

High Dose Ibandronate Formulation

The invention relates to a pharmaceutical composition for oral application consisting of a high dose of bisphosphonates or physiologically safe salts thereof as active substance and to a process for the preparation of such compositions.

Aminoalkyl-1,1-diphosphonic acid derivatives (hereinafter called by the general term bisphosphonates) are important pharmaceutical agents in the treatment of bone diseases and some disturbances of calcium metabolism such as hypercalcaemia, osteoporosis, tumour osteolysis, Paget's disease, etc.

Bisphosphonates as pharmaceutical agents are described for example in EP-A-170,228, EP-A-197,478, EP-A-22,751; EP-A-252,504, EP-A-252,505, EP-A-258,618, EP-A-350,002, EP-A-273,190, WO-A-90/00798 each of which are incorporated herein by reference.

Pharmaceutical forms of currently marketed bisphosphonates are oral formulations (tablets or capsules) or solutions for intravenous injection or infusion. They are systemically well tolerated when administered at therapeutic doses. However, bisphosphonates as a class are irritant to skin and mucous membranes and when given orally on a continuous basis may result in digestive tract side effects, e.g. esophageal adverse events or gastrointestinal disturbances. In consequence, and due to their low oral bioavailability, the oral route of administration has, to date, to follow inconvenient recommendations of use for the patient.

US 6294196 describes a tablet formulation comprising 50 mg of ibandronic acid. The tablets are made by mixing granules comprising the active and filler material together with disintegrant and other excipients and compressing this mixture.

As described, bisphosphonates are accepted as providing strong efficacy in the management of osteoporosis. However, given the administration restrictions related to low oral bioavailability and potential for gastro-intestinal side effects, there is a clear opportunity for regimens which offer improved convenience and flexibility, leading to a higher level of compliance and superior patient management / satisfaction.

Furthermore it has been found in the Ibandronate clinical development program, that Ibandronate showed fracture reduction efficacy with a drug-free interval beyond daily administration. It was quite unexpected that fracture reduction benefit could be derived from a weekly or monthly administration of an oral bisphosphonate with a single or multiple tablet administration scheme.

For this purpose a new composition comprising a high dose, namely up to 250 mg, preferably comprising 150 mg or 100 mg of a bisphosphonate derivative, especially of ibandronate or physiological safe salts thereof had to be prepared, which on the one hand has an increased ratio of active substances vs excipients and on the other hand which fulfills the requirements of stability.

It has been found that the stability of such high dose formulations is substantially increased by adding the disintegrant already in the granulation step together with the active substance and with a part of the filler material. Such compositions are easily dissolvable and have an increased stability on storage both with regard to temperature and humidity.

The pharmaceutical composition may comprise up to 250 mg, preferably up to 200 mg, especially comprising 150 mg or 100 mg of a bisphosphonate, especially of ibandronate or a physiological safe salt thereof as an active substance.

The following bisphosphonates are active substances which can be used in the pharmaceutical compositions in the form of free acids in the physiological safe salts or hydrates, particularly sodium salts:

- (4-amino-1-hydroxybutylidene)bis-phosphonate (alendronate),
- (dichloromethylene)bis-phosphonate (clodronate),
- [1-hydroxy-3-(1-pyrrolidinyl)-propylidene]bis-phosphonate (EB-1053),
- (1-hydroxyethylidene)bis-phosphonate (etidronate),
- [1-hydroxy-3-(methyl pentyl amino)propylidene]bis-phosphonate (ibandronate),
- [Cycloheptylamino]-methylene]bis-phosphonate (incadronate),
- (6-amino-1-hydroxyhexylidene)bis-phosphonate (neridronate),
- [3-(dimethylamino)-1-hydroxypropylidene]bis-phosphonate (olpadronate),
- (3-amino-1-hydroxypropylidene)bis-phosphonate (pamidronate),
- [1-hydroxy-2-(3-pyridinyl)ethylene]bis-phosphonate (risedronate),
- [[4-(4-chlorophenyl)thiol]-methylene]bis-phosphonate (tiludronate),
- [1-hydroxy-2-imidazo-(1,2-a)pyridin-3-yl ethylidene]bis-phosphonate (YH 529),
- [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis-phosphonate (zoledronate); especially [1-hydroxy-3-(methyl pentyl amino)propylidene]bis-phosphonate (ibandronate)

