquid, that has a high viscosity that allows it to be deposited and retained in oral cavities of target animals. Similarly, for the purposes of this specification, the use of the word oral in terms of routes of administration is to be taken as a reference to both oral administration (via swallowing and introduction via the gastrointestinal tract) and oral transmucosal delivery, unless otherwise indicated.

Example 1 - 5mg/mL meloxicam suspension with dissolved 2mg/mL xylazine (as hydrochloride) for oral administration

The following ingredients are used to make the meloxicam/xylazine oral suspension of the present example.

Ingredient	Amount % w/v
Meloxicam	0.50%
Xylazine HCl	0.23%
Glycerol	12.0%
Xylitol	14.0%
Sodium Benzoate	0.10%
Citric Acid	0.14%
NaH ₂ PO ₄ .2H ₂ O	1.54%
Sodium Saccharin	0.10%
Xanthan Gum	0.50%
Sorbitol	18.0%
Water	qs

-Charge an appropriate vessel with 500g of water and commence stirring at medium speed.

-To the water add the following in order: Citric Acid, Sodium Benzoate, $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, Sodium saccharin, Xylazine HCl, Xylitol

5 -To the above solution add the Xanthan gum, do this slowly while stirring and directly into the mixing vortex. Continue stirring until evenly dispersed.

-To the bulk solution, add Glycerol and Sorbitol and continue stirring until the Xanthan is fully hydrated. To the bulk solution, introduce while mixing, the Meloxicam. Continue mixing until uniformly dispersed.

10 -Make the product to volume, mix and homogenise using high shear until a uniform suspension is obtained

Example 2 - 5mg/mL meloxicam/ 2mg/mL xylazine (as hydrochloride) gel for buccal administration

15 The following ingredients are used to make the meloxicam/xylazine gel of the present invention.

Ingredient	Amount % w/v
Meloxicam	1.00%
Xylazine HCl	0.23%
Meglumine	0.75%
Ethanol	15.0%
Natrosol HHX (HEC)	1.0%
Water	qs

-Collect 830g of water in an appropriate vessel and commence stirring.

-To the water add the Xylazine HCl, mix until dissolved.

-To the bulk solution add the Meglumine and mix until dissolved.

-To the bulk solution add the Meloxicam and mix until dissolved.

20 -To the bulk solution add the Ethanol and mix until uniform.

-To the bulk solution, slowly add the Natrosol HHX. Continue stirring until the Natrosol HHX is fully hydrated and a clear gel is formed.

-Make compounded product to volume and continue stirring until uniform.

Example 3 – Addition of a registered veterinary medicine containing 2% xylazine (as hydrochloride) to a 1% meloxicam oral gel

In the present example, combination therapy is achieved by co-administering meloxicam and xylazine in a single administration via the oral route, however, meloxicam and xylazine are not co-formulated but rather, are contained in separate formulations which are mixed prior to administration. It was not thought that the mixing of such formulations would result in a formulation that would contain both actives in dissolved form, be stable and able to be effectively administered to subject animals. Surprisingly however, the mixing of the meloxicam and xylazine containing formulations can be achieved in that a homogeneous and stable solution/gel results which can be administered to subject animals without the issues of instability and double handling of animals to treat with two separate injectable preparations. Further, the ratio of meloxicam and xylazine can be adjusted to achieve dose rates for specific species or sizes.

Provided below are the constituent formulations and instructions for their mixing.

CONSTITUENT 1: 2% xylazine (as hydrochloride) solution for injection

(Trade Name: ILIUM XYLAZIL-20)

Ingredient	Amount % w/v
Benzyl alcohol	1.00
Citric acid	0.35
Sodium chloride	0.37
Sodium citrate	1.02
Sodium metabisulphite	0.1
Xylazine hydrochloride	2.33
Water	94.83

Steps for making constituent 1:

1. Dissolve the xylazine hydrochloride, sodium citrate, citric acid, sodium chloride and sodium metabisulphite in WFI (water for injections).
2. Add benzyl alcohol slowly and mix for 5 – 10 minutes.
3. Adjust the pH to 4.5 – 5.5.
- 5 4. Make to volume with WFI and mix for 5 minutes.
5. Report to QC for sampling and approval.
6. Filter sterilise the finished batch.

CONSTITUENT 2: 1% meloxicam gel for oral/buccal administration where this formulation comprises the following constituents:

Ingredient	Amount % w/v
Brilliant Blue RM6735	0.02%
Meloxicam	1.000%
Propylene Glycol	37.000%
Monoethanolamine	1.000%
Benzyl Alcohol	1.000%
Natrosol HHX (HEC)	1.000%
Water	62.500%

10

Steps to form Constituent 2:

i) PHASE A

1. Collect the water in an appropriate vessel.
2. Add the Brilliant Blue to the water and mix until dissolved.
- 15 3. Disperse the HEC in the 10% portion of propylene glycol and add to the water.

ii) PHASE B

1. In a separate vessel add the remaining propylene glycol and disperse the meloxicam.
- 20 2. Add the monoethanolamine and mix until a clear solution is obtained.
3. Add benzyl alcohol.

iii) Combine Phase B into Phase A and mix until uniform.

