"Use of bisphosphonic acid derivatives for the preparation of a medicinal product for treating limps"

The present invention relates to the use of bisphosphonic acid derivatives for the preparation of medicinal products for treating limps which occur in osteoarthrosis, osteochondrosis or enthesopathies of the bony insertions of the tendons, of the ligaments or of the aponeuroses, in veterinary medicine.

The term limp is understood to refer to irregular gait caused by the perception of a pain by partially or fully bearing weight on one or more limbs during the functioning of limbs prompted into motion.

A limp can manifest itself clinically in an intermittent or continuous manner for several days, several weeks or several months.

Limps result more specifically from the appearance of painful lesions on the bone structure, the cartilages, the ligaments, the synovial membrane or the connective tissue or from an anomaly of local vascularization. Thus, limps are generally associated with one or more of the following components:

- a bony component which is the result of a change in the bone architecture and/or in the bone growth cartilages at the site of the limp, such as, for example, losses of bone substance, the formation of cysts, deformation of the bone or excessive thickening of the growth cartilages;

- an articular component which is the result of a change in the structure of the articular cartilages, such as, for example, erosions of the cartilaginous surfaces and/or a change in the synovial membrane and/or a change in the articular ligaments;

- a muscular component which is the result of a change in muscle development, such as, for example, a muscular atrophy; and

- a vascular component which is the result of a change in local vascularization, such as, for example, a reduction in vascularization of the injured region.

The invention is directed towards providing medicinal products which can be used in the treatment of limps occurring in osteoarthrosis, osteochondrosis or enthesopathies of the bony insertions of the tendons, of the ligaments or of the aponeuroses in an animal not suffering from fractures, arthritis or exostoses.

Among the factors which can bring about such limps, mention may be made of constant and/or intense mechanical stresses on the locomotor apparatus. In the case of an animal that is unprepared for physical exercise, the intensity of the mechanical stress capable of bringing about a limp may be relatively low.

In contrast, in the case of an animal that is prepared for physical exercise, the limp will appear if he or she is subjected to a mechanical stress whose force or repetitive nature exceeds the resistance capacities of his or her limbs. Certain animal species are more particularly inclined to develop this type of limp. This is especially the case for equine animals.

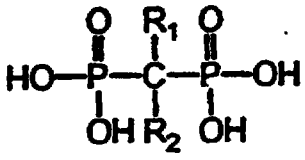
In point of fact, in horses, the locomotor apparatus is stressed more frequently than it is in other animal species, either during sporting competitions or when the horse is used by people as a mount. In this animal species, limps represent one of the main clinical conditions requiring veterinary consultation. Their clinical description is well known; a fairly exhaustive review on this subject is presented in the book "Les boiteries du cheval" [Limps in horses] edited by O.R. Adams (published by Maloine, 1990). Among the most common limps, mention may be made of bony spavin or osteoarthrosis of the distal stage of the tarsus in horses, horse osteochondrosis and enthesopathy of the bony insertions of the tendons, of the ligaments or of the aponeuroses in horses.

Thus, according to one preferred embodiment, the invention relates to the use of bisphosphonic acid derivatives for the preparation of medicinal products for treating limps which occur in osteorthrosis,

osteochondrosis or enthesopathies of the bony insertions of the tendons, of the ligaments or of the aponeuroses in a horse not suffering from fractures, arthritis or exostoses.

More generally, the invention relates to the use of bisphosphonic acid derivatives for the preparation of medicinal products for treating limps which occur in osteoarthrosis, osteochondrosis or enthesopathies of the bony insertions of the tendons, of the ligaments or of the aponeuroses in an animal not suffering from arthritis, fractures or exostoses.

