An Oral Pharmaceutical Formulation Containing Ibandronate

The invention relates to pharmaceutical formulations of ibandronate or its physiologically tolerable salts for oral application, and to processes for producing same.

The active substance ibandronaic acid (1-hydroxy-3-(N-methyl-N-pentyl)aminopropyl-1,1-diphosphonic acid) and its salts (ibandronates), respectively, are among the class of diphosphonic acids which, in particular, are of interest in the treatment of bone diseases and particular disorders in the calcium metabolism such as hypercalcaemia, osteoporosis, tumor osteolysis or Paget's disease. In the treatment of the diseases mentioned, these active substances must be administered frequently and over a long period of time and therefore, the aim should be especially oral application in addition to intravenous application since it is the former which is more accepted by many patients.

Fundamentally, however, oral treatment is generally complicated by the well-known problems with oral tolerability of diphosphonic acids. Diphosphonic acids or their physiologically safe salts, and particularly aminodiphosphonic acids are known to give rise to irritations of the upper gastrointestinal tract (Fleisch H., Bisphosphonates in Bone Disease, Herbert Fleisch, Bern 1993, pp. 126-131). The same applies for diphosphonates which are also ingested at relatively low dosages of, e.g., less than 50 mg per single administration form. WO 93/09785 points out that the active substance risedronate ([1-Hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonate), for example, may give rise to erosions and ulcerations in the upper sections of the digestive tract. Various references allude to the gastrointestinal intolerability of the active substances pamidronate (Dodwell D. et al., Biochemical Effects, Antitumor Activity and Pharmacokinetics of Oral and Intravenous

Pamidronate (APD) in the Treatment of Skeletal Breast Cancer, Br. J. Cancer 62, 496 (1990)) and tiludronate (Reginster J.Y., Efficacy and Tolerability of a New Formulation of Oral Tiludronate (Tablet) in the Treatment of Paget's Disease of Bone, J. Bone Miner. Res. 9, 615-619 (1994)). In addition, it is also well-known that motility disorders may occur when swallowing the tablets and/or the tablets to be ingested get stuck due to the particular anatomic situation in the oesophagus. This may give rise to odynophagia or oesophageal strictures as well. Frequently, this is the case with elderly patients or with patients who, due to their disease, are forced to take the required tablets predominantly in a lying position.

Accordingly, in order to solve these problems, the art demanded that fundamentally, orally available administration forms be coated with a gastric juice-resistant film so that the active substance is released only subsequent to the passage through the stomach and thus, irritations of the stomach and the oesophagus would be avoided. For example, WO 95/08331 describes administration forms by which it is possible to reduce the irritating potential of alendronate and other diphosphonates in oral application.

Due to the above-described oral intolerability of diphosphonates, there has been a search for more tolerable administration forms for a number of these active substances. In particular, oral administration forms coated with gastric juice-resistant coatings have been developed in this context. Such coatings are the choice in protecting the upper sections of the gastrointestinal tract, particularly the oesophagus or the stomach, from intolerable active substances. These gastric juice-resistant coatings on solid oral administration forms dissolve only at higher pH values of about 5.5 on, so that in the acidic gastric medium, being at a pH value far below 5.5, no active substance will be released from the administration form and

thus, the stomach is protected from irritations caused by the active substance. As no active substance is released in the stomach, it is possible at the same time to prevent oesophagitis or other irritations of the oesophagus caused by the refluxing gastric contents containing active substance. As a consequence, DE 59 005 517 (EP 421,921) describes a gastric juice-resistant oral administration form for pamidronate which is suitable in reducing the risk of gastric ulcerations. Furthermore, WO 93/09785 illustrates such an administration form for risedronate, WO 95/08331 for alendronate and other diphosphonates.