Example 3A : Mixing formulation for use with smaller to medium sized animals

To mix the constituent formulations to achieve a concentration suitable for administration to smaller food producing animals (for example lambs), the

5 following steps are carried out:

- (i) Draw the desired volume (10mL) of a 2% xylazine (as hydrochloride) injection
- (ii) dispense into 200mL of 1% meloxicam gel.
- (iii) Shake vigorously until the solution clears.

10 The resultant formulation solution (now 210mL) contains the following dissolved active constituents; 0.95% meloxicam (w/v) and 0.095% xylazine (w/v) (as hydrochloride) suitable for administration via the oral route (Meloxicam 9.52 mg/mL, xylazine is 0.952 mg/ mL)

Example 3B Mixing formulation for use with larger sized animals

15 To mix the formulation to achieve a concentration suitable for administration to larger food producing animals, specifically, calves (100kg and larger where calves are more sensitive to xylazine), the following steps are carried out:

- (i) Draw the desired volume (5mL) of a **2%** xylazine (as
20 hydrochloride) injection
- (ii) dispense into 200mL of 1% meloxicam gel.
- (iii) Shake vigorously until the solution clears.

The resultant solution (now 205mL) contains the following dissolved active constituents; 0.98% meloxicam (w/v) and 0.049%% xylazine (w/v) (as

25 hydrochloride) suitable for co-administration via the oral route (9.75 mg/mL meloxicam and 0.49 mg/mL xylazine).

Example 3C Stability of the proposed mixture of meloxicam and xylazine as set out in Example 3A.

Once combined, the mixture of actives is stable for a minimum of seven days.

Day	Storage	Appearance	Specific gravity	pH	Meloxicam	Xylazine	Benzyl alcohol
0	Initial	Clear viscous liquid	1.034	10.06	9.45	0.98	9.61
1	25°C, air conditioning	Clear viscous liquid	1.034	10.08	9.39	0.97	9.51
2	25°C, air conditioning	Clear viscous liquid	1.034	10.06	9.42	0.98	9.50
7	25°C, air conditioning	Clear viscous liquid	1.034	10.07	9.41	0.98	9.55

Example 4. Bioavailability of co-administered xylazine and meloxicam via Oral,

5 Intramuscular and Intravenous routes of administration

The bioavailability of xylazine and meloxicam following oral administration to sheep was investigated. Sheep were randomly allocated to one of three groups each signifying a different route of administration, Group A (Intravenous - IV), Group B (Intramuscular - IM) or Group C (Oral).

10 Prior to administration animals were weighed using calibrated electronic stock scales and the weight recorded. Individual doses were calculated according to individual bodyweight and rounded up to the nearest minor increment on the syringe.

The dose of xylazine investigated was 0.2mg/kg bodyweight. The dose of meloxicam investigated was 0.5mg/kg bodyweight. Separate injections of a commercially available 20mg/mL meloxicam (METACAM 20MG/ML SOLUTION FOR INJECTION) and 20mg/mL xylazine (ILIUM XYLAZIL-20 ANALGESIC, SEDATIVE AND MUSCLE RELAXANT INJECTION -20mg/mL xylazine as hydrochloride) were administered intravenously into the jugular vein of Group A animals. A dose from the same commercially available injections was administered intramuscularly to the gluteus muscle of Group B animals.

An oral dose of the suspended meloxicam/ dissolved xylazine formulation from Example 1 was administered to the animal's mouth at the commissure of the lips and dose deposited at the back of the tongue (oral route via swallowing).

Blood samples were obtained from each animal immediately prior to administration of the drugs and at 1, 2, 4, 8, 16, 30, 60, 120, 240, 360 minutes after, and again 24, 48 and 72 hours after treatment. 5-10mL blood was drawn into a heparinised vacutainer at nominated sampling times. Blood samples were centrifuged within 1-2 hours of sampling to obtain plasma which was subsequently tested. Analysis results are presented graphically for xylazine (Fig. 3, 4) and meloxicam (Fig. 1, 2).

Xylazine concentrations in plasma were determined by Ultra Performance Liquid Chromatography (UPLC) using Ultra-violet (UV) detection. Table 1 sets out the key parameters with respect to xylazine levels detected in the three treatment groups.

Table 1: Pharmacokinetic parameters following IV, IM and Oral xylazine 0.2mg/kg bw in sheep

	Intravenous (IV)	Intramuscular (IM)	Oral
Xylazine dose	0.2mg/kg bw	0.2mg/kg bw	0.2mg/kg bw
T _{max} min		4	8
C _{max} ng/mL		16	19
AUC _(0-t) ng-min/mL	1466	266	288
Bioavailability %		18%	19%

A surprising outcome of this investigation is the confirmation that the absorption of xylazine administered orally (predominantly via the gastrointestinal tract) to sheep is delayed. This is evident when the xylazine plasma concentration versus time profiles are compared with the data obtained from the intramuscular dose.

