The present invention relates to kits and methods for administering pharmaceutically active drugs and nutrients. More particularly, these kits are useful for continuous dosing schedule having once-weekly, twice-weekly, biweekly dosing, once-monthly and twice monthly dosing interval of bisphosphonate and a nutrient.
KITS FOR ADMINISTERING BISPHOSPHONATES

Field of the invention

The present invention relates to kits and methods for administering pharmaceutically active drugs and nutrients. More particularly, these kits are useful for continuous dosing schedule having once-weekly, twice-weekly, biweekly dosing, once-monthly and twice monthly dosing interval of bisphosphonate and a nutrient.

Background of the invention

Various bisphosphonic acid derivatives are well known for use in the treatment of diseases involving bone resorption. These bisphosphonic acids include alendronic acid, risedronic acid, pamidronic acid, ibandronic acid, clodronic acid, etidronic acid, tiludronic acid and other such therapeutic agents belonging to this class of compounds, and their salts and solvates.

In general patients taking bisphosphonates are instructed to take a daily calcium supplement. US 2004/0188316 disclosed that the bisphosphonate and the calcium supplement should not be taken at the same time. Because bisphosphonates chelate calcium, taking a unit dose of a bisphosphonate at the same time, calcium supplement interferes with the absorption of the bisphosphonate, thereby potentially decreases the efficacy of the bisphosphonate.

To avoid the problems associated with simultaneous dosing of both a bisphosphonate and a calcium-containing supplement, US 2004/0188316 discloses a kit for promoting the proper sequential oral administration of a bisphosphonate and accompanying nutrients, said kit comprising: (a) at least one unit dose of a bisphosphonate to be given continuously on a frequency of once a week, twice a week, once every two weeks, twice a month, or once a month; (b) at least one unit dose of a nutrient to be given subsequent to the active dose administration; and (c) a blister card individually and releasably containing the unit doses; wherein said unit doses of pharmaceutical active and nutrient are arranged horizontally or vertically in order of their use across the blister card.
The combination of bisphosphonate and nutrients, which are commercially available, include FOSAMAX® PLUS D marketed by Merck and ACTONEL® with CALCIUM marketed by Procter & Gamble approved for weekly dosage regimen.

FOSAMAX PLUS D is a single tablet containing 70mg of alendronic acid and 2800IU or 5600IU of cholecalciferol as active ingredients and excipients such as microcrystalline cellulose, anhydrous lactose, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidalsilicon dioxide, magnesium stearate, butylated hydroxy toluene, modified food starch, sodium aluminum silicate.

ACTONEL with CALCIUM is a co-package product containing 35 mg of risedronate and calcium carbonate tablets (equivalent to 500 mg elemental calcium) for daily dosing for the remaining 6 days of the week.

Many types of kits and containers are commercially available for dispensing various class of drugs. These containers are intended for dispensing dosages of the drug on a daily basis. See e.g., U.S. 5,265,728, EP 0 511 726 A2, WO 99/51214, U.S. 3,677,397, and U.S. 3,504,788, which describe dispensers for administering various drugs including oral contraceptives, on a continuous daily basis. However, none of these dispensers or kits are designed or intended for administering a drug according to a continuous schedule having a dosing interval of once weekly, i.e. for administering a unit dosage of drug once per week. When the drug is not for daily administration, particularly bisphosphonates which are to be administered for once-weekly, twice-weekly, biweekly and once-monthly, it may be confusing for the patient to remember which day the drug is to be taken and which leads into poor patient compliance.

US 5,366,965 discloses a method for treatment of osteoporosis in a patient, while minimizing the occurrence of gastrointestinal problems, said method comprising administering a bone resorption inhibiting polyphosphonate compound according to a schedule comprising at least two cycles. However, this patent does not disclose any specific kit containing polyphosphonate and nutrient.