The potential advantages of the gastric juice-resistant administration forms are contrasted by a number of drawbacks. Thus, resorption with these administration forms may be reduced as compared to forms releasing in a pH-independently rapid fashion, or resorption is substantially more variable as compared to conventional forms, thus impairing or jeopardizing therapeutical safety. Therefore, there is a demand in alternative administration forms for these active substances in order to avoid the disadvantages of the gastric juice-resistant forms and nevertheless, be capable of providing sufficient protection from these aminobisphosphonates having aggressive effects on the gastric mucosa.

Surprisingly, it was found that improved oral tolerability in the case of the ibandronate active substance is already achieved when peroral administration forms are coated with an adjuvant coating or film in such fashion that the active substance is dissolved within a short period of time and correspondingly high local concentrations of active substance are achieved in the stomach. The film dissolving upon contact with digestive juice is preferably a coating which dissolves pH-independently. The adjuvant coating may be coated using methods common in pharmaceutical technology. Although this coating does not prevent dis-

solution of ibandronate in the stomach, it was surprising that no significant side effects were observed in clinical studies using ibandronate even at high dosages. Despite the fact that the administration forms are coated with a film which quickly releases the active substance, there are no irritations in the oesophagus when swallowing the tablets, and oesophagitis does not occur. This is particularly advantageous since the administration forms of the invention are also well-tolerated by patients lying in bed.

According to the invention, solid oral formulations of ibandronate are provided, consisting of a core containing the active substance, which is coated with an adjuvant coating free of active substance, which either dissolves independently of the pH value or is removed from the solid oral formulation upon contact with digestive juice. In this way, relatively rapid disintegration of the drug form and release of the active substance within a short period of time are ensured, whereby high local concentrations of the active substance are achieved. The coating may be applied using methods such as film coating, press coating, tablet coating, encapsulating or micro-encapsulating. The release of active substance from the appropriately coated solid administration forms for oral application, such as film tablets, coated tablets, laminated tablets, capsules, or microcapsules, takes place more rapidly as compared to the gastric juice-resistant administration forms. According to the invention, at least 30% of the contained ibandronate dose, but preferably at least 75% and, in particular, at least about 85% is released rapidly and independently of the pH value within the physiological pH range. Preferably, the time period required to achieve these release percentages is less than 2 hours, more preferably less than 1 hour, with about 1-30 minutes being particularly preferred. It is particularly preferred that the release is about 80-90% within a time period of up to 15 minutes. Conveniently, the release of active substance is estimated

within the scope of an in vitro experiment according to well-known standardized procedures.

Surprisingly, rapid release of the active substance does not result in the undesirable side effects usually known for diphosphonic acids as described above, despite the high local concentrations of active substance (i.e., despite the high gradient of active substance) thereby generated in the stomach. Rather, it was found that despite the rapid release of active substance, the problem of occurring gastrointestinal disorders is avoided, quite surprisingly. Furthermore, it has been observed that among patients treated with such rapidly releasing administration forms of ibandronate, there were significantly less cases of nausea, vomiting, pain or diarrhoea than otherwise observed when administering aminobisphosphonates.

The coatings with rapid release of active substance in the meaning of the invention can be applied to all the suitable peroral administration forms such as tablets, capsules, coated tablets, pellets, granulates or powders. These administration forms consist of mixtures of active substances with pharmaceutical adjuvants or of pure active substances. Coating may be performed using various methods common in pharmacy. For example, suitable methods use tablet coating units, film coating units, tablet presses for press coating, encapsulating machines, or micro-encapsulating units, such as facilities for spray freezing and spray embedding, facilities for producing simple or complex coacervates.

In the meaning of the invention, pharmaceutically common or physiologically safe polymers are possible as film-forming agents. Film-forming agents in the meaning of the invention are derived from, e.g., the groups of cellulose derivatives, dextrins, starches and starch derivatives, polymers based on other carbohydrates and deriva-

tives thereof, natural gums such as gum arabic, xanthans, alginates; polyacrylic acid, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, polymethacrylates and derivatives thereof (Eudragit®), chitosan and derivatives thereof, shellac and derivatives thereof. In addition to these film-forming agents, substances from the class of wax and fat substances may be used to produce the coatings according to the invention.