The bisphosphonic acid derivatives which can be used in the context of the invention have the general formula:



in which:

- R_1 represents a hydrogen atom, a halogen atom, a hydroxyl, an amino, a mono(C_1-C_4)alkylamino or a di(C_1-C_4)alkylamino;

- R_2 represents a halogen atom, a linear alkyl comprising from 1 to 5 carbon atoms which is unsubstituted or substituted with a group chosen from a chlorine atom, a hydroxyl, an amino, a mono(C_1-C_4)alkylamino, a di(C_1-C_4)alkylamino; a cyclo(C_3-C_7)alkylamino,

or R_2 represents a phenoxy, a phenyl, a thiol, a phenylthio, a chlorophenylthio, a pyridyl, a pyridylmethyl, a 1-pyridyl-1-hydroxymethyl, an imidazolylmethyl or a 4-thiomorpholinyl.

The salts of these compounds with pharmaceutically acceptable inorganic or organic acids or bases can also be used in the context of the invention. Examples of salts with acids are hydrochloride, hydrobromide, sulphate, acetate, hydrogensulphate, dihydrogenphosphate, methanesulphonate, methylsulphate, maleate, fumarate, sulphonate, 2-naphthalenesulphonate,

glycolate, gluconate, citrate, isethionate, benzoate, salicylate, ascorbate, tartrate, succinate, lactate, glutarate, toluenesulphonate and ascorbate. As examples of salts with inorganic or organic bases, mention may be made of ammonium salts or alkali metal salts such as, for example, sodium salts.

The hydrates of these compounds can similarly be used according to the invention.

These compounds are described in particular in EP 623,347.

Among these bisphosphonic acid derivatives, mention may be made in particular of the following compounds:

- 1-hydroxyethylidenebisphosphonic acid, whose international nonproprietary name is etidronic acid, and its sodium salts;

- 2-pyrid-2-ylethylidenebisphosphonic acid, whose international nonproprietary name is piridronic acid, and its sodium salts;

- dichloromethylenebisphosphonic acid, whose international nonproprietary name is clodronic acid, and its sodium salts;

- 3-amino-1-hydroxypropylidenebisphosphonic acid, whose international nonproprietary name is pamidronic acid, and its sodium salts;

- 4-amino-1-hydroxybutylidenebisphosphonic acid, whose international nonproprietary name is alendronic acid, and its sodium salts;

- 6-amino-1-hydroxyhexylidenebisphosphonic acid and its salts;

- phenoxymethylenebisphosphonic acid and its salts;

- thiomorpholinomethylenebisphosphonic acid and its salts;

- 4-chlorophenylthiomethylenebisphosphonic acid, whose international nonproprietary name is tiludronic acid, and its pharmaceutically acceptable salts, in particular the disodium salt;

- 1-hydroxy-2-(3-pyridyl)ethylidenebisphosphonic acid, whose international nonproprietary name is risedronic acid, and its sodium salts;

- 1-hydroxy-2-(2-imidazolyl)ethyl-1,1-bisphosphonic acid and its salts;

- (cycloheptylamino)methylenebisphosphonic acid and its salts;

- 2-hydroxyethylidene-2-(3-pyridyl)-1,1-bisphosphonic acid and its sodium salts.

According to the present invention, the use of tiludronic acid and of its pharmaceutically acceptable salts, in particular the disodium salt, or of its hydrates is particularly preferred.

Bisphosphonic acid derivatives are known to inhibit bone resorption and to decrease the activity of osteoclasts, as is found in particular in the following articles:

- "Diphosphonates inhibit hydroxyapatite dissolution in vitro and bone resorption in tissue culture and in vivo", Fleisch H., Russell R., Francis M., Science, 1969, 165, 1262-1264

- "Two modes of action of bisphosphonates on osteoclastic resorption of mineralized matrix", Boonekamp P.M., Van Der Wee-Pals L.J.A., Van Wijk-Lennep, Thesing C.W., Bijvoet O.L.M., Bone Miner., 1986, 1, 27-39

- "Dichloromethylene bisphosphonate (Cl_2MBP) inhibits bone resorption through injury to osteoclasts that resorb CIMBP coated bone", Flanaghan A.M., Chambers T.J., Bone Miner., 1989, 6, 33.

