THE PATENT OFFICE

PATENTS ACT 1977 PATENTS FORM NO. 54/77

£35

RECEIVED IN
20 OCT 1995
EUROPEAN TRANSLATIONS

P54/7700 3.82 0 0625355 4 002094

Please write or type in BLOCK LETTERS using dark ink. For details of current fees please contact the Patent Office.

1 European Patent Number
0625355

Enter the name and address for the proprietor(s) of the European Patent (UK). If you do not have enough space please continue on a separate sheet.

2 Name BOEHRINGER MANNHEIM GMBH

Addr. D-68298 MANNHEIM
GERMANY

Enter the date on which the mention of the grant of the European Patent (UK) was published in the European Patent Bulletin, or, if it has not yet been published, the date on which it will be published

3 European Patent Bulletin Date:
27 SEP 1995

4 Agent VENNER SHIPLEY & CO

Agent's Patent Office
ADP number (if known)

PATENT OFFICE
20 OCT 1995
RECEIVED BY HAND

A UK Address for Service MUST be provided to which all communications from the Patent Office will be sent

5 Address for Service:
20 Little Britain,
London EC1A 7DH

Please sign here

6 Signature

Venner, Shipley & Co

Date: 12 OCT 1995.

Attention is drawn to rules 90 and 106 of the Patents Rules 1982

This form must be filed in duplicate and must be accompanied by a translation into English in duplicate of:
1 the whole description
2 those claims appropriate to the UK (in the language of the proceedings),
3 all drawings, whether or not these contain any textual matter
but excluding the front page which contains bibliographic information.
The translation must be verified to the satisfaction of the comptroller as corresponding to the original text.

Reminder

Have you attached

Duplicate copy of this form ✕

Two copies of the Translation... ✕

Any continuation sheets ... (if appropriate)

093 55 54/77 23

DECLARATION

I, Dr. Reinhold MINK c/o Boehringer Mannheim GmbH of Sandhofer Straße 116, 68298 Mannheim, Federal Republic of Germany, declare that I have a competent knowledge of the English and German languages and that the attached document ist a true and accurate translation of the text of European Patent Specification No. 0 625 355 from German into English.

Dated this 5th day of October 1995

Dr. Mink

Boehringer Mannheim GmbH
3815/00

Tablets with improved bio-availability containing the active ingredient dichloromethylen-diphosphonic acid

The invention concerns tablets with improved bio-availability of the active ingredient dichloromethylen-diphosphonic acid (clodronic acid), or of a physiologically tolerated salt thereof, and an additive of microcrystalline cellulose as a pharmaceutical auxiliary substance, a pharmaceutical package containing such tablets, the use of dichloromethylendiphosphonic acid together with micro-crystalline cellulose for the production of a tablet with improved bioavailability as well as the process for producing this tablet.

It is currently known that the active ingredient dichloromethylendiphosphonic acid, also known by the name of clodronate, is used in certain drug forms for the treatment of osteolysis induced by bone metastasis of solid tumors as well as for the treatment of hypercalcemia (compare, e.g., DE-1813659). In the meantime, it has also turned out that bisphosphonates, such as clodronic acid or their physiologically tolerated salts, can be used successfully in the treatment of osteoporosis and osteoporotic pain.

In order to treat osteolysis, the compound must be administered in a relatively high dosage over a long

period of time, in order to develop its effect. Ostac™ is a pharmaceutical preparation in capsule form that contains the active ingredient in its sodium salt form (clodronic acid, disodium salt x 4 H_2O; MW = 360 g/Mol) in a quantity of 500 mg per capsule. This formulation results in a quantity of approximately 340 mg of the active ingredient (MW = 244,9 g/Mol). The average treatment with Ostac™ consists of the administration of four capsules per day, and up to eight capsules per day in severe cases may be necessary, indicating a daily dose of 1360 - 2720 mg of clodronic acid to be administered.

To accommodate the requirement of high levels of the active ingredient, pharmaceutical administration forms have been developed that contain a high quantity of the active ingredient, in order to reduce as much as possible the size of the single administration form. Such formulations are described in EP 0275468 which have an 80% - 95% content of the active substance. The preparation Ostac™ has a percentage content of the active ingredient disodiumclodronate tetrahydrate of approximately 500 mg (corresponding to 91%) with a total weight of capsule filling material of about 550 mg.

