**Title:** USE OF NABUMETONE AGAINST CALCIUM DEPLETION

**Abstract**

The use of nabumetone in the manufacture of a medicament for the prophylaxis and/or treatment of disorders associated with calcium depletion in the bone.
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| AT  | Austria     | ES  | Spain     | MG  | Madagascar |
| AU  | Australia   | FI  | Finland   | ML  | Mali       |
| BB  | Barbados    | FR  | France    | MN  | Mongolia   |
| BE  | Belgium     | GA  | Gabon     | MR  | Mauritania |
| BF  | Burkina Faso| GB  | United Kingdom | MW  | Malawi |
| BG  | Bulgaria    | GN  | Guinea    | NL  | Netherlands |
| BJ  | Bonin       | GR  | Greece    | NO  | Norway     |
| BR  | Brazil      | HU  | Hungary   | PL  | Poland     |
| CA  | Canada      | IT  | Italy     | RO  | Romania    |
| CF  | Central African Republic | JP  | Japan     | SD  | Sudan      |
| CG  | Congo       | KP  | Democratic People's Republic of Korea | SE  | Sweden    |
| CH  | Switzerland | KR  | Republic of Korea | SN  | Senegal    |
| CI  | Côte d'Ivoire | LI  | Liechtenstein | SU* | Soviet Union |
| CM  | Cameroon    | LK  | Sri Lanka | TD  | Chad       |
| CS  | Czechoslovakia | LU  | Luxembourg | TG  | Togo       |
| DE* | Germany     | MC  | Monaco    | US  | United States of America |

+ Any designation of “SU” has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.
Use of nabumetone against calcium depletion

The present invention relates to a method for the treatment of disorders associated with calcium depletion in the bone and to a compound for use in such a method.

G.B. Patent 1,474,377 discloses the compound 4-(6'-methoxy-2'-naphthyl)-butan-2-one and in example 5, a process by which it can be prepared. The compound which is referred to herein by its common name, nabumetone, is described as possessing anti-inflammatory activity and is therefore useful in the treatment of arthritis.

It has now been surprisingly found that nabumetone also has potential therapeutic utility as a calcium reabsorption agent.

Accordingly, the present invention provides a method for the prophylaxis and/or treatment of disorders associated with calcium depletion in the bone in human or non-human animals, which method comprises administering an effective, non-toxic amount of nabumetone to human or non-human animals suffering from such a disorder.

The present invention also provides the use of nabumetone in the manufacture of a medicament for use in the prophylaxis and/or treatment of disorders associated with calcium depletion in the bone.

A nabumetone medicament, for use in the prophylaxis and/or treatment of disorders associated with calcium depletion in the bone may be prepared by admixture of nabumetone with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.
Examples of disorders associated with calcium depletion in the bone include osteoporosis, ricketts and calcium depletion in females associated with pregnancy.

Preferably, the medicament is in unit dosage form and in a form adapted for use in the medical or veterinariai fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of calcium depletion in bone.

The suitable dosage range for nabumetone depends on the nature of the calcium depletion and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

Nabumetone may be formulated for administration by any route, and examples are oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow release of nabumetone.

The medicaments may, for example, be in the form of tablets, dispersible tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The medicaments, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycerine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable
setting agents such as sodium lauryl sulphate.

Solid medicaments may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute nabumetone throughout those medicaments employing large quantities of fillers. When the medicament is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The medicament may also be in the form of an ingestible capsule, for example of gelatin containing nabumetone if desired with a carrier or other excipients.

Medicaments for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid medicaments may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Nabumetone may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the
medicaments may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi-dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

As mentioned hereinbefore, the effective dose of nabumetone depends on the nature of the calcium depletion in the bone, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 2000 mg of nabumetone and preferably will contain from 30 to 1000 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 750, 800 or 1000 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of nabumetone and be administered in multiples, if desired, to give the preceding daily dose.

Most preferably nabumetone compositions are in the form of 500 mg swallow tablets.

The present invention further provides a pharmaceutical composition for use in the prophylaxis and/or treatment of
-5-

disorders associated with calcium depletion in the bone which comprises an effective amount of nabumetone and a pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinbefore described.

5

The efficacy of nabumetone in treating calcium depletion in bone is illustrated by the following clinical study.

Clinical Data

Nine patients (3 males and 6 females) aged 48.2 years in average (range 25-66), with baseline values of urinary calcium excretion above the normal range, were treated with nabumetone, 1g/daily orally for 2 weeks. Nabumetone reduced urine calcium excretion in all subjects. The average reduction was 31%: from 365.8 mg/24 hrs. to 252 mg/24 hrs. (baseline and after 2 weeks respectively).

The change was statistically significant (P<0.005).

20 Urinary excretion of hydroxyproline was reduced in 8 out of 9 patents (5 had baseline values above the normal range).

The average reduction was 31.8%: from 25.7 mg/ml/hr. to 17.5 mg/ml/hr. (P<0.05).

25

Conclusion

This study suggests that nabumetone may be able to reduce the amount of bone resorption in patents with IH and may have a prophylactic role in hypercalciuric patients with high bone turnover who are candidates for developing osteoporosis.
Claims

1. The use of nabumetone in the manufacture of a medicament for the prophylaxis and/or treatment of disorders associated with calcium depletion in the bone.