Preferably, the soluble alkyl- or hydroxyalkylcellulose derivatives such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, or sodium carboxymethylcellulose are possible as cellulose derivatives. In a preferred variant of an embodiment of the invention, methylhydroxypropylcellulose is employed. The usual cellulose derivatives suitable for pharmaceutical purposes, with varying degrees of substitution and/or varying molecular weights corresponding to varying viscosity levels of the aqueous solutions, may be used as suitable film-forming agents on the basis of cellulose. Likewise, insoluble cellulose derivatives such as ethylcellulose may be employed.

In the case of polymethacrylates, cationic copolymerizates of dimethylaminoethyl methacrylate with neutral methacrylic esters (Eudragit® E), copolymerizates of acrylic and methacrylic esters having a low content of quaternary ammonium groups (described in "Ammonio Methacrylate Copolymer Type A or Type B" USP/NF, Eudragit® RL and RS, respectively), and copolymerizates of ethyl acrylate and methyl methacrylate with neutral character (in the form of an aqueous dispersion, described in "Polyacrylate Dispersion 30 Per Cent" Ph. Eur., Eudragit® NE 30 D) are possible.

Similarly, the use of film-forming agents usually employed in the production of gastric juice-resistant films is possible as long as pH-independently rapid release of the active substance from the appropriately coated administration form, as described above, is ensured, e.g., by a thin layer thickness of the coating or other measures such as an extremely high percentage of pore-forming agents or the like. Anionic copolymerizates of methacrylic acid and methyl methacrylate (described in "Methacrylic Acid Copolymer, Type C" USP/NF, Eudragit® L and S, respectively, or in the form of the Eudragit® L 30 D aqueous dispersion), acidic cellulose derivatives such as cellulose acetate phthalate, cellulose acetate trimellitate and methylhydroxypropylcellulose phthalate, polyvinyl acetate phthalate, etc. may be used as such films.

In principle, all the film-forming agents may be employed alone as well as in mixtures of two or more film-forming agents.

If required, the films may contain additional adjuvants such as plasticizers, pore-forming agents, filling agents, colorants, pigments, antifoam agents, antistick agents, and the like.

According to the invention, polymers and adjuvants possibly required in addition, as were described in the preceding paragraph, are possible for press coating as far as they can be processed by means of press coating technology. In addition, all the pharmaceutically common or physiologically tolerable adjuvants which are suited to form a closed coat by press coating on the drug forms to be covered may be used in the meaning of the invention. In particular, these include adjuvants as are common in conventional tabletting, specifically filling agents from the group of carbohydrates such as lactose, saccharose, glucose and other sugars, microcrystalline cellulose, starches and

starch derivatives, sugar alcohols such as mannitol, sorbitol, xylitol, inorganic filling agents such as phosphates and carbonates. According to the invention, other adjuvants as required in the production of conventional tablets, such as binding agents, disintegrants, flow agents, release agents, taste improvers, pigments, and coloring agents may be contained in addition to the filling agents.

According to the invention, all the adjuvants described above may be employed for tablet coating, in principle. In addition, special adjuvants for tablet coating may be employed according to the invention, such as palatinite, bentonite, calcium sulfate as filling agents, polyethylene glycol or polyethylene glycol fatty acid esters as release agents, colloid silicic acid as drying agent and structuring agent, magnesium oxide as spreading powder, pharmaceutically common or physiologically safe fats and waxes as glossing agents.

In the meaning of the invention, all the pharmaceutically common capsules such as gelatin hard capsules, soft gelatin capsules, starch capsules are possible as capsules. The capsules may be filled with powders, granulates, pellets or tablets. In general, all the pharmaceutically common solid, liquid and semi-solid formulations may be filled into the capsules of the invention.

For micro-encapsulating the active substance or formulations of the active substance, all the polymeric film-forming agents mentioned above may be used according to the invention. Here, the polymers may be used alone as well as in mixtures of multiple polymers, and also together with other adjuvants, if necessary.

In the following, the invention will be illustrated by way of embodiments which are not intended as limitation.