It is difficult for some patients, due to their state of health, to swallow large capsules that contain between 550 - 570 mg of filling mass several times daily over a long period of time.

On the other hand, in order to improve the patient's compliance with the mode of administration, it would be desirable to reduce the daily intake of four to eight capsules, since experience shows that, for example, a

single or double administration is adhered to more resolutely than a multiple administration. With regard to the necessary total dosage amount of approximately 1,400 mg, more severe disease cases require up to 2,700 mg of clodronate to be administered daily, making the necessary dosage of two relatively large capsules with a total weight of at least 1,100 mg each. However, such large capsules are disadvantageous, due to their size.

The object of the invention, therefore, is to make available an administration form with increased bioavailability of the active ingredient clodronic acid by which the total daily dose to be administered to the patient could be reduced, and thus the number of administration forms to be taken daily would be decreased or by which, utilizing the current frequency of administration, smaller administration forms (e.g., smaller tablets) could be used.

It was surprisingly found that tablets with a microcrystalline cellulose additive have a considerably higher bioavailability of the active ingredient when administered to humans than does the capsule form. By this finding, it is then possible to decrease the daily dosage of clodronic acid to lower dosage levels. In particular, it was found that, by the utilization of the invention, the new tablet form causes a reduction of up to 60% in the daily dosage of clodronic acid, which results in, instead of a daily dose of 1,360 mg of clodronic acid, for instance, a reduced daily dosage of approximately 820 mg of clodronic acid to achieve a comparable therapeutic effect.

Assuming that a patient usually had to take four capsules of the preparation Ostac™ with a single dose of approximately 340 mg of clodronic acid (corresponding to a daily total dosage of 1,360 mg of clodronic acid), the tablets according to the invention lead to a reduction of the daily dosage amount to approximately 800 - 1,100 mg. This firstly means a decrease in the single dosage amounts of the active ingredient to approximately 200 - 270 mg of clodronic acid and a subsequent reduction of the total tablet weight to 350 - 500 mg, assuming a daily administration regimen of four tablets, which is particularly beneficial for patients who have difficulty swallowing larger tablets. By reducing the total content of active ingredient, tablet weight can be decreased so that a relatively small tablet can be produced.

Secondly, in order to achieve a decrease in administration frequency, tablets can be produced that replace the previously customary intake of four Ostac™ capsules. Due to the excellent bioavailability attained with the formulation according to the invention it is possible, depending on the desired daily frequency of administration, to vary the content of active substance per tablet and thus to vary as desired the size of the tablet within certain limits.

Assuming, for instance, a total daily dosage of 1,360 mg of clodronic acid, which was previously administered by four capsules of Ostac™, and applying the higher bioavailability of the active ingredient found in clinical trials of the new tablets produced according to the formula of the invention that allows for a reduction of the total dose of clodronic acid by approximately 65%

(corresponding to 884 mg of clodronic acid), then this daily dosage can be administered by two, three or four tablets that according to the invention respectively contain a content of 442 mg, 295 mg or 211 mg of clodronic acid. Thus, tablet size can be adapted to meet various administration requirements. The larger tablets are of particular advantage when there is a risk that the patient will not follow the necessary intake several times over the day and would prefer a once- or twice-daily administration. The smaller tablets are more beneficial to patients in such cases in which the patient has difficulty swallowing large tablets and consequently prefers to ingest smaller tablets several times per day. In the case of a higher or lower daily total dose than the dose of 1,360 mg clodronic acid described here as an example, the content of active substance per tablet is determined in an analogous manner according to the desired requirement with regard to frequency of application and size of the tablets.