Many bisphosphonic acid derivatives are in development or are already marketed in human medicine in the treatment of bone complaints. A review of the therapeutic uses of these derivatives is presented in the book "Bisphosphonate on bones" edited by Bijvoet O.L.M., Fleisch H.A., Canfield R.E. and Russell R.G.G. (Elsevier Science BV, 1995). The main uses concern the treatment of bone complaints such as Paget's disease or

osteoporosis. The other uses usually described are directed towards the treatment of malignant hypercalcaemia, bone tumours or bone metastasis. It has also been possible to demonstrate the anti-inflammatory activity of certain bisphosphonic acid derivatives in a model of arthritis in rats, induced by injection of mycobacterium.

However, the authors are unaware of any studies demonstrating the anti-inflammatory activity of these bisphosphonic acid derivatives in pathologies other than arthritis or more generally in other species. More recently, the value of certain bisphosphonic acid derivatives in improving the repair of fractures has been described. Reference will be made in particular to EP 600,834 or US 5,488,041.

Finally, it has been demonstrated in Ann. Med. Vet. vol. 132, 198, p. 391-399, that 3-amino-1-hydroxypropylidene 1,1-bisphosphonate is effective in the treatment of exostoses. In the said study, the ossification induced by raising the periosteum was selected as the experimental model. Although the presence of exostoses can cause a limp an animal, this activity of 3-amino-1-hydroxypropylidene 1,1-bisphosphonate does not in any way suggest the efficacy of phosphonates in treating limps occurring in osteoarthroses, osteochondroses or enthesopathies.

In another field, the use of bisphosphonic acid derivatives is also described in the diagnosis of certain bone complaints by scintigraphy. An example of such a use is reported by Keegan K.G., Wilson D.A., Lattimer C.L., Twardock A.R., Ellersieck M.R. (Am. J. Vet. Res., 1996, 57, 415-421) in the scintigraphic evaluation of ^{99m}Tc-methylene diphosphonate labelling of the navicular region in horses with a limp localized on the foot, although no mention is made of the clinical benefit provided by binding the bisphosphonic acid derivative in the bones of the palmar region.

The medical treatments most usually prescribed

for limps are directed towards pain relief; this is the case, for example, for treatments with non-steroidal anti-inflammatory medicines. However, these treatments are unsatisfactory since they do not treat the injuries which are the cause of the inflammation. Their efficacy is moreover limited to the period of administration, since the beneficial effects of the anti-inflammatories disappear as soon as treatment has ended. Rest is also often recommended to allow the region of the locomotor apparatus, which is the cause of the limp, to return to a normal state. More specifically, in horses, the use of orthopaedic shoes is recommended. Even more particularly, in this animal species, the use of compounds which modify vascularization in the navicular region is recommended in the treatment of navicular disease; it is for these conditions that isoxsuprine, a vasodilator, is prescribed by Gabriel A., Caudron I., Serteyn D., Collin B. in "Syndrome naviculaire: anatomie, étiopathogénie, diagnostic, traitement" [Navicular syndrome: anatomy, aetiopathology, diagnosis and treatment], Ann. Med. Vet., 1994, 138, 309-330).

Surprisingly, it has been found that bisphosphonic acid derivatives are useful in the treatment of limps occurring in osteoarthrosis, osteochondrosis or enthesopathies of the bony insertions of the tendons, of the ligaments or of the aponeuroses. It has been shown, entirely unexpectedly, that the use of these derivatives allows a significant and long-lasting improvement in the clinical signs of limping, or even curing of the limp, even beyond the treatment period, and without any increase in bone density being detectable by radiological examination.

Thus, the beneficial effects observed are not thought to be linked to the bone resorption-inhibiting activity of the bisphosphonic acid derivatives.

Such medicines can be used in veterinary medicine.

They can be administered via various routes of

administration, for example parenterally, orally, rectally, intra-articularly, cutaneously, transcutaneously or transdermally.

The mode of administration of such medicines is determined depending on the species treated, age, weight and the severity of the pathology.

