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NOTICE OF ENTITLEMENT

I, John Gordon Hinde, of Spruson & Ferguson, St Martins Tower, 31 Market Street, Sydney, New South Wales 2000, Australia, being the patent attorney for the Applicant(s)/Nominated Person(s) in respect of Application No 39550/93 state the following:-

The Applicant(s)/Nominated Person(s) has/have entitlement from the actual inventor(s) as follows:-

The Applicant(s)/Nominated Person(s), by virtue of a Contract of Employment between the actual inventor(s) as employee(s) and the Applicant(s)/Nominated Person(s) as employer(s), is a person entitled to have the patent assigned to it if a patent were granted on an application made by the actual inventor(s).

The Applicant(s)/Nominated Person(s) is/are the applicant(s) of the application(s) listed in the Declaration under Article 8 of the PCT. The basic application(s) listed on the Declaration under Article 8 of the PCT is/are the first application(s) made in a Convention country in respect of the invention.

DATED this FOURTEENTH day of NOVEMBER 1994

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- (54) Title
A PHARMACEUTICAL PREPARATION OF DICHLOROMETHYLENE BISPHOSPHONIC ACID WITH ENTERIC COATING FOR ORAL USE
- (51)⁵ International Patent Classification(s)
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SPRUSON & FERGUSON , GPO Box 3898, SYDNEY NSW 2001
- (56) Prior Art Documents
EP 313845
EP 275468
EP 63014
- (57) This particular preparation solves the poor bioavailability associated with this drug.

CLAIM


1. Pharmaceutical preparation for oral use containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, characterized in that the preparation is a drug delivery form which is enteric coated with a film which dissolves at a pH-value of from 5 to 7.2.

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<p>(51) International Patent Classification ⁵ : A61K 9/30, 31/66</p>	<p>A1</p>	<p>(11) International Publication Number: WO 93/21907 (43) International Publication Date: 11 November 1993 (11.11.93)</p>
<p>(21) International Application Number: PCT/FI93/00166 (22) International Filing Date: 21 April 1993 (21.04.93) (30) Priority data: 9201299-6 24 April 1992 (24.04.92) SE (71) Applicant (for all designated States except US): LEIRAS OY [FI/FI]; Pansiontie 45-47, FIN-20210 Turku (FI). (72) Inventors; and (75) Inventors/Applicants (for US only): POSTI, Juhani [FI/FI]; Varnankatu 4 P, FIN-20320 Turku (FI). KATILA, Kirsi [FI/FI]; Pohjantähdentie 6 A 8, FIN-20200 Turku (FI). RANTALA, Pertti [FI/FI]; Kierrekuja 3, FIN-20660 Lintainen (FI).</p>		<p>(74) Agent: OY JALO ANT-WUORINEN AB; Iso Rooberinkatu 4-6 A, FIN-00120 Helsinki (FI). (81) Designated States: AU, CA, CZ, FI, HU, JP, NO, NZ, PL, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.</p> <p>67 1830</p>
<p>(54) Title: PHARMACEUTICAL PREPARATION AND PROCESS FOR ITS MANUFACTURE A Pharmaceutical Preparation of Dichloromethylene Bisphosphonic Acid with Enteric Coating for oral use. (57) Abstract The invention concerns a pharmaceutical preparation for oral use containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid. According to the invention the preparation is a drug delivery form which is enteric coated with a film which dissolves at a pH-value of from 5 to 7.2. The invention also relates to a process of manufacture of the said preparation.</p> <p></p>		

A Pharmaceutical Preparation of Dichloromethylene Bisphosphonic Acid with Enteric Coating for Oral Use

The object of the present invention is a pharmaceutical preparation for oral use, especially a tablet, which as its active ingredient contains a pharmacologically acceptable salt of
5 dichloromethylene bisphosphonic acid, i.e. a clodronate, especially disodium clodronate.

Dichloromethylene bisphosphonic acid, especially in the form of its salt, such as the disodium salt, is a known drug for example for the treatment of diseases relating to the calcium metabolism and to the skeletal system, such as to the metabolism of the bone, for example for osteoporosis.

10 Clodronate has previously been administered orally in the form of conventional compressed tablets or capsules. Such a tablet or capsule disintegrates in the stomach of the patient releasing the active agent, which in the acidic environment of the stomach is converted to the free acid form. As clodronic acid is poorly absorbed, the bioavailability of the active agent will be low, and consequently the required dosage level has to be
15 increased. This in turn is a disadvantage as a large tablet has to be used, which is inconvenient for the patient and reduces patient compliance. Also a large dose increases the risk for side-effects.