The following examples detail some of the preferred administration forms of the invention:

a) A customary capsule of Ostac™ (340 mg of clodronic acid) can be replaced by one tablet produced according to the invention formula that contains approximately 220 mg of the active ingredient. In the case that the active ingredient is used in the form of the tetrahydrate of the sodium salt this means a reduction of the active ingredient in the administrative form of 500 mg down to approximately 325 mg;

b) Two customary capsules of Ostac™ (indicating a total dosage 680 mg of clodronic acid) can be replaced by one tablet that contains approximately 440 mg, which has been produced according to the invention formula. This means that, utilizing the data given in a) above, there is a reduction of the active ingredient concentration from 1,000 mg to 650 mg of the tetrahydrate of disodium clodronate, or a reduction of the water-free form from 800 mg to 520 mg, respectively;

c) Three customary capsules of Ostac™ (indicating a total dosage of 1,020 mg of clodronic acid) can be replaced by one tablet produced according to the invention formula with an active ingredient content of approximately 660 mg or by two tablets with an active ingredient content of 330 mg each; and

d) Four customary capsules of Ostac™ (indicating a total dosage of 1,360 mg of clodronic acid) can be replaced by one tablet produced by the invention formula with an active ingredient content of approximately 880 mg, by two tablets with an active ingredient content of approximately 440 mg or by three tablets with approximately 300 mg of clodronic acid.

The results of bioequivalence studies in humans were used as the basis for the above calculations of the active ingredient content of the tablet according to the formula of the invention, and from these results it was determined that the ingestion of one tablet with an active ingredient content of 520 mg (as related to the water-free form of the sodium clodronate) is

bioequivalent to the intake of two capsules of Ostac™, which contain 400 mg of active ingredient each. The determination of serum concentration of clodronic acid in the blood of several patients revealed substantially comparable values over a period of 16 hours.

The tablets according to the invention are particularly beneficial in the treatment of osteoporosis. Because osteoporosis normally demands a long term treatment, the advantageous reduction of the daily dose of clodronic acid is of particular importance, and thus can minimize the possibility of certain adverse reactions to the drug.

The tablet made in accordance to the formula of the invention contains 200 - 700 mg of the active ingredient dichloromethylen-diphosphonic acid, related to the content of clodronic acid. Preferably, the physiologically tolerable salts of clodronic acid, particularly alkali-salts, are used, preferably the disodium salt, either in the form of tetrahydrate or in the water-free form. There certainly are other physiologically tolerable salts, such as lithium, potassium, ammonium or calcium salts or their hydrates that can be effectively used. The percentage of the active ingredient content (related to clodronic acid) is in the range of 10% - 65% weight, preferably 50% - 60% and particularly 55%, relative to the total weight of the tablet core. By using the sodiumclodronic acid tetrahydrate as a reference magnitude, the active ingredient content would fall within the 74% - 88% range, with the preferable content being approximately 80% of the total weight of the tablet.

The addition of microcrystalline cellulose to the formula according to the invention accounts for 1% - 20% weight of the total weight of the tablet core, particularly in the range of 5% - 15% or 8% - 12% weight. As is specifically preferred, the content of microcrystalline cellulose is approximately 10% of the total weight of the tablet. Avicil™ is the chosen form of microcrystalline cellulose to be used in the tablet. Other similarly acting compounds, such as other modified cellulose derivatives or polyethylene glycol (PEG) 4000 - 6000 can be used in place of microcrystalline cellulose.

The tablet also contains one or more pharmaceutical customary excipients, such as filling compounds, lubricants, disintegrates, binders, or materials that prevent the tablet from sticking to the die. Substances, such as starch (potato, wheat or corn starches), lactose, glucose, mannitol, calciumcarbonate, calciumphosphate, cellulose, talcum or other such compounds known to be utilized for this purpose, can be used. The proportion of the pharmaceutical factors and carrier compounds can vary to a greater extent, depending on the selected active ingredient quantity of the tablet and is typically 0.1% - 20 % of the total weight of the tablet.

The proportion of the filler compounds is approximately 3% - 10%, preferably 5% - 7%, of the total weight of the tablet. Filler compounds can be selected from corn starch, talcum and/or lactose. The proportion of talcum is preferred in the range of 3.5% - 5%, the proportion of corn starch in the 2% - 5% range, and specifically 2.5% of the total weight of the tablet.