The said substances and their preparation are known and described, for example, in the following references:

- US Patent No. 4,705,651 (Alendronate), US Patent No. 4,927,814 (Ibandronate), US Patents Nos. 3,468,935, 3,400,147, 3,475,486 (Etidronate), O.T. Quimby et al, J. Org. Chem. 32, 4111
5 (1967) (Clodronate) and US Patent No. 4,505,321 (Risedronate) and US Patents Nos. 4,134,969 and 3,962,432 (Pamidronate), US Patent No. 5,130,304 (EB-1053), US Patent No. 4,970,335 (Incadronate), Belgian Patent No. 885139 (Neridronate), US Patent No. 4,054,598 (Olpadronate), US Patents Nos. 4,746,654, 4,876,248 and 4,980,171 (Tiludronate), US Patent No. 4,990,503 (YH 529) and US Patent No. 4,939,130
10 (Zoledronate).

- Preferred are compositions comprising the equivalent of 150 mg bisphosphonates or physiological safe salts thereof and compositions comprising the equivalent of 100 mg bisphosphonates or physiological safe salts as active substances, respectively. Ibandronate or a physiological safe salt thereof is a particularly preferred active substance, particularly
15 in the form of Na-Ibandronate monohydrate.

- The composition may further comprise adjuvants such as binders for example polyvinylpyrrolidone (e.g. Povidone®) or hydroxypropylmethyl cellulose (e.g. Pharmacoat®), fillers for example lactose in hydrate or anhydrate form, cellulose in microcrystalline or fibrous form (e.g. Avicel®), or starch, disintegrants for example cross-linked polyvinyl pyrrolidone
20 (e.g. Crospovidone® USPNF) or cross carmellose, lubricants for example stearic acid or magnesium stearate, and flow-regulators for example colloidal silicon dioxide.

The preferred form of the composition are tablets preferably coated by a film coating mixture and a plastiziser. Such film coating mixtures and plastizisers are known to the person skilled in the art.

In a first aspect, there is provided a tablet for the treatment of bone diseases and disturbance of the calcium metabolism containing as active substance up to 250 mg of ibandronic acid or physiologically safe salts thereof for oral application, characterised in that the disintegrant is added in the granulate together with the active substance and with part of the filler material.

The tablet kernel may consist

- of 30.0 to 36.0, preferably of 33.3% of active substance;
- of 4.0 to 6.0, preferably of 4.8 to 5.2 % by weight of binder;
- of 39.6 to 59.4, preferably of 47.0 to 52.0 % by weight of filler;
- of 4.5 to 5.5, preferably of 4.8 to 5.2 % by weight of disintegrant;
- of 1.8 to 2.2, preferably of 1.9 to 2.1 % by weight of lubricant; and
- of 0.9 to 1.1, preferably of 0.95 to 1.05 % by weight of flow regulator.

Preferably the active substance is ibandronate or a physiological safe salt thereof; preferably the binder is polyvinylpyrrolidone; preferred fillers are lactose in hydrate or anhydrate form, or cellulose in microcrystalline or fibrous form; and a preferred disintegrant is cross-
35 linked polyvinyl pyrrolidone. Preferred are compositions wherein the disintegrant is added

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already in the granulate together with the active substance and with a part of the filler material.

In a second aspect, there is provided a tablet for the treatment of bone diseases and disturbance of the calcium metabolism containing

Ibandronic acid	100.0 mg	--
- as mono-sodium salt (IH ₂ O) of Ibandronic acid	112.50 mg	
Povidone K25®	15.0 mg	
Lactose, monohydrate	108.50 mg	
Cellulose, microcrystalline	40.0 mg	
Crospovidone	15.0 mg	
Stearic acid 95	6.0 mg	
Silica, anhydrous colloidal	3.0 mg	
Film-coat		
Film-coating mixture*	10.20 mg	
Macrogol 6000®	1.80 mg	

In a third aspect, there is provided a tablet for the treatment of bone diseases and disturbance of the calcium metabolism containing