Of further significance is the higher absorption of xylazine achieved through the oral route (predominantly via the gastrointestinal tract), reaching a higher maxima than the comparable intramuscular dose of 19ng/mL some 8 minutes after administration. Detectable levels of xylazine are present up to 30
5 minutes after dosing, also comparable to the pharmacokinetics demonstrated by sheep administered xylazine by intramuscular and intravenous routes.

The Area Under Curve (AUC) is a key pharmacokinetic parameter used to characterise the absorption and elimination phases of a particular drug/ administration route. The bioavailability of an intramuscular or oral dose is
10 calculated as the percentage of the AUC of the intravenous dose, which is considered instantly, systemically available i.e. 100% bioavailable.

It was a surprising outcome that the calculated bioavailability of orally administered xylazine was comparable to the equivalent intramuscular dose. This is a surprising outcome that links orally administered xylazine to the same
15 pharmacological effect as obtained from intramuscular administered xylazine without serious occupational health and safety drawbacks.

Furthermore, the novel delayed absorption demonstrated by sheep administered an oral dose of xylazine is a significant finding. The delayed absorption enhances the efficiency of the process by producing a time window
20 to allow veterinarians to dose several subjects prior to returning to and operating on the first animal and then each additional animal in sequence.

Another factor assessed during this study was the degree of sedation of animals administered xylazine at 0.2mg/kg. Sheep administered xylazine by IV and IM routes displayed advanced sedation which is undesirable. Surprisingly,
25 sheep administered xylazine via the oral route, did not demonstrate advanced sedation, ensuring safe and practical management of the animal during the surgery. The lack of advanced sedation demonstrated following administration

of an equivalent dose of xylazine is considered a significant and critical outcome of this investigation.

Meloxicam concentrations in plasma were determined by Ultra Performance Liquid Chromatography (UPLC) using Ultra-violet (UV) detection.

- 5 Pharmacokinetic parameters were determined. Table 2 sets out key parameters with respect to meloxicam levels detected in the three treatment groups.

Surprisingly, the pharmacokinetic parameters such as bioavailability and Mean Residence Time (MRT) associated with an oral dose of 0.5mg
10 meloxicam/kg bodyweight in a ruminant are similar to oral dose pharmacokinetic parameters obtained in other non-ruminant species, dogs and horses.

Table 2: Pharmacokinetic parameters following IV, IM and Oral meloxicam 0.5mg/kg bw in sheep

	Intravenous (IV)	Intramuscular (IM)	Oral
Meloxicam dose	0.5mg/kg bw	0.5mg/kg bw	0.5mg/kg bw
T _{max} min		120	360
C _{max} ng/mL		1804	858
AUC _(0-t) ng-min/mL	1570575	1770356	1219391
MRT (area) min		775	1024
Bioavailability		113%	78%

- 15 The significance of the oral MRT compared to IV, IM doses indicates that meloxicam absorbed orally (predominantly via the gastrointestinal tract) is retained longer systemically, allowing it to exert its analgesic effect for a longer period than an equivalent dose administered by intravenous or intramuscular routes.

- 20 Example 5. Bioavailability of co-administered xylazine and meloxicam via Buccal and Intramuscular routes of administration

A total of 12 young lambs of between 13 to 24 kg of bodyweight each were randomly divided into two treatment groups of 6 lambs each (Groups A and B). Each group was exposed to each dose route across two test periods as presented in Table 3 as per the schedule in Table 4.

5 The washout period between the two treatment periods was 10 days.

Table 3 – Study Design

Group	Period 1	Period 2
A	Intramuscular	Buccal (OTM)
B	Buccal (OTM)	Intramuscular

Intramuscular injection treatments involved administering Ilium Xylazil (xylazine as hydrochloride) 20mg/ml solution via the intramuscular route at a dose rate of 0.1mg xylazine /kg bodyweight and administering Metacam (meloxicam) 20mg/ml solution via the intramuscular route at a dose rate of 1.0mg meloxicam/kg bodyweight.

Buccal administration (oral transmucosal) involved the administration of the formulation of Example 3A administered at the dose of 0.1mg xylazine /kg and 1.0mg meloxicam/kg bodyweight.

15 Blood sampling time points were: pre-treatment then at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 min; 3, 4, 8, 10, 12, 24, 48, 72 and 96 hours post-treatment for each period. Blood was collected in heparin tubes and plasma extracted immediately after collection and kept frozen at -20°C. Plasma was shipped frozen to the designated laboratory for analysis.

