



Office de la Propriété

Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2497340 C 2012/01/10

(11)(21) **2 497 340**

(12) **BREVET CANADIEN**
CANADIAN PATENT

(13) **C**

(86) Date de dépôt PCT/PCT Filing Date: 2003/09/03
(87) Date publication PCT/PCT Publication Date: 2004/03/18
(45) Date de délivrance/Issue Date: 2012/01/10
(85) Entrée phase nationale/National Entry: 2005/03/01
(86) N° demande PCT/PCT Application No.: US 2003/027603
(87) N° publication PCT/PCT Publication No.: 2004/022007
(30) Priorité/Priority: 2002/09/04 (US10/235,881)

(51) Cl.Int./Int.Cl. *A61K 8/55* (2006.01),
A61K 31/66 (2006.01), *A61Q 3/00* (2006.01)

(72) Inventeurs/Inventors:
ROSENBERG, E. WILLIAM, US;
SKINNER, ROBERT B., JR., US

(73) Propriétaires/Owners:
ROSENBERG, E. WILLIAM, US;
SKINNER, ROBERT B., JR., US

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : COMPOSITION ET PROCEDES DE TRAITEMENT D'ONGLES MOUS

(54) Title: COMPOSITION AND METHOD FOR TREATING SOFT NAILS

(57) Abrégé/Abstract:

A composition and method for treating soft nails, particularly soft fingernails, the composition including bisphosphonate, preferably alendronate sodium, in a vehicle effective for topical administration.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 March 2004 (18.03.2004)

PCT

(10) International Publication Number
WO 2004/022007 A1

(51) International Patent Classification⁷: A61K 6/00,
7/00, 7/04

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:
PCT/US2003/027603

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date:
3 September 2003 (03.09.2003)

Published:

— with international search report

(25) Filing Language: English

(48) Date of publication of this corrected version:

17 June 2004

(26) Publication Language: English

(15) Information about Correction:

see PCT Gazette No. 25/2004 of 17 June 2004, Section II

(30) Priority Data:
10/235,881 4 September 2002 (04.09.2002) US

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(71) Applicants and

(72) Inventors: ROSENBERG, E. William [US/US]; 6055
Sweetbriar Cove, Memphis, TN 38120 (US). SKINNER,
Robert, B., Jr. [US/US]; 347 Riverbluff Place, Memphis,
TN 38103 (US).

(74) Agents: MURTAUGH, John, P. et al.; Pearne & Gordon, LLP, 1801 East 9th Street, Suite 1200, Cleveland, OH 44114-3108 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,



WO 2004/022007 A1

(54) Title: COMPOSITION AND METHOD FOR TREATING SOFT NAILS

(57) Abstract: A composition and method for treating soft nails, particularly soft fingernails, the composition including bisphosphonate, preferably alendronate sodium, in a vehicle effective for topical administration.

1 COMPOSITION AND METHOD FOR TREATING SOFT NAILS

2 FIELD OF THE INVENTION

3 This invention relates to pharmaceutical compositions and more particularly to
4 pharmaceutical compositions and methods for treating soft nails such as fingernails and toenails
5 to make them harder.

6 DESCRIPTION OF THE RELATED ART

7 Nail softness is a widespread affliction affecting many humans and animals. Women
8 frequently complain about soft fingernails. Due to the general public's pervasive interest in
9 general well-being and physical appearance, much effort has been expended to find a means of
10 increasing the hardness of otherwise soft nails. Conventionally known nail hardening treatments
11 typically involve calcium and fluoride salts, ammonium hexafluoride phosphate, potassium
12 iodide and other more traditional applications. U.S. Pat. Nos. 5,478,551; 6,200,553; 5,478,551;
13 4,871,553; and 4,933,175, disclose compositions and methods for the treatment of soft nails.

14 The methods for treating nail softness disclosed in the above-cited patents have not been
15 sufficiently successful. Therefore, there is a need for an effective composition and method for
16 treating soft nails and increasing the hardness thereof.

17 SUMMARY OF THE INVENTION

18 The present invention provides a pharmaceutical composition for use in treating soft nails
19 to make them harder, said composition comprising bisphosphonate and a vehicle effective for
20 topical administration to a patient. The present invention also provides a method for treating soft
21 nails of a patient having soft nails tissues so as to make said soft nails harder, said soft nails
22 tissues comprising said soft nails, said method comprising the step of topically administering to
23 said soft nails tissues of said patient a composition comprising bisphosphonate and a vehicle
24 effective for topical administration to said patient, said bisphosphonate being in said vehicle.