The tablet can also contain customary lubricants, preferably such as silicium-dioxide, talcum and/or stearic acid or their salts, particularly their magnesium or calcium salts, can be used. The total content of lubricants is approximately up to 6% of the total weight of the tablet. One or more lubricant(s) in equal or varying amounts can be used. The preferred content amount of lubricants is up to 3%, specifically 0.1% - 2% of the total weight of the tablet. The preferred substances and weight are magnesium stearate and/or talcum in the range of 0.2% - 2% of the total weight of the tablet.

In addition to the above-mentioned excipients, disintegrates can be added to cause a more rapid disintegration of the tablet upon contact with gastric juices. Such disintegrates, such as sodium carboxymethyl starch, cross-carmellose, crospovidone and other compounds with similar actions, can be included in the tablet formula in an amount up to 10% of the total weight of the tablet, but the preferred content would be up to 3% of the total weight of the tablet. Sodium carboxymethyl starch is the preferred substance of use as a disintegrant in the range of 1% - 5%, with a desired amount of 1% - 2%, of the total weight of the tablet.

The tablet core, which serves as the standard for the calculation of the above-mentioned weight relationships, can be coated. On one side, the coat can serve as a method of eliminating the unpleasant taste of the tablet as such. In this case, fragrances are added during the production of the coating materials. On the other side, the coating can additionally retard the release of the

active ingredient. For this purpose, certain compounds in the form of an applied diffusion film are used and act to retard the release of the active ingredient.

It has been determined from bioavailability studies that, according to the formula of the invention, a tablet with an active ingredient content of approximately 420 - 460 mg of clodronic acid, for example, would exhibit a bioavailability of the active ingredient that is equivalent to that of two customary capsules containing approximately 340 mg of clodronic acid each. The total weight of such a tablet made in accordance to the formula of the invention, which by that contains an amount that is twice that of the customary dose, accounts for between 750 - 850 mg, preferably 790 - 810 mg, by the use of the tetrahydrate of the sodium clodronate. When utilizing the water-free clodronate, the tablet will necessarily have a lower total weight due to the lower weight of the active ingredient. In such cases, it can be useful to reduce the amount of the pharmaceutical excipients in the production of the tablet to the same ratio that is proportionate to the lower weight of the active ingredient.

In the same context, tablets with an active ingredient content of 500 - 530 mg and a maximum total weight (related to sodium clodronic acid tetrahydrate) of 870 - 970 mg, preferably 900 - 950 mg, can be produced according to the formula of the invention. By this, following the formula of the invention, tablets containing a single or a double dose can be made available that are smaller in size and are, therefore, better orally administered than were the previously

known formulations. Of the 340 mg of clodronic acid (corresponding to approximately 500 mg of disodium clodronate tetrahydrate or 400 mg of water-free disodium clodronate) contained in a previously customary capsule, only approximately 220 mg of the active ingredient is still necessary when compared to the tablet produced by the formulation of the invention, resulting in a tablet with a typical total weight between 395 - 410 mg.

The tablet produced according to the formula of the invention also exhibits good dissolution characteristics. Thus, by the use of the formula of the invention, the dissolution rate of the 440 mg dose (determined by the use of the USP paddle method) is at least 60% dissolution after 15 minutes and 75% dissolution after 30 minutes.

Another subject of the invention is the final drug products, which contain 30 - 400 tablets according to the formula of the invention for administration in a daily dosage of one to three tablets, preferably two tablets (with an active ingredient content of 420 - 460 mg or 500 - 530 mg per tablet) or four to eight tablets, preferably four (with an active ingredient content of 200 - 270 mg per tablet).

Furthermore, the use of the active ingredient dichloro-mehtylendiphosphonic acid or the use of a physiologically well-tolerated salt thereof in combination with microcrystalline cellulose as the pharmaceutical excipient is also subject of the invention, in order to produce a tablet with an improved bioavailability, preferably in the form of a tablet of

customary size with double efficacy as compared to the currently available customary capsule.