According to the invention it has now been discovered that it is possible to achieve a substantially improved bioavailability if the active agent is prevented from being
20 transformed into its acid form, that is, if it is allowed to pass the stomach region in unliberated form into the lower digestive tract to be released at a site thereof which is optimal from the point of view of the absorption of the active agent.

According to the invention it has now been discovered that the said objective is reached if the preparation is a drug delivery form which is enteric coated with a film which dissolves
25 at a pH of from 5 to 7.2.

According to a first embodiment of this invention, there is provided a pharmaceutical preparation for oral use containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, characterized in that the preparation is a drug delivery form which is enteric coated with a film which dissolves at a pH-value of from 5
30 to 7.2.

According to a second embodiment of this invention, there is provided a process for the manufacture of a pharmaceutical preparation according to the first embodiment, characterized in that a pharmaceutically acceptable salt of dichloromethylene bisphosphonic acid is combined with a pharmacologically acceptable carrier or other



adjuvants, the mixture obtained is made into a drug delivery form, which is coated with a film which dissolves at a pH-value of from 5 to 7.2.

Preferably the film dissolves at a pH of from 5.0 to 6.5.

There is a number of film forming agents suitable for the purpose of the invention.
5 Important from the point of view of the invention is that the agent used dissolves at the pH mentioned, i.e. at pH 5 to 7.2. These agents are known as such and there is a number of commercially available substances. Of such agents may be mentioned i.e. shellac, cellulose acetate phthalate (CAP) (e.g. Aquateric® by FMC Corporation), hydroxypropyl methylcellulose acetate succinate (HPMCAS, e.g. Aqoat® by ShinEtsu), hydroxypropyl
10 methylcellulose phthalate (HPMCP, HP 50 and HP 55 by ShinEtsu), polyvinyl acetate phthalate (PVAP), cellulose acetate trimellitate (CAT, by e.g. Eastman Fine Chemicals), as well as various metacrylic acid derivatives (Eudragits by RöhmPharma).

The film forming agents are used dissolved either in suitable organic solvents (e.g. alcohols, chlorinated hydrocarbons, acetone etc), or in water, optionally in mixture with
15 an organic solvent, and optionally using plasticizers, also known in the art, e.g. phthalic esters, citric esters, triacetin.

A preferred film forming agent to be used in the invention is hydroxypropyl methylcellulose phthalate, which is e.g. commercially available in forms that dissolve at pH 5 or alternatively pH 5.5.

20 The pharmaceutical preparation can be of any shape and form suitable to be provided with an enteric coating, representative examples being a tablet, granule, pellet,

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capsule or the like.

It has, according to the invention, surprisingly been discovered that the level of absorption of clodronate from
5 a drug delivery form, which is enteric coated with a film forming agent which dissolves at the said pH of 5.0 to 7.2, is more than twice as high as from a corresponding drug delivery form which is uncoated, and even 4 to 5 times better than the absorption from a tablet suspended in water
10 or from a sachet. This is be apparent from the absorption tests and their results presented later.

In the preparation according to the invention clodronate is used preferably as its disodium salt, either as the
15 anhydrate or as a hydrate (tetrahydrate), the latter forming needle-shaped crystals of a size $< 100 \mu\text{m}$. The preparation according to the invention may, in addition to the active agent, contain conventional additives, such as carriers, diluents, fillers, lubricants, disintegrating
20 agents etc. These are known in the art. The amount of clodronate in the preparation can vary within wide limits, e.g. from 10 to 95 % by weight, being typically 50 to 90 % by weight. The film constitutes usually about 2 to 10 %
25 by weight of the total weight of the preparation, typically about 3 to 5 % by weight. The exact amount and the thickness of the film are not critical, as long as the film is intact.

The invention also concerns a process for the preparation
30 of the said oral preparation according to which a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid is combined with a pharmacologically acceptable carrier or other additives, whereafter the mixture obtained is formulated into a drug delivery form and coated
35 to form a film which dissolves at a pH-value of from 5 to 7.2.

The preparation thus takes place by combining the active agent with per se known carrier and other additives and adjuvants. As a filler for example lactose, microcrystalline cellulose (e.g. Emcocel 90 M), mannitol and corn starch
5 may be used. Also a disintegrating substance, such as croscarmellose sodium (Ac-Di-Sol), a binder, such as polyvidone (e.g. Kollidon K 30) and stearic acid may be used, which last mentioned substance may also function as a lubricant, as also magnesium stearate. As a lubricant
10 also talc and colloidal silicon dioxide (e.g. Aerosil 200) may be used. When formulating the preparation, water and/or ethanol is used, typically as solvents for the binder in the granulation. The preparation is carried out using per se known tableting, granulating or pelletization
15 techniques.