1 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE
 2 INVENTION

3 As used herein and in the claims, "nails" means fingernails, toenails, claws, talons and
 4 hooves; "soft nail tissue" means a soft nail and the tissue surrounding or adjacent the soft
 5 nail; "patient" includes humans and animals. As used herein and in the claims,
 6 "bisphosphonate", "amino-bisphosphonate", "alendronate", "etidronate", etc. include the
 7 pharmaceutically acceptable salts and esters thereof. As used herein, parts are parts by weight
 8 and percents are weight percents unless otherwise indicated or apparent. When a preferred
 9 range such as 5-25 is given, this means preferably at least 5 and, separately and
 10 independently, preferably not more than 25. A nail-hardening agent is an agent for hardening
 11 nails.

12 The inventive composition comprises a nail-hardening agent dissolved, dispersed or
 13 carried in a vehicle effective for topical administration to a patient. As used herein and in the
 14 claims, a vehicle effective for topical administration to a patient includes creams, ointments,
 15 lotions, liniments, gels, solutions, suspensions, and pastes, as well as any other preparation
 16 that is pharmaceutically suitable for topical administration on human and/or animal skin and
 17 nails. Such vehicles, and their compositions and formulations, are known in the art. The
 18 inventive composition, comprising the nail-hardening agent and vehicle, can be provided or
 19 dispersed in a conventional manner, including sticks, sprays, aerosols, fluids, gels, creams,
 20 etc.

21 The inventive composition preferably has the formulation and ingredients as described
 22 below in Table 1. The nail-hardening agent should be present in a sufficient or effective
 23 weight percent effective to produce an effective nail-hardening result in the patient. All
 24 values in Table 1 are percentages, by weight. The inventive composition has the following
 25 preferred formulation.

26 Table 1.

27 INGREDIENT	PREFERRED WEIGHT PERCENT	LESS PREFERRED WEIGHT PERCENT	LESS PREFERRED WEIGHT PERCENT	LESS PREFERRED WEIGHT PERCENT	LESS PREFERRED WEIGHT PERCENT
28 Nail-Hardening 29 Agent	0.2	0.6 to 0.06	2 to 0.02	5 to 0.005	10 to 0.001
30 Vehicle	99.8	99.4 to 99.94	98 to 99.98	95 to 99.995	90 to 99.999

1 Less preferably, the composition is 0.0001 to 20 weight percent nail-hardening agent and
2 80 to 99.9999 weight percent vehicle. The composition comprises a pharmaceutically effective
3 weight percent of nail-hardening agent. The nail-hardening agent is bisphosphonate or a
4 bisphosphonate. More preferably, the nail-hardening agent is an amino-bisphosphonate. More
5 preferably, the nail-hardening agent is alendronate ((4-amino-1-hydroxybutylidene) bis-
6 phosphonate). Even more preferably, the nail-hardening agent is a pharmaceutically acceptable
7 salt of alendronate, such as alendronate sodium ((4-amino-1-hydroxybutylidene) bisphosphonic
8 acid monosodium salt trihydrate), available under the trademark FOSAMAX from Merck & Co.
9 in Whitehouse Station, New Jersey.

10 Other less preferred bisphosphonates may also be used as nail-hardening agents. Such
11 other bisphosphonates include etidronate (1-hydroxyethylidene bis-phosphonate), clodronate
12 (dichloromethylene bis-phosphonate), and pamidronate (3-amino-1-hydroxypropylidene bis-
13 phosphonate). A comprehensive study of known bisphosphonates is provided by Fleisch, H.,
14 Dregs 42 (6): 919-944, 1991. The bisphosphonates useful in carrying out the present invention
15 are, however, not intended to be limited to the above-mentioned compounds.

16 Preferably, the vehicle is hydrophilic ointment USP or other oil-in-water cream.
17 Alternatively, the vehicle can be an emulsion having water with enough oil to make it spread,
18 such as a vanishing cream base, or other oil and water or water and oil emulsion or emulsion
19 base. Other vehicles known in the art may be used, preferably those suitable for carrying water-
20 soluble components. A less preferred vehicle is polyethylene glycol.

21 As part of the vehicle, emollients, humectants, and other customary additives can be
22 included in conventional amounts. Other preferred vehicles for the inventive composition are
23 described as follows. For example, the vehicle can be an oil system, such as fat or oil or synthetic
24 fat such as petrolatum. Alternatively, the vehicle can be (1) a lotion, such as water and fat or oil
25 with an emulsifier and with or without ethanol; (2) a cream or cream base, which is generally the
26 same as a lotion but with less water and a higher viscosity and customarily a higher
27 concentration of the active ingredients ; (3) an ointment, which is generally the same as a cream
28 but without the water; it is nearly 100% oil or fat; (4) a gel, which is normally water only which
29 optionally can have a little ethanol but with no or substantially no fat or oil; a thickening agent is
30 added to provide gel viscosity; (5) a foam,

1 which is generally an emulsified type of cream; or (6) a solution or suspension of water or
2 ethanol or a mixture thereof, without fat or oil, and with an emulsifier as needed.

3 Alternatively, the composition can be provided as or in a liniment, a paste, a stick, an aerosol,
4 or other suitable form.