20 The buccal/oral transmucosal treatments were administered by syringe. They were applied into the sulcus between the molar teeth and the inside of the cheek. The intramuscular injections were administered according to label directions. Individual dose volumes were calculated according to individual

body weight and prepared to the dose volume or to the closest upward increment on the syringe.

Table 4 – Study Schedule

Date	Study Day	Activity
	-28	Lambs were moved into feeder pens and drenched with broad spectrum anthelmintic
	-15	Lambs were weighed for allocation to groups. Blood sample for haematology was collected, clinical examinations were carried out. Lambs were transferred into individual pens in 'hard times house'
	-7 to -2	Lambs were being handled
Mon	-1	Blood samples collected for PCV; cannulae in jugular veins placed; cannulae flushed twice daily with heparinised saline
Tue	0	Pre treatment blood samples collected. Treatment according to individual body weight at 0h. Collected blood samples, at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 min; 3, 4, 8, 10, 12h
Wed	1	Collected blood samples at 24 hours; flushed cannulae twice daily with heparinised saline
Thu	2	Collected blood samples at 48 hours; flushed cannulae twice daily with heparinised saline
Fri	3	Collected blood samples at 72 hours; flushed cannulae twice daily with heparinised saline
Sat	4	Collected blood samples at 96 hours; flushed cannulae twice daily with heparinised saline
Sun	5	Checked cannulae; flushed cannulae twice daily with heparinised saline
Mon –	1	Collected blood samples for PCV; flushed cannulae twice daily with heparinised saline
Tue	0	Collected pre- treatment blood samples. Treated according to individual body weight at 0h. Collected blood samples, at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 min; 3, 4, 8, 10, 12h
Wed	1	Collected blood samples at 24 hours; flushed cannulae twice daily with heparinised saline
Thu	2	Collected blood samples at 48 hours; flushed cannulae twice daily with heparinised saline
Fri	3	Collected blood samples at 72 hours; flushed cannulae twice daily with heparinised saline
Sat	4	Collected blood samples at 96 hours; removed cannulae; applied long-acting antibiotic therapy.

Meloxicam and xylazine concentrations in plasma were determined

5 using two separate, validated analytical methods based on instrumental

determination using Ultra High Performance Liquid Chromatography - tandem mass spectrometry. Sample preparation involved a deproteination step, and for xylazine determination, this was followed by clean-up and concentration using Solid Phase Extraction prior to instrumental determination. Ultra High Pressure Liquid Chromatography provided high resolution, and when coupled with the unique Multiple Reaction Monitoring (MRM) transitions obtained using the triple quadrupole mass spectrometer, resulted in methods demonstrating high sensitivity and selectivity for meloxicam and xylazine. Analysis results are presented graphically for xylazine (Fig. 6) and meloxicam (Fig. 5).

Table 5 – Meloxicam Bioavailability Calculation

	AUC (0-t)	AUC ∞
	(ng-hr/mL)	(ng-hr/mL)
Buccal Treatment Average	40792	41104
IM Treatment Average	49470	49739
Bioavailability	82%	83%

Table 6 – Bioavailability Xylazine

	AUC (0-t)	AUC∞
	(ng-min/mL)	(ng-min/mL)
Buccal Treatment Average	364	367
IM Treatment Average	735	765
Bioavailability	50%	48%

Notable differences in meloxicam and xylazine absorption and elimination are evident when the two administration routes are compared. The rate and extent of absorption of meloxicam and xylazine from intramuscular administration is higher than that obtained from an equivalent dose administered by the oral trans mucosal route. The resultant bioavailability for each drug was calculated to be approximately 80% for meloxicam and 50% for xylazine as set out in Tables 5 and 6.

The lower bioavailability of xylazine could be advantageous in terms of target animal safety, providing a clinical analgesic effect using this dose

regimen can be demonstrated. Although a total of four animals treated with the injectable reference products showed signs from marked to slight sedation none of the animals required veterinary intervention and recovered unremarkably within one hour and 10 minutes.

- 5 The co-administration of two effective analgesic agents will provide farmers distinct advantages in efficiency, user safety and added compliance with 'control of use' legislation. The concentrations detected in plasma would result in animals receiving the analgesic benefit of xylazine if the operation was conducted within 15-30 minutes post-treatment, and extended postoperative
- 10 pain relief, provided by meloxicam, for in excess of 24 hours. Procedures such as tail docking, dehorning, castration and mulesing would be less painful and less traumatic to the animal under these treatment conditions.

- The pharmacokinetics determined in this investigation confirms that a combination of two or more analgesic agents, more specifically an NSAID and
- 15 α_2 -agonist, more specifically meloxicam and xylazine, administered orally, results in a delayed, higher absorption of the α_2 -agonist during the period of surgery, and maintains concentrations of NSAID in plasma past 24 hours.

INDUSTRIAL APPLICABILITY

- The present invention has industrial applicability in the field of pharmaceutical
- 20 formulations and methods of providing therapy to animals.