Ibandronic acid	150.0 mg	--
- as mono-sodium salt (IH ₂ O) of Ibandronic acid	168.75 mg	
Povidone K25®	22.5 mg	
Lactose, monohydrate	162.75 mg	
Cellulose, microcrystalline	60.0 mg	
Crospovidone	22.5 mg	
Stearic acid 95	9.0 mg	
Silica, anhydrous colloidal	4.5 mg	
Film-coat		
Film-coating mixture	12.75 mg	
Macrogol 6000	2.25 mg	

Furthermore, disclosed herein is a process for the preparation of pharmaceutical compositions for the oral application comprising a high dose of bisphosphonates, especially of ibandronate or a physiological safe salt thereof. According to the disclosed method, the pharmaceutical composition can be prepared

- by wet granulation of the bisphosphonate or pharmaceutically acceptable salt thereof in the presence of adjuvants such as the binder and a part of fillers mentioned above, characterized in that the disintegrant is added into the granulation mixture;
- 10 - fluidising the granulation mixture in a manner known per se;
- subsequently drying the wet granulate and screening the dried granulate through a screen having a suitable mesh width;
- adding the remaining adjuvants such as the fillers, lubricant and flow regulators mentioned above and blending the mixture before processing it by techniques known per
- 15 se to form pharmaceutical compositions.

In a preferred form the active substance, a part of the filler, and the disintegrant in dry powder form are granulated by spraying an aqueous binder solution into the powder mixture. The process is preferably carried out at a temperature of 60 to 80 °C, preferably at about 70°C.

The spray granulated material may then be dried preferably at a temperature of 60 to 80 °C preferably at about 70°C and subsequently screened through a fine sieve; the dried granulate is mixed with the remaining amount of the filler, the lubricant, and the flow regulator which were previously passed through a fine sieve. The final blend may then be pressed into tablet kernels which are coated with a coating suspension using purified water and a

25 film-coating mixture.

The process can be carried out as follows:

- a) dissolving the binder, preferably Povidone K25® in purified water;
- b) charging a drier, preferably a fluid-bed drier with the bisphosphonate, preferably with the mono-sodium salt ($\text{1H}_2\text{O}$) of Ibandronic acid, a part of the filler preferably with
- 30 lactose monohydrate and up to 60 % by weight of the total amount of microcrystalline cellulose, and the disintegrant;
- c) spray-granulating the raw materials of step b) at a temperature of 60 to 80 °C, preferably at about 70°C with the granulation fluid of step a),

- e) drying the spray granulated material of step c) at a temperature of 60 to 80 °C, preferably at about 70°C (setpoint of inlet-air temperature) and subsequently screening the dried intermediate through a fine sieve;
- f) mixing the granulate of step e) with the remaining amount of the filler e.g. micro-crystalline cellulose, the lubricant, preferably stearic acid and the flow regulator, for example anhydrous colloidal silica which were previously passed through a fine sieve (e.g. 1mm);
- g) compressing the final blend of f) into tablet kernels; and coating the tablet with a coating suspension using purified water and a film-coating mixture comprising for example hypromellose, titanium dioxide and talc (the mixture is purchased from the market e.g. Opadry® 00A28646) and Macroglol 6000®.

In a fourth aspect, there is provided a process for the preparation of a tablet as defined above, said process comprising

- a) dissolving the Povidone K25® in purified water;
- b) charging a drier, preferably a fluid-bed drier with ibrandronic acid mono-sodium salt (1H₂O), a part of the lactose monohydrate and up to 60% by weight of the total amount of microcrystalline cellulose, and Crospovidone;
- c) spray- granulating the raw materials of step b) at a temperature of 60 to 80°C, preferably at about 70°C with the granulation fluid of step a);
- e) drying the spray granulated material of step c) at a temperature of 60 to 80°C, preferably at about 70°C (setpoint of inlet-air temperature) and subsequently screening the dried intermediate through a fine sieve;
- f) mixing the granulate of step e) with the remaining amount of microcrystalline cellulose, the stearic acid, and the anhydrous colloidal silica which were previously passed through a fine sieve (e.g. 1mm);
- g) compressing the final blend of f) into tablet kernels; and coating the tablet with a coating suspension using purified water and a film-coating mixture comprising hypromellose, titanium dioxide and talc and Macroglol 6000®.

In a fifth aspect, there is provided a pharmaceutical composition for the treatment of bone diseases and disturbance of the calcium metabolism obtainable by the process as defined above.