EP 0 162 510 B1 discloses a kit for use in a regimen for treatment of osteoporosis, said regimen comprising one or more cycles whereby each cycle
consists of a 1 to 5 day bone activation period followed by a 10 to 20 day bone resorption inhibition period followed by a 30 to 100 day rest period.

The above prior art references discloses the administration of bisphosphonate according to cyclic dosage regimen.

US 6,978,894 and US 2001/0044427 discloses a kit comprising: (a) at least one unit dosage of a pharmaceutical active for administration according to a once weekly regimen, and (b) a card for administering said unit dosage.

In case of complicated dosage regimen such as administration of bisphosphonate and nutrient, wherein the patient has to take a unit dose of a bisphosphonate on a continuous schedule and a unit dose of a nutrient on the days in between the days of bisphosphonate, it is difficult for the patient to remember which day the drug or nutrient has to be taken. To improve the patient compliance, the inventors of the present invention have developed a kit for administering bisphosphonate and nutrient, in which the bisphosphonate is administered according to continuous dosing schedule having once-weekly, twice-weekly, biweekly dosing, once-monthly and twice monthly dosing interval, which can lead to greater patient compliance and maximum benefit from such treatment regimens.

**Objective of the invention**

Accordingly, the main objective of the present invention is to provide a kit for administering bisphosphonate according to continuous dosing schedule having once-weekly, twice-weekly, biweekly, once-monthly and twice monthly dosing interval and a nutrient.

**Summary of the invention**

Accordingly, the main embodiment of the present invention is to provide a kit comprising a blister card containing:

i) a unit dose of bisphosphonate according to a continuous schedule having dosing interval selected from once-weekly, twice-weekly, biweekly, and twice-monthly and
ii) at least six unit doses of nutrient for administration subsequent to bisphosphonate; wherein the bisphosphonate and nutrients are arranged in a circular shape across the blister card.

**Brief description of the Drawings**

Fig. 1, 2, 3, 4, 5 & 6 represents blister card a (bisphosphonate) and b (nutrient) arranged in circular shape.

**Detailed description of the invention**

In another embodiment, the blister card further comprises instructions for administering bisphosphonate and nutrient. Such instructions include order of use, when or how to take the dose.

In another embodiment of the present invention, bisphosphonate includes alendronate, risedronate, pamidronate, ibandronate, clodronate, etidronate, tiludronate and their pharmaceutically acceptable salts and solvates.

The unit dosage form according to the present invention may be in the form capsules, tablets, chewable tablets and the like, where the active ingredient can be combined with one or more pharmaceutically acceptable excipients such as binders, diluents, disintegrants, lubricants and/or glidants and the like prepared by direct compression, wet granulation or dry granulation.

In another embodiment, the amount of risedronate includes 35mg per week, 75mg two consecutive days per month or 150 mg per month; alendronate includes 70 mg and 35 mg per week; ibandronate includes 150 mg per month.

In another embodiment of the present invention nutrient includes calcium supplement and vitamin D and its derivatives that are to be administered on the days in between the days of bisphosphonate.

Suitable calcium supplement includes calcium carbonate, calcium citrate, calcium malate, calcium citrate malate, calcium gluconate, calcium lactate, dibasic calcium phosphate, and tribasic calcium phosphate and can be administered at doses of 400 to 1500 mg per day.
Suitable vitamin D and its derivatives include vitamin D₂ (ergocalciferol), vitamin D₃ include cholecalciferol and are administered at doses 1000IU to 10,000IU per day.

Continuous schedule means at regular specified intervals i.e. a continuous frequency of once a week i.e. that the bisphosphonate is given once a week for an unspecified period of time or as long as treatment is required.