CLAIMS:

1. A pharmaceutical composition comprising a NSAID or a salt or derivative thereof, in combination with an α_2 -agonist or a salt or a derivative thereof, pharmaceutically acceptable carrier, as well as any one or more of a number of desired excipients.
2. The composition of claim 1 wherein the NSAID is meloxicam.
3. The composition of claim 2 wherein the α_2 -agonist is xylazine.
4. The composition of claim 3 wherein the concentration of meloxicam is between 0.25% and 1% (w/v) and the concentration of Xylazine is between 0.04% and 0.2% w/v).
5. A method of using a pharmaceutical composition of any of claims 1 to 4 wherein the method comprises orally administering to a subject animal the composition of any of claims 1 to 4.
6. The method of claim 5 wherein the animal subjects of the present method are sheep and where the method comprises administering to a sheep between 0.1 and 0.2mg/kg of xylazine and 1.0 mg/kg of meloxicam.
7. The method of claim 5 wherein the animal subjects of the present method are cattle and the method comprises administering to cattle between 0.1 and 0.2mg/kg of xylazine and 0.5 mg/kg of meloxicam.

8. The method of claim 6 or 7 wherein the composition is administered via the oral transmucosal route and where the composition is adapted to be administered via that route.

9. The method of claim 5 wherein the method comprises co-administering a mixture of meloxicam containing formulation and xylazine containing formulations.

10. The method of claim 9 wherein the co-administration involves mixing separate meloxicam and xylazine containing formulations and administering the mixture via the oral transmucosal route and where the meloxicam containing formulation is formulated as a gel.

10. The method of claim 10 wherein the meloxicam gel formulation contains meloxicam at a concentration of about 1mg/ml.

11. The method of claim 10 wherein the mixing includes the step of mixing the meloxicam containing formulation and xylazine containing formulation in ratios such that the resulting formulation has a concentration of meloxicam of between 9.5 and 9.8mg/ml meloxicam and between 0.95 to 0.48mg/ml of xylazine.

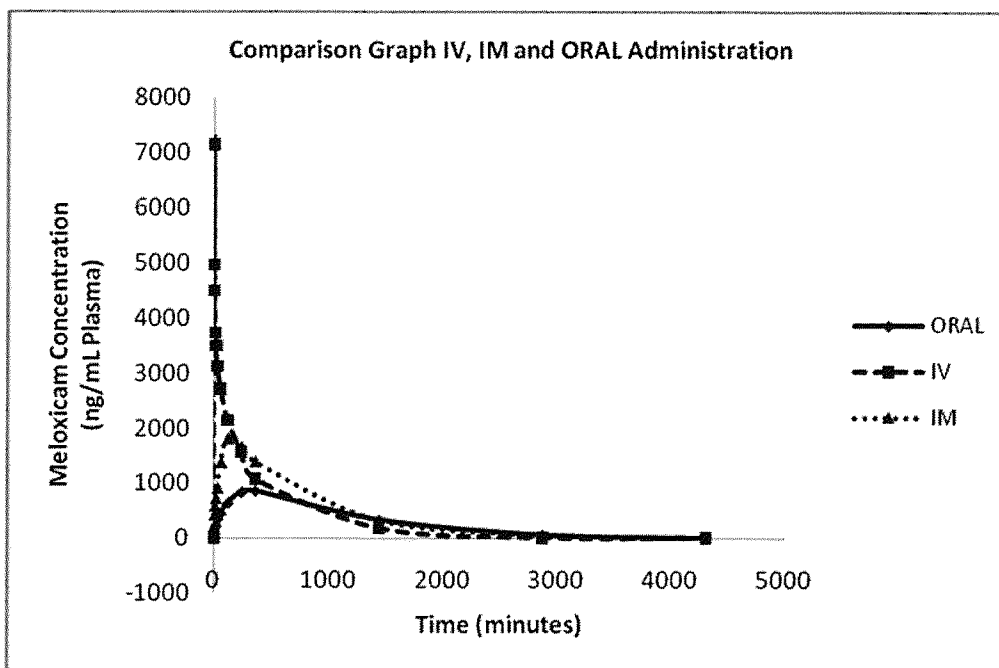


Fig. 1 Meloxicam plasma concentration vs time for 0.5mg meloxicam/kg bw dose administered via IM, IV and Oral routes in sheep