The cores thus prepared are then coated and this purpose any apparatus suitable for film coating may be used, such as Accela-Cota type of apparatus (Manesty) or apparatuses
20 based on air suspension technique, e.g. Aeromatic or Glatt.

For this purpose the film forming agent is dissolved, depending on the agent, either in a suitable organic solvent, such as methanol, methylene chloride or acetone,
25 or in water or e.g. a water-alcohol mixture, the alcohol typically being e.g. methanol, ethanol or isopropanol.

In the following the invention is illustrated by means of an example, which is in no way intended to be limiting.

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Example 1

For the preparation of a tablet according to the invention the following ingredients were used for the tablet core:

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	Disodium clodronate	
	anhydrate	800.00 mg
	Polyvidon.	30.00 mg
	Croscarmellose sodium	29.40 mg
5	Microcrystalline cellulose	38.70 mg
	Lactose	119.91 mg
	Stearic acid	18.75 mg
	Coll. anhydrous silicon dioxide	20.00 mg
	Talc	34.00 mg
10	Magn. stearate	9.24 mg

In the first stage of the tablet preparation, the clodronate is granulated with polyvidon in a mixture of water and ethanol. The drug is wet granulated and sieved through a 1.5 mm sieve. The wet mass of granules is dried at about 40 °C to a suitable total moisture content of appr. 19%. The dried granules are then sieved on a 1.25 mm sieve. Thereafter the clodronate-polyvidon-granules are mixed with the colloidal silicon dioxide, Croscarmellose sodium and microcrystalline cellulose. The mixture is wetted with a solution of stearic acid and ethanol, wet-sieved and dried at +30 °C to a moisture content of appr. 18%. Thereafter the mass is dry-sifted through a 1.5 mm sieve. The remaining colloidal silicon dioxide as well as the talc, magnesium stearate and the lactose is added while mixing. Thereafter the mixture is formed into tablets in tableting apparatus, using 9 x 21 mm punches to form tablets of a mean weight of 1.3 g (\pm 5%).

The prepared tablets were then coated with a coating solution, the composition of which per tablet was

	Hydroxypropyl methyl-cellulose phthalate (HP 55)	52.00 mg
35	Diethylphthalate	7.80 mg
	Ethanol	516.60 mg
	Purif. water	135.70 mg

The diethylphthalate is the plasticizer and the ethanol and the water form the evaporating part of the system. The "solids" content of the HPMCP-solution was about 9 %.

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The coating took place in an apparatus of Accela Cota-type under the following coating conditions.

Accela Cota 24"-coating apparatus (Ecco 40 DA-spray gun;
10 Watson-Marlow peristaltic pump)

Cores	9 kg
Inlet air temp.	appr. + 50 °C
Outlet air temp.	appr. + 35 °C
15 Core temp.	appr. + 10 °C
Injection speed	30-20 rpm
Preheating time	appr. 10 min
Drum speed	appr. 8 rpm
Atomizing air pressure	2.5 bar

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In the following test report the results of experiments are reported wherein the bioavailability of an enteric coated tablet according to the invention (Example 1) was compared to an uncoated, but otherwise to its composition identical
25 clodronate tablet, as well as to that of a clodronate sachet formulation and a clodronate solution.

The composition of the sachet was:

30 Disodium clodronate	800.00 mg
Polyvidon.	50.00 mg
Aspartame	50.00 mg
Arom. Passion	62.50 mg
Mannitol	87.50 mg
35 Spir. fort.	q.s.
Aq. purif.	q.s.

Method

The panel consisted of 6 healthy volunteers, 3 women and 3 men, 24 to 28 years of age. Each subject received one 800 mg dose of clodronate sachet and one 800 mg enteric coated tablet of clodronate with 200 ml of water. All six subjects had participated in an earlier study wherein i.a. an uncoated tablet had been tested, and four of them had received a 800 mg clodronate tablet suspended in 200 ml of water. These data were used as historical controls for the present study. The interval between the studies was six months.

The study was of a balanced, randomized, two-period cross over design.

Fourteen (14) venous blood samples (10 ml each) were taken during each study period according to the following schedule: 0 (pre-drug), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 24.0 hours following drug administration.