For example, The ibandronate active substance is employed in amounts of 0.1 - 100 mg per single dosage unit. Preferably, the dosage is at least ca. 1 mg, 5 mg, 10 mg, or 20 mg as lower limit for the amount of active substance in a single administration form. The upper limit is about 250 mg, particularly 100 mg and 50 mg, respectively.

Example 1

Ibandronate-containing core:			
Ibandronate dose [mg] in 200 mg tablet core:	10.0	20.0	50.0
Ibandronate-free coat [mg]:			
Methylhydroxypropylcellulose	5.1425	5.1425	5.1425
Titanium dioxide	2.4650	2.4650	2.4650
Macrogol	1.5000	1.5000	1.5000
Talc	0.8925	0.8925	0.8925
Total film coated	10.0000	10.0000	10.0000

Film-coating is carried out in common apparatus. Coating conditions: tablet charge 140 kg; feed air temperature: 60°C.

Example 2

Ibandronate-containing core:			
Ibandronate dose in 100 mg tablet core [mg]:	0.1	2.5	5.0
Ibandronate-free coat [mg]:			
Methylhydroxypropylcellulose	2.057	2.057	2.057
Titanium dioxide	0.986	0.986	0.986
Macrogol	0.600	0.600	0.600
Talc	0.357	0.357	0.357
Total film coated	4.000	4.000	4.000

Film-coating in a conventional 250 l tablet coating tank. Coating conditions: tablet charge 144 kg.

Example 3

Ibandronate-containing core:			
Ibandronate dose [mg] in 200 mg tablet core:		10.0	20.0
50.0			
Ibandronate-free coat [mg]:			
Talc	2.00	2.00	2.00
Lactose	1.40	1.40	1.40
Methylhydroxypropylcellulose	0.80	0.80	0.80
Titanium dioxide	0.80	0.80	0.80
Macrogol	0.40	0.40	0.40
Ethyl methyl methacrylate copolymer*		0.04	0.04
0.04			
Polysorbate	0.04	0.04	0.04
Total film coated	5.48	5.48	5.48

* Employed in the form of Eudragit™ NE 30 D as an aqueous dispersion.

Film-coating in a conventional 15 l tablet coating tank. Coating conditions: tablet charge 13.0 kg.

Example 4

Ibandronate-containing core:	
Ibandronate dose in 74 mg tablet core [mg]:	20
Ibandronate-free coat [mg]:	
Methylhydroxypropylcellulose phthalate	4.580
Triacetin	1.374
Polysorbate	0.046
Total film coated	6.000

Film-coating in a conventional 5 l tablet coating. Coating conditions: tablet charge 0.25 kg.

Example 5

Ibandronate-containing core:
Ibandronate dose [mg] in 86 mg tablet core: 10

Ibandronate-free coat [mg]:

Saccharose	37.844	
White clay	8.138	
Talc	1.000	
Macrogol	2.848	
Glucose syrup	2.035	
Titanium dioxide	1.628	
Polyvidone	0.407	
Montan glycol wax		0.100
Total tablet coating applied	54.000	

Tablet coating in a conventional 15 l tablet coating tank with dip pipe.

Example 6

Ibandronate-containing core:
Ibandronate dose [mg] in 400 mg granulate: 20 mg and 50 mg

Ibandronate-free coat [mg]: hard gelatin two-piece capsule, size 0, white opaque.
Encapsulation of the drug mass performed on a Harro-Höfliger type encapsulating machine.

Example 7

Ibandronate in laminated tablet

Ibandronate-containing core:	
Final weight:	86 mg
Format of core :	7 mm in diameter, plane, with facettes
Ibandronate dose in tablet core:	10 mg
Ibandronate-free coat:	
Lactose	270 mg
Microcrystalline cellulose:	90 mg
Pressing tool:	12 mm in diameter
Final weight of laminated tablet:	446 mg

Pressing by means of a hand press using conventional procedures.