The adjuvants are known in the art and are commercially available.

The invention will now be explained in further detail with reference to examples, without being limited thereto.

Example 1:

the preparation of a film coated tablet containing 150 mg active substance is carried out as follows:

1. Dissolve Povidone K25® in purified water.
2. Charge a fluid-bed drier with mono-sodium salt ($1H_2O$) of Ibandronic acid, lactose monohydrate, crospovidone and microcrystalline cellulose. Crospovidone and the microcrystalline cellulose were passed through a fine sieve (e.g. 1mm) before mixing.
3. Spray-granulate the raw materials of step 2 at 70°C (set point of inlet-air temperature) with the granulation fluid of step 1.
4. Perform a final drying of the spray granulated material of step 3 at 70°C (setpoint of inlet-air temperature).
5. Screen the dried intermediate granulate through a fine sieve (e.g. 2mm perforations) and
6. where required, repeat steps 1-5 to obtain the required final batch size.
7. Mix the granulate of step 6 in a container mixer with microcrystalline cellulose, stearic acid and anhydrous colloidal silica. The microcrystalline cellulose, the stearic acid and the anhydrous colloidal silica were passed through a fine sieve (e.g. 1mm) before mixing.

8. Compress the final blend of step 7 into tablet kernels using a rotary tablet press.
9. Prepare the coating suspension using purified water, film-coating mixture comprising hypromellose (60.5%), titanium dioxide (29%) and talc (10.5%); the mixture is purchased from the market (e.g. Opadry® 00A28646) and Macrogol 6000®.
- 5 10. Spray the coating suspension of step 9 onto the tablet kernels using a coating unit.

The tablet composition is as follows:

	Tablet kernel	
	Ibandronic acid	150.0 mg --
	- as mono-sodium salt (1H ₂ O) of Ibandronic acid	168.75 mg
10	Povidone K25®	22.5 mg
	Lactose, monohydrate	162.75 mg
	Cellulose, microcrystalline	60.0 mg
	Crospovidone	22.5 mg
	Stearic acid 95	9.0 mg
15	Silica, anhydrous colloidal	4.5 mg
	Film-coat	
	Film-coating mixture *	12.75 mg
	Macrogol 6000	2.25 mg

*this film-coating mixture contains: hypromellose (60.5%), titanium dioxide (29%) and talc (10.5%); the
 20 mixture is purchased from the market (e.g. Opadry® 00A28646)

The kernel weight is 450 mg and the total tablet weight is 465 mg, the amount of active substance per tablet is equivalent to 150mg of free Ibandronic acid.

Example 1a: for a batch of 110 000 tablets

1. A suitable vessel was charged with 14.850 kg demineralised water and 2.475 kg of
 25 Povidone K25® was added under constant stirring. The time of addition was about 15 minutes.
2. A fluid-bed dryer was charged with 18.563 kg ibandronic acid mono sodium salt, 17.903 kg of lactose monohydrate 100, 4.125 kg Avicel PH-102® and 2.475 kg Crospovidone CL®.
- 30 3. The components were mixed and spray granulated at a temperature of 70°C with the aqueous solution of Povidone K25® prepared above which was added at 300 g/min with a pressure of 2.5 bar.

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4. The granulate was then dried in a fluid-bed dryer at 70°C; and
 5. subsequently screened (2.0 mm meshes) to yield 44.540 kg of dried granulated material.
 6. 2.426 kg AVICEL PH-102®, 0.970 kg stearic acid and 0.4850 kg silicic acid AEROSIL 200® were screened and added to the dried granulated material (44.650 kg), the components were mixed; and
 7. the final blend was compressed into tablets kernels, yield 103 244 kernels.
 8. A coating suspension was prepared by dissolving 0.290 kg PEG 6000® (MACROGOL 6000) in 7.743 kg demineralised water and subsequently dispersing 1.645 kg OPADRY 100A28646® into this solution.
 9. The kernels were coated with the coating suspension under standard conditions.
- The tablets have the composition and the weight given in example 1.