Once-weekly dosage regimen means that a unit dosage of the bisphosphonate is administered once a week, i.e. one time during a seven-day period, preferably on the same day of each week. Biweekly dosage regimen means that a unit dosage of the bisphosphonate is administered once during a two week period, i.e. one time during a fourteen day period, preferably on the same day during each two week period. Twice-weekly dosing means that a unit dosage of the bisphosphonate is administered twice a week, i.e. two times during a seven day period, preferably on two consecutive days of the weekly period. Once monthly dosing means that a unit dosage of the bisphosphonate is administered once a month, i.e. one time during a thirty day period, preferably on the same day of each month. Twice monthly dosing means that a unit dosage of the bisphosphonate is administered twice in a month, i.e. two times during a thirty day period, preferably on two consecutive days per month.

Circular shape includes but not limited to oval, modified oval, circular and caplet shaped form.

The kits of the present invention are useful for administering bisphosphonate and nutrients on continuous basis. The kits comprise at least one unit dose of a bisphosphonate and at least one unit dose of a nutrient on a single blister card. In addition, dosage units of more than one week may be present on one card and more than one card may be packaged together.

In another embodiment of the present invention, the blister card optionally comprises memory card. Memory card includes but is not limited to a listing of the days of the week, numbering, illustrations, arrows, calendar stickers, reminder cards.

The preferred embodiment of the present invention provides a kit comprising a blister card containing:
i) a unit dose of risedronate according to a continuous schedule having dosing interval selected from once-weekly, twice-weekly, biweekly, and twice-monthly and
ii) at least six unit doses of calcium supplement for administration subsequent to risedronate; wherein the risedronate and calcium supplement are arranged in circular shape across the blister card.

In another preferred embodiment of the present invention provides a kit comprising a blister card containing:

i) a unit dose of risedronate according to a continuous schedule having dosing interval selected from once-weekly, twice-weekly, biweekly, and twice-monthly,

ii) at least six unit doses of calcium supplement for administration subsequent to risedronate; wherein the risedronate and calcium supplement are arranged in circular shape across the blister card and

iii) instructions for administering risedronate and calcium supplement.

In yet another preferred embodiment, the present invention also provides a kit comprising a blister card containing:

i) a unit dose of alendronate according to a continuous schedule having dosing interval selected from once-weekly, twice-weekly, biweekly, and twice-monthly and

ii) at least six unit doses of calcium supplement for administration subsequent to alendronate; wherein the alendronate and calcium supplement are arranged in circular shape across the blister card.

In yet another embodiment, there is provided a method of improving patient compliance for the treatment of post-menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis, Paget's disease, periodontal disease, bone fractures, osteoarthritis, and rheumatoid arthritis comprising providing a patient in need thereof the kit of the present invention.

In another embodiment, a blister card containing "a" (bisphosphonate) and "b" (nutrient) are arranged in circular shape where one cavity "a" represents a unit dose of bisphosphonate administered once monthly and twenty nine cavities of "b"
represents a unit dose of nutrient taken on subsequent days of bisphosphonate as shown in Fig. 1.

In another embodiment, a blister card containing two cavities "a" represents a unit dose of bisphosphonate administered once monthly on two consecutive days and twenty eight cavities of "b" represents a unit dose of nutrient taken on subsequent days of bisphosphonate as shown in Fig.2.

In yet another embodiment, a blister card containing one cavity "a" represents a unit dose of bisphosphonate administered biweekly and fourteen cavities of "b" represents a unit dose of nutrient taken on subsequent days of bisphosphonate as shown in Fig.3.

In yet another embodiment, a blister card containing one cavity "a" represents a unit dose of bisphosphonate administered once weekly and six cavities of "b" represents a unit dose of nutrient taken on subsequent days of bisphosphonate as shown in Fig.4 and Fig. 5.

In yet another embodiment, a blister card containing one cavity "a" represents a unit dose of bisphosphonate administered once weekly and twelve cavities of "b" represents two unit doses of nutrient for administering each day following bisphosphonate as shown in Fig.6.
Claims:

1. A kit comprising a blister card containing:
   i) a unit dose of bisphosphonate according to a continuous schedule having
dosing interval selected from once-weekly, twice-weekly, biweekly, and twice-monthly and
   ii) at least six unit doses of nutrient for administration subsequent to
bisphosphonate; wherein the bisphosphonate and nutrients are arranged in a circular
shape across the blister card.

