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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 03/084552 A1

(51) International Patent Classification[7]: A61K 33/22, 35/78, A61P 15/02 // (A61K 35/78, 33:22)

(21) International Application Number: PCT/IT03/00200

(22) International Filing Date: 2 April 2003 (02.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
RM2002A000192 8 April 2002 (08.04.2002) IT
RM2002A000612 5 December 2002 (05.12.2002) IT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, 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, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(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).

Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, 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, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, 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)*

Published:

— *with international search report*

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.

WO 03/084552 A1

(54) Title: COMPOSITION FOR THE TOPICAL TREATMENT OF VULVOVAGINITIS AND MYCOSES

(57) Abstract: Composition for the treatment of vulvovaginitis and other cutaneous mycoses, comprising bergamot and boric acid in appropriate percentages. The bergamot-boric acid composition has a synergetic effect because it allows to lower the amount of boric acid (which is toxic at high percentage ratios) without reducing the efficacy of the active principles (bergamot and boric acid). The invention further discloses administration means for the treatment of these kinds of mycoses, which are not limited to pessaries (treatment of vulvovaginitis), and further, it discloses some additives of the compound which are included in said administration means.

COMPOSITION FOR THE TOPICAL TREATMENT OF VULVOVAGINITIS AND MYCOSES

Technical Field

The present invention relates to the use of a mixture of boric acid and bergamot as a specific antimycotic for vulvovaginitis and for acute, chronic, and relapsing cutaneous mycoses. In particular, the invention refers to the confection of pessaries that contain two active principles, in certain percentages.

Moreover, the present invention more generally relates to a new use, a new dosage and new exhibition pathways related to pharmaceutical forms, in order to obtain a better utilisation, exhibition, and a lower toxicity of boric acid in association with the bergamot extract, in the eradication of mycotic vulvovaginitis and of cutaneous mycoses in general.

Background Art

The global incidence of mycotic vaginal infections has recently noticeably increased. The Candida-induced infections are the second more common cause of vaginitis. Among the various species of Candida, the most common one is the Candida Albicans.

In the treatment of vulvovaginitis induced by Candida Albicans, several medicines are used (nystatin, azole derivatives, etc.), but in any case a considerable number of patients is subject to frequent relapses. Moreover, infections caused by strains that are resistant to common therapies, are more and more frequent, and in the vaginal secretion of these patients it is was possible to isolate the Torulopsis glabrata, in addition to mutated forms of C. Albicans.

Conventional antimycotic treatments for the latter forms of disease, are less effective "in vitro", especially in the case of T. Glabrata, and clinical studies confirm their relative ineffectiveness.

Recent studies have reported a percentage of success exceeding 90%, when using boric acid compounds in the therapy of vulvovaginitis induced by C. Albicans.

The bactericide and bacteriostatic properties of boric acid have been known for a long time, but their therapeutic use for mycotic infections has been proposed only after several years, following studies performed "in vitro", which demonstrated the antimycotic action on C.Albicans of boric acid at 4%.

Boric acid has successively been used thereafter, in the treatment of certain types of candidosis that were resistant to conventionally employed antimycotic therapies.

However, its action directly depends on the concentration employed in its use. Very high concentrations are more effective, but their drawback is a relative loco-regional toxicity and systemic toxicity, which have limited their diffusion for what concerns the common use.

Although boric acid is effective from the therapeutic point of view, as an antiseptic agent, its safety is disputed - due to the above mentioned toxic effects - in case of accidental ingestion of a commonly used solution thereof, or in case of chronic topical exposure to its oily alcoholic preparations. Accidental ingestion may occur because the boric acid solution is colourless, odourless and indistinguishable from water if it is stored in unlabeled bottles.

Boric acid more easily penetrates the inflamed and damaged cutis or mucosa, than it penetrates the healthy cutis. In case of an aqueous solution, the absorption of boric acid by the cutis (of the vulva) may be neglected, and the amount of boric acid for unit dosis, which is used in the preparations that are generally proposed and specifically suggested by the present invention, is in any case extremely lower than the lethal dosis for an adult (which is reported to be greater than 30 g/day).