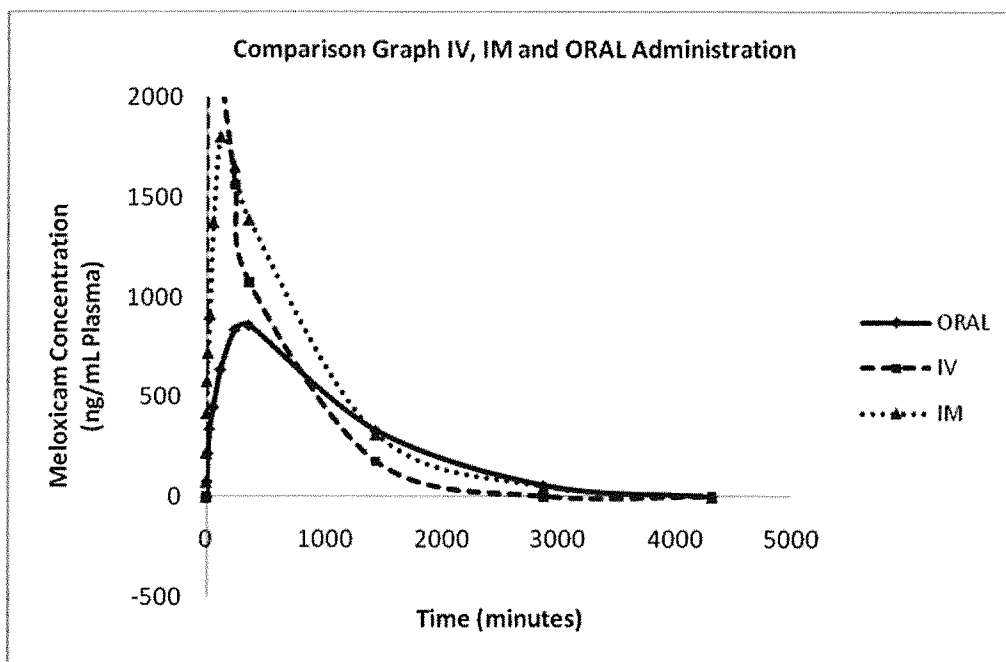


Fig. 2 Closer view of IM, Oral curves in Fig. 1(a)

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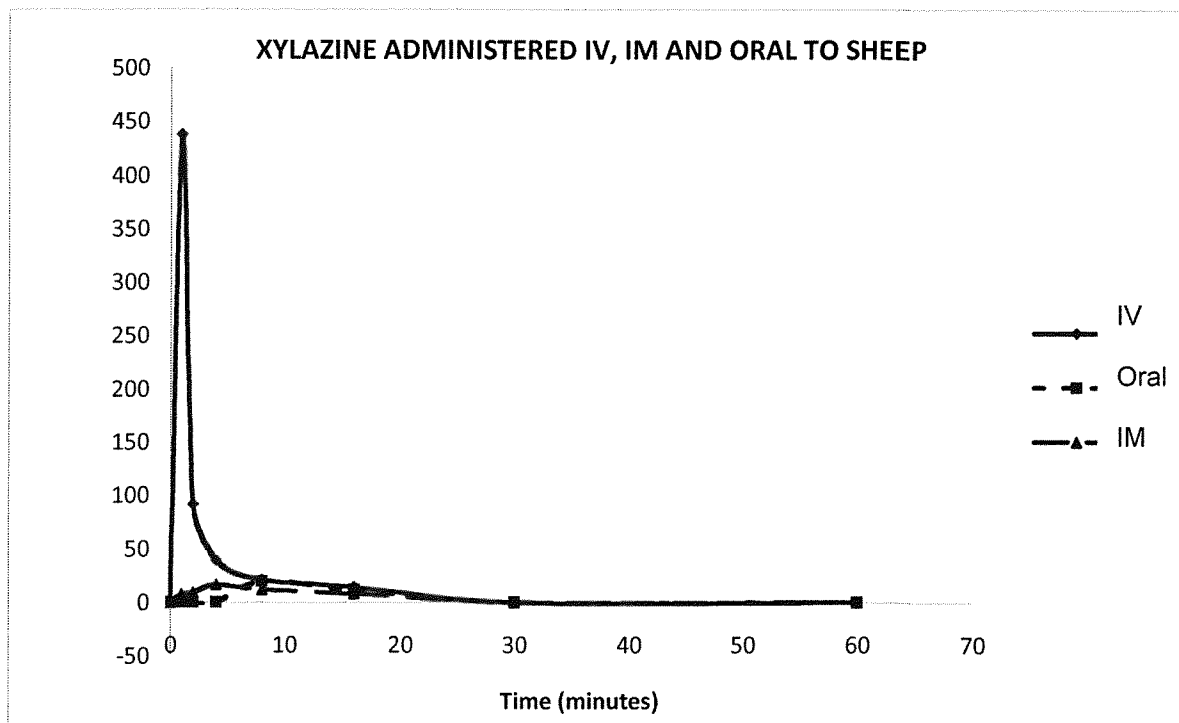