2. The kit of claim 1, wherein the bisphosphonate includes alendronate,
risedronate, pamidronate, ibandronate, clodronate, etidronate, tiludronate and their
pharmaceutically acceptable salts and solvates.

3. The kit of claim 1, wherein the nutrient includes calcium supplement and
vitamin D.

4. The kit of claim 3, wherein calcium supplement includes calcium carbonate,
calcium citrate, calcium malate, calcium citrate malate, calcium gluconate, calcium
lactate, dibasic calcium phosphate, and tribasic calcium phosphate.

5. A kit comprising a blister card containing:
   i) a unit dose of risedronate according to a continuous schedule having dosing
interval selected from once-weekly, twice-weekly, biweekly, and twice-monthly and
   ii) at least six unit doses of calcium supplement for administration subsequent to
risedronate; wherein the risedronate and calcium supplement are arranged in circular
shape across the blister card.

6. A method of improving patient compliance for the treatment of post-
menopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis, disease-
induced osteoporosis, idiopathic osteoporosis, Paget's disease, periodontal disease,
bone fractures, osteoarthritis, and rheumatoid arthritis comprising providing a patient
in need thereof the kit of claim 1.
7. A kit according to claim 1 as shown in Figure 1.

8. A kit according to claim 1 as shown in Figure 2.

9. A kit according to claim 1 as shown in Figure 3.
10. A kit according to claim 1 as shown in Figure 4.

![Figure 4](attachment:image)

11. A kit according to claim 1 as shown in Figure 5.

![Figure 5](attachment:image)

12. A kit according to claim 1 as shown in Figure 6.

![Figure 6](attachment:image)
### A. CLASSIFICATION OF SUBJECT MATTER

INV. A61J1/03 A61J7/04 A61K31/66

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)
A61J A61K B65D

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

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

EPO-Internal, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
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<th>Relevant to claim No.</th>
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<td>Y</td>
<td>US 2 971 638 A (ALLISON CRAWFORD G ET AL) 14 February 1961 (1961-02-14) column 1, lines 56-58; figures 1,4</td>
<td>1-5</td>
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<td>A</td>
<td>US 3 483 845 A (HARTMAN MAURICE D JR) 16 December 1969 (1969-12-16) the whole document</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

1 Special categories of cited documents:
   
   1'A' document defining the general state of the art which is not considered to be of particular relevance.
   
   1'E' earlier document but published on or after the international filing date.
   
   1'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).
   
   1'O' document referring to an oral disclosure, use, exhibition or other means.
   
   1'P' document published prior to the international filing date but later than the priority date claimed.

'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.

'S' document member of the same patent family.

Date of the actual completion of the international search: 3 June 2009

Date of mailing of the international search report: 10/06/2009

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2 NL- 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer: Mammeri, Damya
INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 
   because they relate to subject matter not required to be searched by this Authority, namely:

   see FURTHER INFORMATION sheet PCT/ISA/210

2. ☒ Claims Nos.: 7-12
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

   see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.: 
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
Continuation of Box II.1

Claims Nos.: 6

Method claim 6

- either the method of improving patient compliance for the treatment includes the use of the medication and it is considered as a method of treatment by therapy. According to Rule 39.1(iv), no search nor preliminary written opinion have to be carried out on this subject-matter,
- either the method consists in providing a kit to a patient and it is therefore not clear how just giving a blister to a patient can improve the patient compliance to said treatment.

Continuation of Box II.2

Claims Nos.: 7-12

Dependent claims 7 to 12 contain references to the drawings. According to Rule 6.2(a) and PCT Guidelines 5.10, claims should not contain such references except where absolutely necessary, which is not the case here.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.
<table>
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