Recent clinical tests show that boric acid, by itself, presented in a vaginal pessary, is effective and does not give rise to loco-regional toxicity and/or systemic toxicity, apart from very exceptional cases. Keller-Van-Slvke et al. have treated 400 mycotic patients with boric acid, obtaining a successful percentage of 90%. A more accurate

study, which used a double-blind technique, has been performed in order to evaluate the effectiveness and safety of boric acid and nystatin. Thirty days after treatment, the patients that received boric acid showed a success ratio of 72%, while those which received nystatin showed a success ratio of 50% (p=0.02). Jovanovic et al. have compared the effectiveness of antimycotic preparations against boric acid. Boric acid is - in 98% of all cases - effective in eliminating the symptoms, in contrast with other antimycotics, which are effective in 52% of the tests. The cited authors have however used high doses of boric acid (600 mg/day of gel for 2 weeks). For external use, as a preparation, boric acid is normally dissolved in water or vaseline at V/V percentages that vary in the interval from 3 to 5%.

Disclosure of Invention

The association of boric acid and bergamot, for intra vaginal preparations, allows to use even lower amounts of boric acid, for the same effectiveness, thereby obtaining an ingenuous and useful opportunity for the eradication of mycotic infections induced by C.Albicans, tropical fungi and/or mycetes that are intrinsically resistant to common therapies.

The boric acid in association with bergamot represents a new compound obtained by means of appropriate mixtures of these two substances.

Disclosure of Preferred Embodiments

According to the present invention, it has been determined the "in-vitro" effectiveness of bergamot oil, and of two of its derivatives, that is, defurocoumarinised extract and distilled extract, against 40 strains of Candida. This evaluation has similarly been conducted with each of said compounds in association with boric acid. The 40 strains that were considered, comprised: 19 Candida albicans, 13 C. glabrata, 4 C. krusei, 2 C. tropicalis, 1 C. parapsilosis, and 1 C. dubliniensis. Tests have been conducted using the method of micro-dilutions in a broth, by

adhering to the N.C.C.L.S. (National Committee for Clinical Laboratory Standard) standard, for sensitivity tests of yeast against antimycotic agents.

Briefly, for the bergamot natural oil, the defurocoumarinised extract of bergamot, and the distilled extract of bergamot, variable concentration values, from 10% down to 0.02% V/V, have been tested in a RPMI (1640 medium-Sigma Aldrich) culture medium. In the tests, which employed boric acid in association with the mentioned substances, the boric acid concentration was initially at the fixed value of 3%.

The results have shown – for the bergamot natural oil – an MIC_{90} (Minimal Inhibitory Concentration) referred to 24 hours, equal to 5%, which increased (when referred to 48 hours) to a value exceeding 10%; better values were obtained for the defurocoumarinised extract, for which the MIC_{90} - referred to 24 hours – was 2.5%, and 5% for 48 hours; finally, the distilled extract of bergamot had the lowest MIC_{90} values among those of the three tested substances, with values of 1.25% referred to 24 hours, and 2.5% referred to 48 hours.

The association of boric acid at 3% and each of the three substances mentioned above, gave for the latter an MIC_{90} value – for 24 and 48 hours alike –, which was less than 0.02%, thereby emphasising the antimycotic activity of the boric acid itself.

Thereafter, the activity of boric acid (taken alone) was studied, and this study has furnished values of MIC_{90} equal to 0.094, at 24 and 48 hours alike. Later tests, performed with sub-MIC concentrations of boric acid in association with different concentrations of each of the three above mentioned substances, have shown an evident synergistic effect.

These results have shown the efficacy of the natural extract of bergamot, and above all, of the defurocoumarinised and distilled extracts - representing derivatives thereof-, against all tested strains (the sensitivity "interval" was similar among the non-Albicans strains resistant to fluconazole and the sensitive C. Albicans strains); but the essential feature resides in the possibility of using small concentrations of

bergamot in association with small concentrations of boric acid, in order to reduce possible toxic effects thereof without reducing its efficacy at all.

Preferably, the above described chemical compound is prepared in the form of vaginal pessaries.

In the above description, the use of the defurocoumarinised or distilled extracts of bergamot in association with boric acid has been disclosed exclusively for gynaecologic applications, and specifically when these substances are presented as a vaginal pessary for the eradication of mycotic infections induced by C. Albicans, tropical mycetes and/or mycetes which are intrinsically resistant to the usual therapies. The present invention, according to a further aspect thereof, has shown that even generic mycoses may be cured by means of these active principles combined with each other. Obviously, although vaginal pessaries are very handy, they do not allow any dosage or application flexibility, since they do not provide for any other topical application nor for the splitting up (subdivision) of the pessary, which necessarily must maintain its rounded shape.