According to the invention, the tablets are produced by the customary method, inasmuch as, before the pressing of the tablet, its mass is made into a suitable granule form by the use of granulation methods (dry, wet, spray granulation). For the standard production of the administration form, the desired amount of the active ingredient is mixed with approximately 4% - 8% weight of the filling excipients in a dry form and is granulated with a customary excipient that has binding activity properties, such as corn starch or with only water. In addition, other procedures, such as compacting, can be used. Following the granulation step of the process, the produced granulate is added to and mixed together with 5% - 15% weight of microcrystalline cellulose, up to 6% weight of lubricant and up to 3% weight of disintegrates in a commercially available mixing machine. After the mixing of these ingredients, the granulate is pressed into tablet form, or, if necessary before pressing, has been sprayed with a fragrance containing solution and has been stored for the invading of this solution. The finished tablet can also be coated with a film designed to improve its taste.

The dosage indications in the following examples correlate to the content of clodronic acid (MW = 244.9). For the calculation in relation to the content of disodium-clodronate, water-free (MW = 288.9), the calculation factor is approximately 1.18, and in the case of the tetrahydrate (MW = 360.9) is approximately 1.47.

Example 1:

Tablets with an active ingredient content of 440 mg of clodronic acid:

a) The following table outlines the production of a batch of 200,000 tablets with an active ingredient content of 440 mg of clodronic acid (corresponding to 520 mg of sodium clodronate, water-free, and 650 mg of sodium clodronate tetrahydrate):

Pos. 1:	Clodronic acid disodium tetrahydrate	129,945.4 g
Pos. 2:	Corn starch	3,900.0 g
Pos. 3:	Talcum	5,980.0 g
Pos. 4:	Sodium carboxymethyl starch	2,654.6 g
Pos. 5:	Magnesium stearat	520.0 g
Pos. 6:	Microcrystalline cellulose	15,600.0 g
	Batch Weight:	158,600.0 g

The excipients from Positions 1 through 3 are granulated. The excipients from Positions 4 through 6 are subsequently added to and mixed with this granulate, and the resulting mixture is pressed into tablet form by the appropriate machinery. The yield of tablets from the original 200,000 pressed that are optically considered to be used is 177,275 (88.6 %).

b) By the use of the water-free form of sodium clodronate, the following composition of the pharmaceutical mixture is analogous to Example 1a:

Pos. 1:	Clodronic acid disodium tetrahydrate	104,000.0 g
Pos. 2:	Corn starch	3,121.3 g
Pos. 3:	Talcum	4,786.0 g
Pos. 4:	Sodium carboxymethyl starch	2,124.6 g
Pos. 5:	Magnesium stearat	416.2 g
Pos. 6:	Microcrystalline cellulose	12,485.3 g
	Batch Weight:	126,933.4 g

The production of the granulated batch weight and the tablet mass is analogous to Example 1a).

The following table outlines the composition of the tablet core, assuming a 440 mg dosage form:

Sodium clodronate x $4H_20$	649.727 mg
Talcum	29.90 mg
Corn starch	19.50 mg
Microcrystalline cellulose	78.00 mg
Sodium carboxymethyl starch	13.273 mg
Magnesium stearat	2.6 mg
Weight of Tablet/mg:	793.0 mg

The tablets are particularly suitable for the daily administration of two tablets, thereby replacing the customary four capsules of Ostac™.

Example 2:

Tablets with an active ingredient content of 509 mg of clodronic acid:

The production of tablets containing 509 mg is analogous to Example 1 for a production batch of 200,000 tablets with an active ingredient content of 509 mg of clodronic acid (corresponding to 600 mg of sodium clodronate, water-free, and 750 mg of sodium clodronate tetrahydrate) per tablet.

Pos. 1:	Clodronic acid disodium tetrahydrate	150,000 g
Pos. 2:	Corn starch	4,500 g
Pos. 3:	Talcum	6,900 g
Pos. 4:	Sodium carboxymethyl starch	3,063 g
Pos. 5:	Magnesium stearat	600 g
Pos. 6:	Microcrystalline cellulose	18,000 g
	Batch Weight:	183,063 g

The following table outlines the composition per tablet core, assuming a 509 mg dosage form:

Sodium clodronate x $4H_2O$	749.685 mg
Talcum	34.50 mg
Corn starch	22.50 mg
Microcrystalline cellulose	90.00 mg
Sodium carboxymethyl starch	15.315 mg
Magnesium stearat	3.0 mg
Weight of Tablet/mg:	915.0 mg

The tablets are particularly suitable for the daily administration of two tablets, thereby replacing the customary four capsules of Ostac™.