The administration rhythm can consist of a single administration or repeated administrations. In the case of repeated administrations, the treatment can be administered continuously or intermittently. When a continuous treatment is chosen, the preferred administration rhythm may be from a single daily administration to 3 daily administrations over a period which can range from a few days to a few months. When an intermittent treatment is chosen, one of the following administration rhythms may be adopted: an administration every 2 or 3 days or a weekly, fortnightly or monthly administration over periods which can range from a few weeks to a few months.

The concentration of the medicine, in terms of bisphosphonic acid derivative, depends on the activity and on the duration of action of this derivative, the mode of administration, the age, the weight, the sex, the size of the desired effect, the intended species or, for certain animal species, the race.

For liquid preparations for parenteral or oral use, the concentration of the medicine, in terms of bisphosphonic acid derivative, can be between 0.001% and 90% as a weight/volume ratio. For preparations intended for the oral route, it can be between 0.001 mg and 10 g per dosage unit.

The medicine can also be in the form of an implant.

The doses during each administration of the medicines prepared according to the present invention, expressed relative to the body weight, can range between 0.001 mg/kg and 100 mg/kg.

For example, doses of from 0.01 mg/kg/week to

1 mg/kg/week of tiludronic acid or of one of its salts may be administered intravenously to horses.

For an oral administration, the pharmaceutical composition according to the invention may be in the form of a tablet, a gelatin capsule, a powder, a granule, drops or any other form which can be administered orally.

The composition according to the invention may also contain ingredients usually used in pharmacy for the preparation of oral forms. Thus, the composition according to the invention can contain a disintegration agent, a flow agent, a lubricant and any excipient of suitable mass.

Lactose, cellulose or starches can be used as mass excipient. Stearic acid, magnesium stearate, L-leucine or, for example, glyceryl tribehenate can be used as lubricant. Sodium carboxymethylstarch, crosslinked sodium carboxymethylcellulose or, for example, crosslinked polyvinylpyrrolidone can be used as disintegration agent. Pure silica or colloidal silicon dioxide can be used as flow agent.

The present invention also relates to rapidly dissolving oral forms and to effervescent oral forms obtained by adding an effervescent couple to the composition according to the invention. Tartaric acid and sodium bicarbonate or citric acid and sodium bicarbonate can be used as effervescent couple.

The invention also relates to rapidly dissolving tablets, effervescent tablets and tablets covered with a coating. A composition containing sodium lauryl sulphate according to European patent EP 336,851 is particularly suitable.

For rectal administration, use is made of suppositories which are prepared with binders that melt at rectal temperature, for example cocoa butter or polyethylene glycols.

The preparations for injection are prepared by mixing one or more bisphosphonic acid derivatives with a

pH regulator, a buffer agent, a suspension agent, a solubilization agent, a stabilizer, a tonicity agent and/or a preserving agent, and by converting the mixture into an intravenous, subcutaneous or intramuscular injection, according to a standard process. Where appropriate, the preparations for injection can be lyophilized according to a standard process.

Examples of suspension agents include methylcellulose, polysorbate-80, hydroxyethylcellulose, acacia, powdered gum tragacanth, sodium carboxymethylcellulose and polyethoxylated sorbitan monolaurate.

Examples of solubilizing agents include castor oil solidified with polyoxyethylene, polysorbate-80, nicotinamide, polyethoxylated sorbitan monolaurate, macrogol and the ethyl ester of castor oil fatty acid.

In addition, the stabilizer includes sodium sulphite, sodium metasulphite and ether, while the preserving agent includes methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol and chlorocresol.

An example of a tonicity agent is mannitol.

During the preparation of the solutions or suspensions for injection, it is desirable to take care to ensure that these are isotonic with the blood.

Example 1

A clinical study was carried out to evaluate the effects of a treatment with disodium tiludronate on horses which develop a limp during bony spavin (which is osteoarthrosis of the distal stage of the tarsus).