Therefore, a further aspect of the present invention provides for substantial improvements in the treatment of mycoses in general, so as to broaden the exhibition forms and the utilisation forms (means) of the aforesaid mixture, thereby modifying at the same time the respective dosages in order to obtain a versatile product, which may be more easily dosed and which, consequently, is less toxic.

Obviously, this enables a more versatile use and permits a more accurate and more appropriate dosage, according to the virulence, the extension and the location of the mycosis, which must no more be localised exclusively in the vagina for allowing a treatment by means of the above mentioned compounds, but may – instead – be treated even if it affects any region whatever of the skin or of the externally accessible mucosae.

The said compound may easily be prepared in the form of emulsions, pomades, ointments, creams, pastes, gels and foams, as exhibition means of the same

compound, so as to provide new and better means for administering the above specified active principles even externally of the vaginal region, and so as to extend their use to the whole topical sphere.

These new pharmaceutical means for topical administration, allow – besides a better handiness –, also a reduction in the dosis of the active principles contained in the medicine, which, for boric acid, may signify a decrease of up to 66% with respect to the above 3 %, reaching a percentage which starting from 1% does not - in any case - exceed 3%. In particular, the toxicity is reduced together with side effects and sensitisation effects.

Also, the bergamot oil contained in these new pharmaceutical administration means, may be present in doses that may vary from 0.1 to 1.2%, instead of the sole preferred 0.2% concentration that has been used above for the mycotic vulvovaginitis. By broadening in this manner the upper and lower limits of the useful ratio of said active principle, one prevents as much as possible any shortcomings due to toxicity and acute sensitisation.

Claims

1. A therapeutic compound for the treatment of mycotic vulvovaginitis and mycoses in general, characterised in that it contains boric acid and extract of bergamot as active principles, the percentage of boric acid being within the interval from 1% to 3% V/V, and the percentage of the extract of bergamot being within the interval from 0.1% to 1.2% V/V.

2. A compound according to claim 1, wherein the extract of bergamot is bergamot oil, or the defurocoumarinised bergamot derivative (Citrus bergamia), or the distilled bergamot extract.

3. A compound according to claim 2, that is specifically used for mycotic vulvovaginitis, wherein the boric acid percentage is about 3% V/V , and the percentage of bergamot oil, or of the defurocoumarinised derivative of bergamot, or of the distilled bergamot extract, is about 0.2%.

4. A compound according to claims 1 and 2, wherein the said compound is associated with dyes, dispersion agents, excipients, emulsifiers, and friction reducing agents, to form creams, ointments, emulsions, pomades, pastes, gels, and foams, that may be very easily handled and locally dosed on the whole surface of the cutis affected by an acute, chronic or relapsing mycosis , or else by a mycotic vulvovaginitis, thereby improving the administration, broadening the application field and reducing side effects.

5. A compound according to claim 3, presented in the form of a vaginal pessary, and containing excipients, dispersion agents, emulsifiers and/or friction reducing agents, such as to allow a correct and homogeneous dilution of the two active principles

therein, to obtain good handling properties, and a satisfactory consistence at ambient temperature, together with a satisfactory stability of the adequately sealed product.

INTERNATIONAL SEARCH REPORT

PCT/IT 03/00200

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K33/22 A61K35/78 A61P15/02 //(A61K35/78,33:22)

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)
IPC 7 A61K

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, PAJ, MEDLINE, BIOSIS, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 29112 A (MELMAN STEVEN A) 9 July 1998 (1998-07-09) page 3, line 4-20 page 4, line 3-10	1-5
A	US 2001/014314 A1 (HARBECK MARIE) 16 August 2001 (2001-08-16) page 2, paragraph 59 page 3 claim 2	1-5
A	US 4 735 358 A (SUO OSAMU ET AL) 5 April 1988 (1988-04-05) column 3, line 27-33 column 4, line 39-56	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 July 2003	15/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Peris Antoli, B

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 023 144 A (GREATHOUSE GLEN A ET AL) 27 February 1962 (1962-02-27) column 1, line 45,46,57-60,68-72 column 2, line 57-60	1-5
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