Urine was gathered as follows: In fractions of two hours up to 8.0 h (0.0-2.0 h, 2.0-4.0 h, 4.0-6.0 h and 6.0-8.0 h), of four hours up to 12.0 h (8.0-12.0 h) and of twelve hours up to 24.0 h (12.0-24.0 h).

Analysis of free, unmetabolized clodronate in serum was carried out by a gas chromatographic - mass spectrometric method. The detection limit of the method was 30 ng/ml and it was linear from 30 to 3000 ng/ml.

Detection of free, unmetabolized clodronate in urine was executed by a gas chromatographic method. The method was linear from 5 to 250 µg/ml.

The statistical analyses were carried out using Siphar

program.

Results

- 5 The AUC_{0-24h} (area under curve) of the four clodronate formulations are presented in the following table:

Delivery form		AUC_{0-24h} (ng/ml*h)
10	Enteric tablet	
	-mean	2478.60
	-standard deviation (SD)	1787.18
15	Tablet	
	-mean	1195.06
	-SD	930.45
	Sachet	
20	-mean	679.03
	-SD	360.22
	Susp. tablet	
	-mean	564.78
25	-SD	505.05

From the results in the table it clear that the AUC_{0-24h} values for the four clodronate delivery forms, i.e. the enteric coated tablet, tablet, sachet and dissolved tablet differed significantly from each other. The bioavailability of the enteric coated tablet was approximately twice that of an ordinary tablet, and the bioavailability from the solution formulations (sachet and dissolved tablet) were about the half of that from the ordinary tablet.

The claims defining the invention are as follows:

1. Pharmaceutical preparation for oral use containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, characterized in that the preparation is a drug delivery form which is enteric coated with a film which
5 dissolves at a pH-value of from 5 to 7.2.
2. Preparation according to claim 1, characterized in that the film dissolves at a pH-value of 5.0 to 6.5.
3. Preparation according to claim 1 or 2, characterized in that the film is of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose acetate succinate
10 (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate trimellitate (CAT), metacrylic acid derivatives.
4. Preparation according to claim 3, characterized in that the film is hydroxypropyl methylcellulose phthalate.
5. Preparation according to any one of the preceeding claims, characterized in
15 that said preparation is a tablet, capsule, granule or pellet.
6. Preparation according to claim 5, characterized in that said preparation is a tablet.
7. Preparation according to any one of the preceeding claims, characterized in that the salt of dichloromethylene bisphosphonic acid is the disodium salt.
- 20 8. Process for the manufacture of a pharmaceutical preparation according to claim 1, characterized in that a pharmaceutically acceptable salt of dichloromethylene bisphosphonic acid is combined with a pharmacologically acceptable carrier or other adjuvants, the mixture obtained is made into a drug delivery form, which is coated with a film which dissolves at a pH-value of from 5 to 7.2.
- 25 9. Pharmaceutical preparation for oral use containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, which preparation is substantially as herein described with reference to Example 1.
10. A process for the manufacture of a pharmaceutical preparation, which process is substantially as herein described with reference to Example 1.
- 30 11. A method of treating diseases relating to calcium metabolism in an animal in need of such treatment, comprising administering to said animal an effective amount of a pharmaceutical preparation as claimed in any one of claims 1 to 5 or 7.

Dated 8 July, 1996

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 93/00166

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 9/30, A61K 31/66

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)

IPC5: A61K

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

SE,DK,FI,NO classes as above

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

WPI, WPIL, CLAIMS, CA, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, A1, 0313845 (WARNER-LAMBERT COMPANY), 3 May 1989 (03.05.89), page 5, line 54 - page 8, line 22, claims --	1-6
Y	EP, A2, 0063014 (SANKYO COMPANY LIMITED), 20 October 1982 (20.10.82), page 6, line 14 - line 18, claims --	1-6
Y	EP, A1, 0275468 (BOEHRINGER MANNHEIM GMBH), 27 July 1988 (27.07.88) -- -----	1-6

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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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

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

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

& document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/93

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PCT/FI 93/00166

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0313845	03/05/89	JP-A- 1156929 US-A- 5068110	20/06/89 26/11/91
EP-A2- 0063014	20/10/82	JP-C- 1501607 JP-A- 57171428 JP-B- 63040131 US-A- 4533562	28/06/89 22/10/82 09/08/88 06/08/85
EP-A1- 0275468	27/07/88	SE-T3- 0275468 CA-A- 1298196 US-A- 4859472	31/03/92 22/08/89