Example 3:

Tablets with an active ingredient content of 678 mg of clodronic acid.

The production is analogous to Example 1 for a production batch of 100,000 tablets with an active ingredient content of 678 mg of clodronic acid (corresponding to 800 mg of sodium clodronate, water-free, and 1,000 mg of sodium clodronate tetrahydrate) per tablet.

Pos. 1:	Clodronic acid disodium tetrahydrate	99,958 g
Pos. 2:	Corn starch	3,000 g
Pos. 3:	Talcum	4,600 g
Pos. 4:	Sodium carboxymethyl starch	2,042 g
Pos. 5:	Magnesium stearat	400 g
Pos. 6:	Microcrystalline cellulose	12,000 g
	Batch Weight:	122,000 g

The following table outlines the composition per tablet core, assuming a 678 mg dosage form:

Sodium clodronate x $4H_2O$	1,000.0 mg
Talcum	46.0 mg
Corn starch	30.0 mg
Microcrystalline cellulose	120.00 mg
Sodium carboxymethyl starch	20.42 mg

Magnesium stearat	4.0 mg
Weight of Tablet/mg:	1,220.0 mg

The tablet produced in Example 3 replaces approximately three capsules of Ostac™.

Example 4:

Tablet with an active ingredient content of 220 mg of clodronic acid.

The production is analogous to Example 1 for a production batch of 300,000 tablets with an active ingredient content of 220 mg (corresponding to 260 mg of sodium clodronate, water-free, and 325 mg of sodium clodronate tetrahydrate) of clodronic acid per tablet.

Pos. 1:	Clodronic acid disodium tetrahydrate	97,459 g
Pos. 2:	Corn starch	2,925 g
Pos. 3:	Talcum	4,485 g
Pos. 4:	Sodium carboxymethyl starch	1,992 g
Pos. 5:	Magnesium stearat	390 g
Pos. 6:	Microcrystalline cellulose	11,700 g
	Batch Weight:	118,951 g

The following table outlines the composition per tablet core, assuming a 220 mg dosage form:

Sodium clodronate x $4H_2O$	324.864 mg
Talcum	14.95 mg
Corn starch	9.75 mg

Microcrystalline cellulose	39.0 mg
Sodium carboxymethyl starch	6.64 mg
Magnesium stearat	1.30 mg
Weight of Tablet/mg:	396.5 mg

The tablets are particularly suitable for a daily administration of four tablets, and eight tablets per day in more severe cases, replacing the customary Ostac™ capsules with a total weight of 550 mg when produced with sodium clodronate tetrahydrate.

Example 5:

Tablets with an active ingredient content of 254 mg of clodronic acid:

The production is analogous to Example 1 for a production batch of 300,000 tablet with an active ingredient content of 254 mg (corresponding to 300 mg of sodium clodronate, water-free, and 375 mg of sodium clodronate tetrahydrate) of clodronic acid per tablet.

Pos. 1:	Clodronic acid disodium tetrahydrate	112,452 g
Pos. 2:	Corn starch	3,375 g
Pos. 3:	Talcum	5,175 g
Pos. 4:	Sodium carboxymethyl starch	2,298 g
Pos. 5:	Magnesium stearat	450 g
Pos. 6:	Microcrystalline cellulose	13,500 g
	Batch Weight:	137,337 g

The following table outlines the composition per tablet core, assuming a 254 mg dosage form:

Sodium clodronate x $4H_2O$	374.84 mg
Talcum	17.25 mg
Corn starch	11.25 mg
Microcrystalline cellulose	45.0 mg
Sodium carboxymethyl starch	7.66 mg
Magnesium stearat	1.50 mg
Weight of Tablet/mg:	457.5 mg

The tablets are particularly suitable for a daily administration of four tablets, and eight tablets per day in more severe cases, replacing the customary treatment of Ostac™ capsules with at total weight of 550 mg when produced with sodium clodronate tetrahydrate.