Example 2:

- 15 the preparation of a film coated tablet containing 100 mg active substance was carried out as described in example 1:

Tablet kernel

Ibandronic acid	100.0 mg	--
- as mono-sodium salt (1H ₂ O) of Ibandronic acid	112.50 mg	
20 Povidone K25	15.0 mg	
Lactose, monohydrate	108.50 mg	
Cellulose, microcrystalline	40.0 mg	
Crospovidone	15.0 mg	
Stearic acid 95	6.0 mg	
25 Silica, anhydrous colloidal	3.0 mg	
Film-coat		
Film-coating mixture *	10.20 mg	
Macrogol 6000	1.80 mg	

*composition as mentioned example 1

- 30 The kernel weight is 300 mg and the total tablet weight is 312 mg, the amount of active substance per tablet is equivalent to 100mg of free Ibandronic acid.

Claims

1. A tablet for the treatment of bone diseases and disturbance of the calcium metabolism containing as active substance up to 250 mg of ibandronic acid or physiologically safe salts thereof for oral application, characterised in that the disintegrant is added in the granulate together with the active substance and with part of the filler material.
2. A tablet according to claim 1 wherein the tablet kernel consists of
30.0 to 36.0 % of active substance
4.0 to 6.0% by weight of binder;
39.6 to 59.4 by weight of filler;
4.5 to 5.5% by weight of disintegrant;
1.8 to 2.2% by weight of lubricant; and
0.9 to 1.1% by weight of flow regulator.
3. A tablet according to claim 1, wherein the tablet kernel consists of
33.3. % of active substance;
4.8 to 5.2 % by weight of binder;
47.0 to 52.0 % by weight of filler;
4.8 to 5.2 % by weight of disintegrant;
1.9 to 2.1 % by weight of lubricant; and
0.95 to 1.05 % by weight of flow regulator.
4. A tablet according to claim 2 or 3 comprising the equivalent of 150 mg ibandronic acid or physiologically safe salts as active substance.
5. A tablet according to claim 1, 2 or 3 comprising the equivalent of 100 mg ibandronic acid or physiologically safe salts as active substance.
6. A tablet for the treatment of bone diseases and disturbance of the calcium metabolism containing

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Ibandronic acid	100.0 mg	- -
- as mono-sodium salt (H ₂ O) of Ibandronic acid	112.50 mg	
Povidone K25®	15.0 mg	
Lactose, monohydrate	108.50 mg	
Cellulose, microcrystalline	40.0 mg	
Crospovidone	15.0 mg	
Stearic acid 95	6.0 mg	
Silica, anhydrous colloidal	3.0 mg	
Film-coat		

Film-coating mixture*	10.20 mg
Macrogol 6000®	1.80 mg

7. A tablet for the treatment of bone diseases and disturbance of the calcium metabolism containing

Ibandronic acid	150.0 mg	- -
- as mono-sodium salt (1H ₂ O) of Ibandronic acid	168.75 mg	
Povidone K25®	22.5 mg	
Lactose, monohydrate	162.75 mg	
Cellulose, microcrystalline	60.0 mg	
Crospovidone	22.5 mg	
Stearic acid 95	9.0 mg	
Silica, anhydrous colloidal	4.5 mg	
Film-coat		
Film-coating mixture	12.75 mg	
Macrogol 6000	2.25 mg	

8. A process for the preparation of a tablet according to anyone of claims 1 to 7, said process comprising

- a) dissolving the Povidone K25® in purified water;
- b) charging a drier, preferably a fluid-bed drier with ibrandronic acid mono-sodium salt (1H₂O), a part of the lactose monohydrate and up to 60% by weight of the total amount of microcrystalline cellulose, and Crospovidone;
- c) spray- granulating the raw materials of step b) at a temperature of 60 to 80°C, preferably at about 70°C with the granulation fluid of step a);

- e) drying the spray granulated material of step c) at a temperature of 60 to 80°C, preferably at about 70°C (setpoint of inlet-air temperature) and subsequently screening the dried intermediate through a fine sieve;
- f) mixing the granulate of step e) with the remaining amount of microcrystalline cellulose, the stearic acid, and the anhydrous colloidal silica which were previously passed through a fine sieve (e.g. 1mm);
- g) compressing the final blend of f) into tablet kernels; and coating the tablet with a coating suspension using purified water and a film-coating mixture comprising hypromellose, titanium dioxide and talc and Macrogol 6000®.

9. A pharmaceutical composition for the treatment of bone diseases and disturbance of the calcium metabolism obtainable by the process according to claim 8.