5 The vehicle of the composition comprises all ingredients and additives (including
6 optional and/or customary additives as described above) present in the composition other than
7 the nail-hardening agent. Therefore, it is understood that the weight percentage of the vehicle
8 of the composition, e.g., as listed in Table 1, will vary depending only on the weight
9 percentage of the nail-hardening agent in the composition.

10 The ingredients of the composition or formulation are blended and combined in a
11 conventional manner to provide the inventive composition as described above.

12 The inventive composition is applied in a conventional manner to a human's or
13 animal's nail tissue such as fingernails, toenails, claws, talons, hooves, etc. It is rubbed onto
14 the nail and onto and into the flesh and tissues surrounding the nail, particularly where the
15 nail emerges from the flesh. Preferably, the composition is applied to the nail tissue
16 according to a periodic regime (e.g. daily, weekly, etc.) for a period of time sufficient to
17 harden or increase the hardness of the previously soft nails. For example, the inventive
18 composition is preferably applied about or at least once daily, twice daily, three times daily,
19 four times daily, once weekly, twice weekly, three times weekly, or four times weekly, less
20 preferably some other suitable interval. The treatment should be applied when the nails are
21 soft or not sufficiently hard for the desires or needs of the patient and should be continued
22 until the desired result is achieved.

23 The following Examples 1-3 further illustrate various aspects of the invention.

24 EXAMPLE 1

25 A 73 year old Caucasian woman has had soft fingernails for as long as she can
26 remember. She did not have osteoporosis and was in good health. Three months after twice
27 daily applications of a 0.2% alendronate ointment (hydrophilic ointment USP vehicle) to the
28 skin around her fingernail folds, the nails were visibly harder. Six months later, they were
29 very hard and have remained so for one year with continued twice daily applications of the

1 alendronate ointment.

2 EXAMPLE 2

3 A 59 year old man developed very soft, troublesome fingernails after beginning to
4 take acitretin 25mg/day as a treatment for his psoriasis. He began twice daily applications of
5 0.2% alendronate ointment (polyethylene glycol vehicle) to the skin around his fingernail
6 folds while continuing to take acitretin. After three months of using the alendronate
7 ointment, his nails were no longer too soft or troublesome.

8 EXAMPLE 3

9 A 76 year old retired physician and his 60 year old wife both were troubled by soft
10 fingernails. Both were in otherwise good health and did not have osteoporosis. Twice daily
11 applications of 0.2% alendronate ointment (polyethylene glycol vehicle) had improved both
12 of their fingernails after four months of use.

13 The results of Examples 1-3 were surprising and unexpected.

14 Although the preferred embodiments have been described, it is understood that
15 various modifications may be resorted to without departing from the scope of the invention a
16 disclosed and claimed herein.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in treating soft nails to make them harder, said composition comprising one or more bisphosphonates and a vehicle effective for topical administration to a patient, said one or more bisphosphonates being in said vehicle.
2. The composition of claim 1, wherein said composition is 0.0001 to 20 weight percent said one or more bisphosphonates.
3. The composition of claim 1, wherein said composition is 5 to 0.005 weight percent said one or more bisphosphonates.
4. The composition of claim 1, wherein said vehicle comprises water and oil.
5. The composition of claim 1, wherein said one or more bisphosphonates is an amino-bisphosphonate.
6. The composition of claim 1, wherein said one or more bisphosphonates is alendronate.
7. The composition of claim 1, wherein said one or more bisphosphonates is a salt of alendronate.
8. The composition of claim 1, wherein said one or more bisphosphonates is alendronate sodium.
9. The composition of claim 1, wherein said vehicle is hydrophilic ointment USP.
10. The composition of claim 1, wherein said composition is 2 to 0.02 weight percent said one or more bisphosphonates.
11. A method for treating soft nails of a patient having soft nails tissues so as to make said soft nails harder, said soft nails tissues comprising said soft nails, said method comprising the step of topically administering to said soft nails tissues of said patient a composition comprising one or more bisphosphonates and a vehicle effective for topical administration to said patient, said one or more bisphosphonates being in said vehicle.
12. The method of claim 11, wherein said patient is a human.
13. The method of claim 11, wherein said composition is 0.0001 to 20 weight percent said one or more bisphosphonates.

14. The method of claim 11, wherein said composition is 5 to 0.005 weight percent said one or more bisphosphonates.
15. The method of claim 11, wherein said vehicle comprises water and oil.
16. The method of claim 11, wherein said one or more bisphosphonates is an amino-bisphosphonate.
17. The method of claim 11, wherein said one or more bisphosphonates is alendronate.
18. The method of claim 11, wherein said one or more bisphosphonates is a salt of alendronate.
19. The method of claim 11, wherein said one or more bisphosphonates is alendronate sodium.
20. The method of claim 11, wherein said vehicle is hydrophilic ointment USP.
21. The method of claim 11, wherein said composition is 2 to 0.02 weight percent said one or more bisphosphonates.