The study was carried out on 5 horses, the diagnosis of the osteoarthrosis causing the limp being based on the following criteria:

- local signs in the hock region: heat, swelling, pain
- functional signs of limping graded on a scale from 0 (no sign of limping) to 4 (trouble in

bearing weight when at rest and/or in motion and difficulty in moving around)

- a functional test of locomotion after flexing the hock, also assessed on a scale from 0 (locomotion not changed by flexure) to 4 (start of suppression of bearing weight)
- a radiological examination to assess radiological signs in the hock region qualitatively.

To be included, the animal had to show no signs or lesions of septic arthritis, or any fractures of the bones in the hock region, or even show any exostosis in the hock region. Also, it needed to have not received an injection for anti-inflammatory treatment in the joints of the hock region.

The wearing of an orthopaedic shoe was not contra-indicated since most of the animals had been limping for several weeks and were already wearing a shoe of this type.

All the animals received, as a single treatment, disodium tiludronate in the form of an injectable solution administered intravenously at a dose of 0.1 mg/kg, at a weekly administration rate for 6 to 10 weeks. The first day of treatment corresponds to D0.

To assess the effects of the treatment, the animals were reviewed 1 month after D0 (M1), 2 months after D0 (M2) and 6 months after D0 (M6). The effects of the treatment were assessed with regard to:

- the local signs, the functional signs and the test of locomotion after flexure as defined during inclusion of the animal into the test
- a radiological examination to assess the change in the radiological signs
- an assessment of the resumption of the animal's sporting activity.

Taking all these criteria into account allows the horse to be placed in one of the following categories after the 3 control examinations at M1, M2

and M6:

- "very favourable" category: absence of local signs, grade 0 for the functional test and signs; the animal resumed activity comparable to that in which it was engaged before limping
- "favourable" category: the local signs are very much attenuated, the functional signs have been improved by 1 or 2 degrees, the horse is ready to resume physical activity comparable to that in which it was engaged before limping
- "average" category: persistence of local signs, functional signs improved by 1 degree; persistence of a locomotor difficulty preventing the animal from resuming normal physical activity
- "mediocre" category: persistence of the local signs, no improvement in the functional signs
- "poor" category: no improvement in the local or functional signs, or even worsening of the local signs and of the functional signs.

The results obtained were as follows (expressed as a percentage of animals present in each category):

Category	Examination at M1	Examination at M2	Examination at M6
Very favourable	0%	40%	40%
Favourable	40%	60%	20%
Average	60%	0%	20%
Mediocre	0%	0%	0%
Poor	0%	0%	20%

The change in the limp induced by bony spavin is favourable to very favourable in most of the animals after treatment. The persistence of the beneficial effects is also very satisfactory.

Example 2

A clinical study was carried out to evaluate the

effects of a treatment with disodium tiludronate on horses which develop a limp associated with bone lesions in the form of sub-chondral cysts during osteochondrosis.

The test procedure and the clinical monitoring of the animals were the same as those described in Example 1, except that the local, functional and radiological signs were evaluated in the joints affected by osteochondrosis.

5 horses were included in this test.

The results obtained were as follows (expressed as a percentage of animals present in each category):

Category	Examination at M1	Examination at M2	Examination at M6
Very favourable	40%	20%	60%
Favourable	0%	40%	0%
Average	40%	20%	0%
Mediocre	0%	0%	40%
Poor	20%	20%	0%

These results demonstrate the clinical benefit afforded by administration of the bisphosphonic acid derivative on the treatment of limps associated with bone lesions during osteochondrosis.

Example 3

A clinical study was carried out to evaluate the effects of a treatment with disodium tiludronate on horses which develop a limp during enthesopathy of the insertion of the tendons and the ligaments.

The test procedure and the clinical monitoring of the animals were the same as those described in Example 1, except that the local, functional and radiological signs were evaluated in the region of the tendon or ligament insertions at the source of the limp.

6 horses were included in this test.