Example 6:

Twenty-four patients received the customary dose of two capsules of Ostac™ with an active ingredient content of 340 mg of clodronic acid per capsule. The serum concentration of clodronic acid was determined by standard methodology over a period of 16 hours. The resulting time course of serum concentration is detailed in Figure 1 (curve +).

The same patient group received a tablet with an active ingredient content of 440 mg of clodronic acid. When compared with the group receiving Ostac™, the time course of the median serum concentration of clodronic acid is nearly identical, i.e., bio-equivalent, to the administration of two capsules of Ostac™.

Patent Claims

1. Tablet with improved bioavailability of the active ingredient clodronic acid or of a physiologically tolerated salt thereof, a content of microcrystalline cellulose as a pharmaceutical auxiliary agent and a content of active substance of clodronic acid of 200 - 700 mg.

2. Tablet as claimed in claim 1 having a content of microcrystalline cellulose of 5 - 15 % in relation to the total weight of the tablet.

3. Tablet as claimed in claims 1 or 2 containing the active ingredient in the form of the disodium salt, preferably in the form of the tetrahydrate.

4. Tablet as claimed in claims 1 - 3 additionally containing a filler, in particular corn starch or talcum.

5. Tablet as claimed in claims 1 - 4 additionally containing a lubricant and a disintegrant.

6. Tablet as claimed in claim 5, wherein the lubricant is a physiologically tolerated salt of stearic acid, preferably magnesium stearate and the disintegrant is sodium carboxymethyl starch.

7. Tablet as claimed in claims 1 - 6 with an active substance content of clodronic acid of 420 - 460 mg and a total weight of the tablet of 750 - 850 mg, preferably 790 - 810 mg.

8. Tablet as claimed in claims 1 - 6 with an active substance content of clodronic acid of 500 - 530 mg and a total weight of the tablet of 870- 970 mg, preferably 900 - 950 mg.

9. Tablet as claimed in claims 1 - 6 with an active substance content of clodronic acid of about 200 - 270 mg and a total weight of the tablet of 350 - 500 mg.

10. Pharmaceutical pack containing 30 - 400 tablets as claimed in claims 7 or 8 for administration in a daily dose of one to three tablets, preferably two tablets.

11. Pharmaceutical pack containing 30 - 400 tablets as claimed in claim 9 for administration in a daily dose of four to eight tablets, preferably four tablets.

12. Use of microcrystalline cellulose as a pharmaceutical auxiliary agent for improving the bioavailability of the active ingredient clodronic acid or of a physiologically tolerated salt thereof.

13. Process for the production of a tablet as claimed in claims 1 - 9, wherein the active ingredient is mixed together with microcrystalline cellulose and if desired other pharmaceutical auxiliary agents or carrier substances according to known methods and pressed into tablets.

14. Process as claimed in claim 13, wherein the active ingredient is mixed with ca. 4 - 8 % by weight of the fillers, granulated with a conventional binding agent, 5 - 15 % by weight microcrystalline cellulose, up to 3 % by weight disintegrant and up to 6 % by weight lubricant are admixed in a conventional mixing apparatus with the granulate obtained in this way, the granulate is tabletted after the mixing process and if desired, the tablet core obtained is provided with a coating to improve the taste or to retard release of the active substance.

15. Process as claimed in claim 14, wherein the active substance is granulated with 6 - 7 % by weight fillers and 8 - 12 % by weight microcrystalline cellulose, up to 2 % by weight disintegrant and up to 3% by weight lubricant are admixed with the granulate.

16. Process as claimed in one of the claims 14 or 15, wherein corn starch and/or talcum is used as the filler.

17. Process as claimed in one of the claims 14 - 16, wherein magnesium stearate is used as the lubricant and sodium carboxymethyl starch is used as the disintegrant.

Summary

The invention concerns the production of a tablet with improved bioavailability of the active ingredient dichloromethylen-diphosphonic acid, or of a physiologically tolerated salt thereof, and a quantity of microcrystalline cellulose as a pharmaceutical excipient, the finished drug products containing these tablets, the use of the active ingredient dichloromethylendiphosphonic acid together with microcrystalline cellulose for the production of a tablet with improved bioavailability and the procedure for the production of the tablet.