2. The use of nabumetone according to claim 1 wherein the disorder is osteoporosis.

3. The use of nabumetone according to claim 1 wherein the disorder is rickets.

4. The use of nabumetone according to claim 1 wherein the disorder is calcium depletion in females associated with pregnancy.

5. A use according to any one of claims 1 to 4 wherein the medicament is adapted for oral administration.

6. A use according to any one of claims 1 to 4 wherein the medicament is adapted for parenteral administration.

7. A use according to any one of claims 1 to 4 wherein the medicament is adapted for topical administration.

8. A use according to any one of claims 1 to 4 wherein the unit dose medicament is in the range of 20 to 2000 mg.

9. A use according to any one of claims 1 to 4 wherein the unit dose of medicament is in the form of a swallow tablet containing 500 mg of nabumetone.

10. A method for the prophylaxis and/or treatment of disorders associated with calcium depletion in the bone in
human or non-human animals, which comprises administering an effective, non-toxic amount of nabumetone to a sufferer in need thereof.

5 11. A method according to claim 10, for the prophylaxis and/or treatment of osteoporosis in human or non-human animals, which comprises administering an effective, non-toxic amount of nabumetone to a sufferer in need thereof.

10 12. A method according to claim 10, for the prophylaxis and/or treatment of ricketts in human or non-human animals, which comprises administering an effective, non-toxic amount of nabumetone to a sufferer in need thereof.

15 13. A method according to claim 10, for the prophylaxis and/or treatment of calcium depletion in human or non-human females associated with pregnancy, which comprises administering an effective, non-toxic amount of nabumetone to a sufferer in need thereof.

20 14. A method according to claim 10 in which the nabumetone composition is adapted for oral administration.

15. A method according to claim 10 in which the nabumetone composition is adapted for parenteral administration.

16. A method according to claim 10 in which the nabumetone composition is adapted for topical administration.

30 17. A method according to claim 10 in which the unit dose of nabumetone is in the range of 20 to 2000 mg.

18. A method according to claim 10 in which the unit dose of nabumetone is in the form of a swallow tablet containing
500 mg of nabumetone.

19. A pharmaceutical composition for use in the prophylaxis and/or treatment of disorders associated with calcium depletion in the bone which comprises an effective amount of nabumetone and a pharmaceutically acceptable carrier.

20. A pharmaceutical composition according to claim 19 for use in the prophylaxis and/or treatment of osteoporosis.

21. A pharmaceutical composition according to claim 19 for use in the prophylaxis and/or treatment of rickets.

22. A pharmaceutical composition according to claim 19 for use in the prophylaxis and/or treatment of calcium depletion in females associated with pregnancy.

23. A pharmaceutical composition according to any one of claims 19 to 22 which is adapted for oral administration.

24. A pharmaceutical composition according to any one of claims 19 to 22 which is adapted for parenteral administration.

25. A pharmaceutical composition according to any one of claims 19 to 22 which is adapted for topical administration.

26. A pharmaceutical composition according to any one of claims 19 to 22 wherein the unit dose of nabumetone is in the range of 20 to 2000 mg.

27. A pharmaceutical composition according to any one of claims 19 to 22 wherein the unit dose of nabumetone is 500 to 35 mg and the composition is in the form of a swallow tablet.
**INTERNATIONAL SEARCH REPORT**

**I. CLASSIFICATION OF SUBJECT MATTER**

According to International Patent Classification (IPC) or to both National Classification and IPC

| Int.Cl.5 | A 61 K 31/12 |

**II. FIELDS SEARCHED**

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Classification Symbols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int.Cl.5</td>
<td>A 61 K</td>
</tr>
</tbody>
</table>

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

**III. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>La Clinica Therapeutica, volume 133, fasc. 6, no. 812, 30 June 1990, F. Catalano et al.: &quot;Analgesic and anti-inflammatory effect of nabumetone in osteo-articular diseases in the acute phase&quot;, pages 379-386, see abstract in English</td>
<td>1-27</td>
</tr>
<tr>
<td>A</td>
<td>Drugs, volume 40, suppl. 5, 1990, P. Münzel et al.: &quot;Efficacy and safety of nabumetone in 4541 elderly patients from a drug monitoring study&quot;, pages 62-64, see the whole article</td>
<td>1-27</td>
</tr>
<tr>
<td>A</td>
<td>Pharmatherapeutica, volume 3, no. 9, 1984, J. Gillgrass et al.: &quot;Nabumethone: a double-blind study in osteoarthrosis&quot;, pages 592-594, see the whole article</td>
<td>1-27</td>
</tr>
</tbody>
</table>

**IV. CERTIFICATION**

Date of the Actual Completion of the International Search: 31-10-1991

Date of Mailing of this International Search Report: 16.12.91

International Searching Authority: EUROPEAN PATENT OFFICE

Signature of Authorized Officer: [Signature]

*Special categories of cited documents:*
- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document but published on or after the international filing date
- **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 reasons (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other means
- **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

**Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

**&** document member of the same patent family
V. **OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE**

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

1. **Claim numbers**
   Authority, namely: [X]
   
   "Remark : Although claims 10-18 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition."

2. **Claim numbers**
   with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically: 

3. **Claim numbers**
   the second and third sentences of PCT Rule 6.4(a). 

VI. **OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

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 all searchable claims of the international application**

2. **As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the international application for which fees were paid, specifically claims:**

3. **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 claim numbers:**

4. **As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.**

**Remark on Protest:**

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.