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Claims

1. An oral pharmaceutical administration form containing ibandronate or a physiologically tolerable salt thereof as active substance, characterized in that the administration form consists of an active substance-containing inner portion enclosed in such fashion by a coat free of active substance that rapid release of the active substance takes place.

2. The administration form according to claim 1, characterized in that at least 30% of the contained dose of active substance, but preferably at least 75% is released within 2 hours, preferably within 1 hour, and particularly preferred within a half hour upon contact with an aqueous medium at a pH of from 1 to 7.4.

3. The administration form according to claim 1 or 2, characterized in that the active substance-containing inner portion consists of a tablet, capsule, granulate, pellet, or powder in admixture with adjuvants or as a pure active substance.

4. The administration form according to claim 3, characterized in that the coat free of active substance is a film containing at least one ingredient from one of the following groups of substances: cellulose, cellulose derivatives, dextrins, starch and starch derivatives, polymers based on other carbohydrates and derivatives thereof, natural gums such as gum arabic, xanthans, alginates; polyacrylic acid, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, polymethacrylates and derivatives thereof (Eudragit®), chitosan

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and derivatives thereof, shellac and derivatives thereof, fats and waxes.

5. The administration form according to claim 4, containing at least one of the following cellulose derivatives: methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, sodium carboxymethylcellulose, ethylcellulose.

6. The administration form according to claim 4 or 5, containing methylhydroxypropylcellulose.

7. The administration form according to one of claims 1 - 4, containing at least one polymethacrylate.

8. The administration form according to claim 7, containing at least one of the following polymethacrylates: cationic copolymerizate of dimethylaminoethyl methacrylate with neutral methacrylic esters; copolymerizate of acrylic and methacrylic esters; copolymerizate of ethyl acrylate and methyl methacrylate.

9. The administration form according to one of claims 1 - 8, wherein the coat is a film-forming agent of a type having gastric juice-resistant properties, and the layer thickness is that thin or of such nature as to form pores so that essentially, no gastric juice-resistant properties of such a coat will result.

10. The administration form according to claim 9, characterized in that at least one of the following film-forming agents is employed: anionic copolymerizate of methacrylic acid and methyl methacrylate, cellulose acetate phthalate, cellulose acetate trimellitate and methylhydroxypropylcellulose phthalate, polyvinyl acetate phthalate.

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11. The administration form according to one of claims 1 - 10, characterized in that the film contains at least one plasticizer, pore-forming agent, filling agent, coloring agent, pigment, antifoam agent, anti-stick agent.

12. The administration form according to one of claims 1 - 11, which can be obtained by applying the coat free of active substance using press coating, the applied coat containing at least one ingredient according to claims 4 - 11, or at least one ingredient from one of the following groups: carbohydrates, sugar alcohols, inorganic phosphates, sulfates, carbonates.

13. The administration form according to claim 12, containing in its coat at least one binding agent, filling agent, disintegrant, flow agent, release agent, taste improver, pigment, or coloring agent.

14. The administration form according to one of claims 1 - 13, which can be obtained by applying the coat free of active substance by tablet coating, the applied coat containing at least one ingredient according to claims 4 - 11.

15. The administration form according to claim 14, containing at least one of the following ingredients: bentonite, calcium sulfate, fat, colloid silicic acid, magnesium oxide, palatinite, polyethylene glycol, polyethylene glycol fatty acid ester, wax.

17. The administration form according to one of claims 1 - 11, which can be obtained by applying the coat free of active substance by encapsulating, the applied coat containing at least one of the ingredients gelatin, starch or cellulose derivatives.



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18. The administration form according to one of claims 1 - 17, characterized in that the active substance-containing portion consists of solid, liquid or semi-solid formulation.

19. A process for producing an administration form according to one of claims 1 - 17, characterized in that the coat free of active substance is generated by film coating, press coating, tablet coating, encapsulating or micro-encapsulating.

20. Use of an administration form according to one of claims 1 - 17 in the treatment of calcium metabolism diseases, particularly osteoporosis or hypercalcaemia.

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