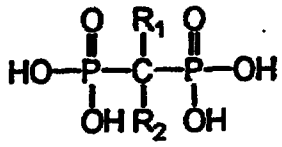
The results obtained were as follows (expressed as a percentage of animals present in each category):

Category	Examination at M1	Examination at M2	Examination at M6
Very favourable	0%	0%	40%
Favourable	50%	67%	40%
Average	33%	33%	0%
Mediocre	17%	0%	20%
Poor	0%	0%	0%

These results demonstrate the clinical benefit afforded by administration of the bisphosphonic acid derivative on the treatment of limps caused by insertion enthesopathies.

CLAIMS

1. Use of a bisphosphonic acid derivative of formula:



in which:

- R_1 represents a hydrogen atom, a halogen atom, a hydroxyl, an amino, a mono(C_1-C_4)alkylamino or a di(C_1-C_4)alkylamino;

- R_2 represents a halogen atom, a linear alkyl comprising from 1 to 5 carbon atoms which is unsubstituted or substituted with a group chosen from a chlorine atom, a hydroxyl, an amino, a mono(C_1-C_4)alkylamino or a di(C_1-C_4)alkylamino; a cyclo(C_3-C_7)alkylamino,

or R_2 represents a phenoxy, a phenyl, a thiol, a phenylthio, a chlorophenylthio, a pyridyl, a pyridylmethyl, a 1-pyridyl-1-hydroxymethyl, an imidazolylmethyl or a 4-thiomorpholinyl,

of one of its pharmaceutically acceptable salts or of one of its hydrates in the preparation of a medicinal product for treating limps in an animal not suffering from arthritis, fractures or exostoses occurring in osteoarthrosis, osteochondrosis or enthesopathies of the bony insertions of the tendons, of the ligaments or of the aponeuroses.

2. Use according to Claim 1, characterized in that the animal belongs to the equine family.

3. Use according to Claim 1, characterized in that the animal is a horse.

4. Use according to any one of Claims 1 to 3, for the preparation of a medicinal product containing 0.001 mg to 10 g of the bisphosphonic acid derivative per dosage unit.

5. Use according to any one of the preceding claims, characterized in that the medicinal product is a

liquid preparation which may be administered orally or parenterally, containing from 0.001% to 90% on a weight/volume basis of the bisphosphonic acid derivative.

6. Use according to any one of Claims 1 to 4, for the preparation of a medicinal product which may be administered orally.

7. Use according to any one of Claims 1 to 4, for the preparation of a medicinal product which may be administered parenterally.

8. Use according to any one of Claims 1 to 4, for the preparation of a medicinal product which may be administered in the form of an implant.

9. Use according to any one of the preceding claims, characterized in that the bisphosphonic acid derivative is selected from:

- 1-hydroxyethylidenebisphosphonic acid and its sodium salts;
- 2-pyrid-2-ylethylidenebisphosphonic acid and its sodium salts;
- dichloromethylenebisphosphonic acid and its sodium salts;
- 3-amino-1-hydroxypropylidenebisphosphonic acid and its sodium salts;
- 4-amino-1-hydroxybutylidenebisphosphonic acid and its sodium salts;
- 6-amino-1-hydroxyhexylidenebisphosphonic acid and its salts;
- phenoxymethylenebisphosphonic acid and its salts;
- thiomorpholinomethylenebisphosphonic acid and its salts;
- 4-chlorophenylthiomethylenebisphosphonic acid and its salts;
- 1-hydroxy-2-(3-pyridyl)ethylidenebisphosphonic acid and its sodium salts;
- 1-hydroxy-2-(2-imidazolyl)ethyl-1,1-bisphosphonic acid and its salts;

* C L M S *

- (cycloheptylamino)methylenebisphosphonic acid and its salts;

- 2-hydroxyethylidene-2-(3-pyridyl)-1,1-bisphosphonic acid and its sodium salts.

10. Use according to Claim 9, characterized in that the bisphosphonic acid derivative is 4-chlorophenylthiomethylenebisphosphonic acid.