Fig 3

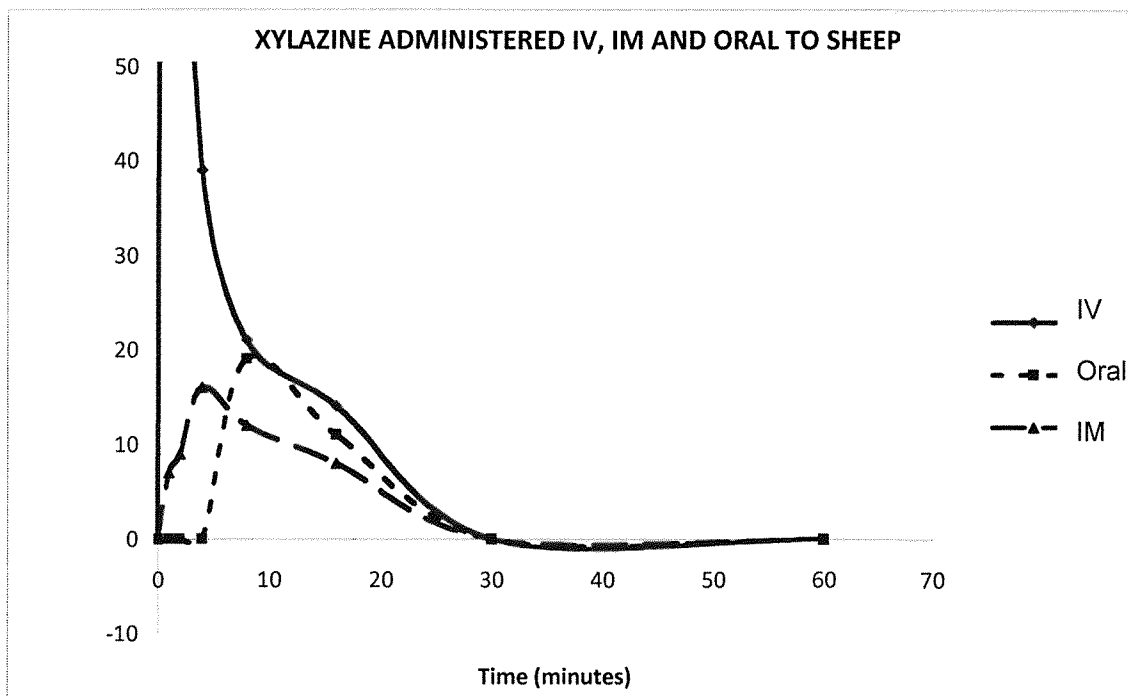


Fig 4

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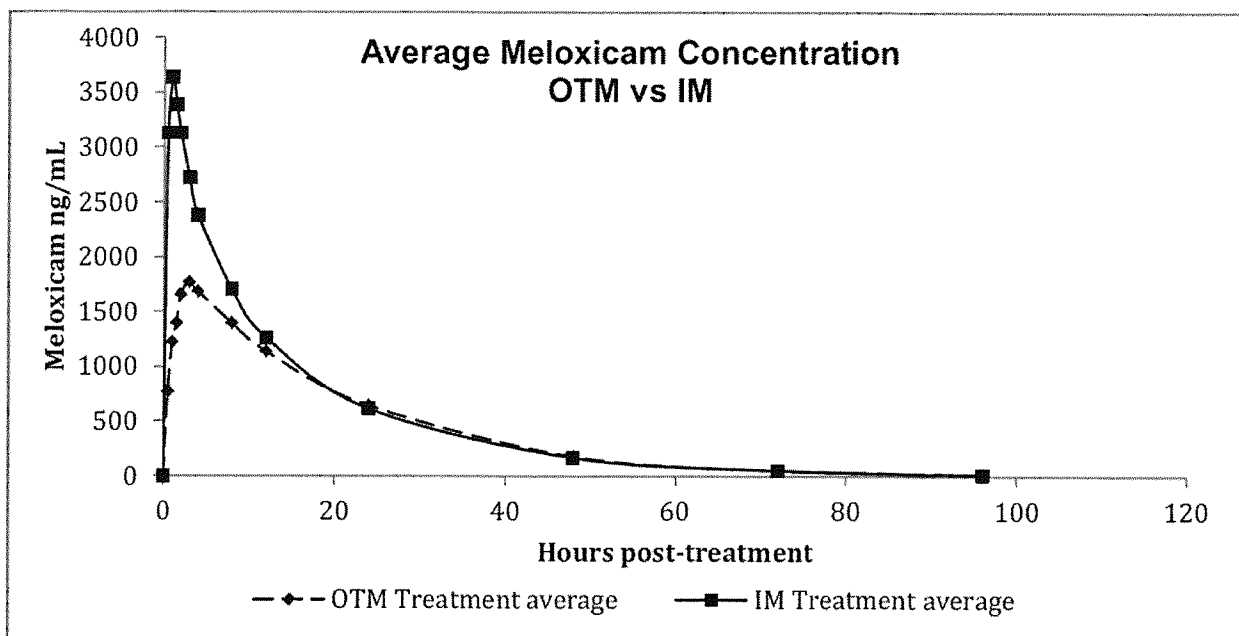


Fig 5 Average meloxicam concentration vs time for lambs administered OTM and IM doses

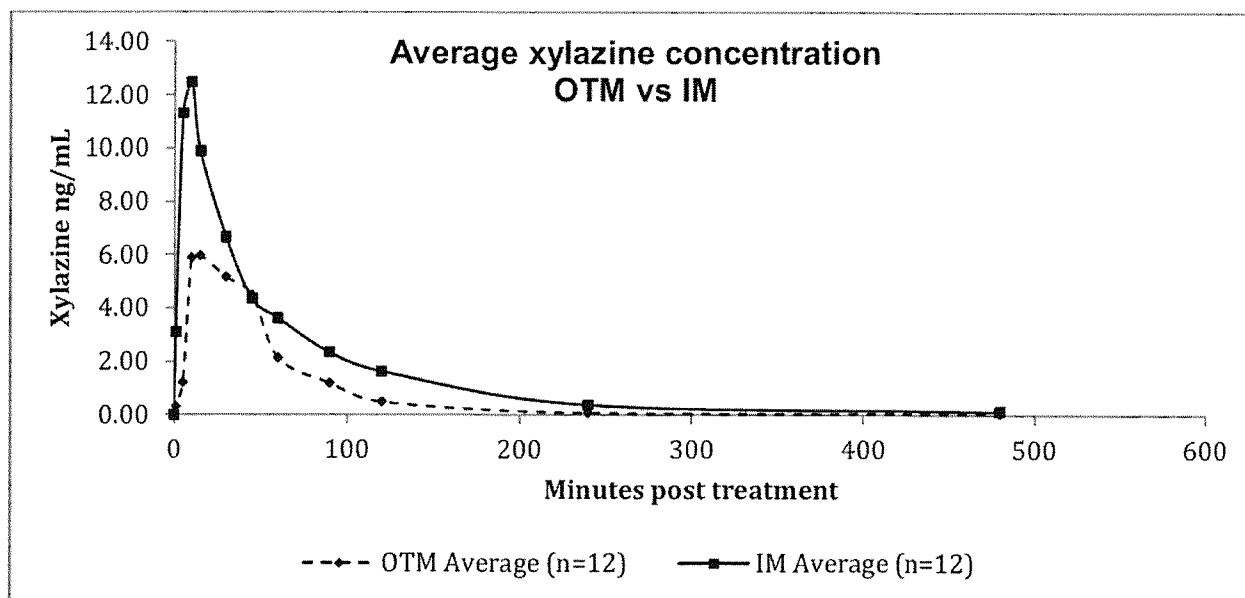


Fig 6 : Average xylazine concentration vs time for lambs administered OTM and IM doses

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2013/000429

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/5415 (2006.01) A61K 31/54 (2006.01) A61P 25/20 (2006.01) A61P 29/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, DWPI, MEDLINE: xylazine, meloxicam, alpha-2-agonist, alpha-2 adrenergic agonist, apraclonidine, brimonidine, clonidine, detomidine, dexmedetomidine, guanabenz, guanfacine, lofexidine, medetomidine, romifidine, tizanidine, tolomidine, xylazine, fadolmidine, xylometazoline, oxymetazoline, NSAID, non steroidal anti-inflammatory drug, aspirin, ibuprofen, naproxen, COX 1 inhibitor, COX 2 inhibitor, piroxicam, tenoxicam, droxicam, lornoxicam, isoxicam, flunixin, ketoprofen, tolafenamic acid, metamizole, dipyron, naproxen, carprofen, phenylbutazone, oral, tablet, buccal, mouth, lozenger, capsule, veterinary, animal, livestock, cattle, cow, bovine, equine, horse, sheep, husbandry

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
9 July 2013

Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2013/000429
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2329849 A1 (GALDERMA RESEARCH & DEVELOPMENT 06410 BIOT (FR)) 08 June 2011 Abstract	1
X	GB 2197198 A (SANDOZ LTD) 18 May 1988 Page 1, lines 49-52; Page 3, lines 29-48	1, 5
X	WO 2007/072503 A2 (PANACEA BIOTEC LTD) 28 June 2007 Abstract; Page 23, lines 28 - Page 24, line 9	1, 5
X	EP 2085076 B1 (LABORATORIOS SENOSIAIN, S.A. DE C.V. DISTRITO FEDERAL 11560 (MX)) 23 February 2011 [0001]	1, 2, 5

Form PCT/ISA/210 (fifth sheet) (July 2009)

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/AU2013/000429	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
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		EP 2085076 A1	05 Aug 2009
		EP 2085076 B1	23 Feb 2011
		GT 200900089 A	13 Jan 2012
		PE 14642008 A1	31 Dec 2008
US 2010166856 A1	01 Jul 2010		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

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INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/AU2013/000429	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		UY 30636 A1	02 May 2008
		WO 2008047208 A1	24 Apr 2008
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			