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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 September 2005 (22.09.2005)

PCT

(10) International Publication Number
WO 2005/087270 A1

(51) International Patent Classification[7]: A61K 45/06, 31/4196, 31/4166, 31/4168, 31/4174, 9/00, A61P 15/02, 31/04, 33/02

(21) International Application Number:
PCT/GB2004/003972

(22) International Filing Date:
17 September 2004 (17.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0405406.0 10 March 2004 (10.03.2004) GB

(71) Applicant *(for all designated States except US)*: **EDKO TRADING AND REPRESENTATION CO. LTD.** [TR/TR]; Eski Büyükdere Caddesi, Tahiraöa Çesme Sokak, Ayazaöa Ticaret Merkezi, N0: 11 Kat: 1, Maslak, Istanbul 34398 (TR).

(71) Applicant *(for GB only)*: **GOLDING, Louise** [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **EMBIL, Koral** [TR/TR]; Edko Trading and Representation Co. Ltd, Eski Büyükdere Caddesi, Tahiraöa Çesme Sokak, Tahiraöa Çesme Sokak, Ayazaöa Ticaret Merkezi, N0: 11 Kat: 1, Maslak, Istanbul 34398 (TR). **BAKTIR, Gul** [TR/TR]; Edko Trading and Representation Co. Ltd, Eski Büyükdere Caddesi, Tahiraöa Çesme Sokak, Tahiraöa Çesme Sokak, Ayazaöa Ticaret Merkezi, N0: 11 Kat: 1, Maslak, Istanbul 34398 (TR). **FIGUEROA, Ray** [US/US]; 4201 N Ocean Drive - 304, Hollywood, FL 33019 (US).

(74) Agents: **GOLDING, Louise** et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, 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, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (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.

(54) Title: ANTI-VAGINITIS COMPOSITIONS COMPRISING A TRIAZOLE

(57) Abstract: The invention provides pharmaceutical compositions for topical administration in treating vaginal infections, e.g. vaginitis. Such compositions comprise: W at least one triazole compound active against *Candida albicans,* preferably at least one such compound which is additionally active against one or more non- albicans *Candida* species, and (ii) at least one additional anti-vaginitis medicament, preferably an anti-fungal, anti-protozoal and/or anti-bacterial agent. Preferred compositions include as active agents is terconazole in combination with tinidazole and/or tioconazole. In a further aspect the compositions in accordance with the invention also include a bioadhesive agent, e.g. a mucoadhesive, to promote adhesion to the vaginal mucosa. The use of a bioadhesive may also provide for controlled, e.g. rapid and/or delayed (sustained), release of the active agents.

WO 2005/087270 A1

ANTI-VAGINITIS COMPOSITIONS

This invention concerns novel pharmaceutical compositions for combating primary and/or secondary vaginal infections. In particular, the invention is concerned with the treatment of mixed vaginal infections, e.g. the treatment of acute and recurrent vulvovaginal candidiasis, bacterial vaginosis, trichomonal vaginitis and/or their causative agents.

Vaginitis is most often caused by infection with *Candida albicans*, *Trichomonas vaginalis* or *Gardnerella sp*, either singly or mixed. Certain derivatives of imidazole and nitroimidazole are known to have anti-fungal, anti-bacterial and/or anti-protozoal activity and are often used to treat such conditions. Examples of such drugs include miconazole, clotrimazole and metronidazole which may be formulated for either oral or topical administration (e.g. as pessaries, vaginal tablets, creams, etc.). Other types of drugs used in treating vaginal infections include nitrofurfuryl derivatives and various antibiotics.

Compositions for topical administration, particularly pessaries, are widely known and used for treating vaginal infections. Such compositions may contain only a single active ingredient, e.g. metronidazole, however those containing two or more active ingredients are generally considered more suitable for the treatment of mixed infections. Topical formulations which contain a combination of actives are, for example, described in WO 97/44032 and include combinations such as metronidazole and miconazole nitrate.

Despite the good activity of those formulations presently used to treat vaginitis and related conditions, there still exists a need for alternative

formulations, in particular for those which can provide a broader spectrum of activity against all the common types of vaginal infection. We have now developed improved topical formulations which address this need, in particular formulations which exhibit an enhanced anti-vaginitis effect over those conventionally used.

The invention thus provides a pharmaceutical composition for topical administration comprising at least one triazole compound active against *Candida albicans*, preferably at least one such compound which is additionally active against one or more non-albicans *Candida* species, in combination with at least one additional anti-vaginitis medicament.

The composition should include at least one triazole compound active against *Candida albicans*. Since non-albicans *Candida* species are now thought to make up as much as 20% of fungal infections, it is preferred that such compounds should also be effective against at least one non-albicans *Candida* species. The advantage of formulations containing such compounds is that these are effective in treating a wider range of infections regardless of their causative agents. Other *Candida* species commonly associated with vaginal infections include *Candida Galbrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida lusitaniae*, *Candida krusei*, *Candida dubliniensis* and *Candida neoformans* and it is desired that the triazole agent should be active against one or more of these species, in addition to exhibiting activity against *Candida albicans*.

The triazole compound may be used in the form of the free base or as a pharmaceutically acceptable salt, for example the nitrate.

Examples of suitable triazole compounds for use in the invention include terconazole, itraconazole, fluconazole, voriconazole and ravuconazole. Of these, terconazole is preferred. It has a particularly broad

spectrum of activity and has been shown to be effective against *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida pseudotropicalis*, *Candida stellatoidea* and *Candida lusitaniae*. Terconazole has the further advantage that this does not kill useful *lactobacillus* microorganisms which form part of a healthy vaginal flora.

The use of a second anti-vaginitis medicament according to the invention also provides for a broader spectrum of activity against vaginal infections. This medicament may be any agent suitable for topical application in the treatment of vaginitis. Typically, this will exhibit anti-fungal, anti-bacterial or anti-protozoal properties (or any combination of these). The presence of a second medicament or combination of medicaments active against *Candida albicans* and/or *Trichomonas vaginalis* and/or *Gardnerella sp.* is particularly preferred.

Preferred formulations in accordance with the invention are those comprising at least one triazole compound as herein described, together with at least one anti-vaginitis medicament selected from the group consisting of the following agents:

(a) an anti-fungal compound, in particular an anti-fungal imidazole;

(b) an anti-protozoal compound, preferably a compound having both anti-protozoal and antibacterial activity, e.g. a nitroimidazole; and

(c) an anti-bacterial agent.

Anti-fungal compounds suitable for use in the invention include griseofulvin, nystatin, polymixin B, terbinafin and atovaquone (Meprone). Preferred anti-fungals are the imidazoles and pharmaceutically acceptable salts thereof. Suitable fungicidally active imidazole compounds include those active against *Candida albicans* such as tioconazole, butoconazole, miconazole (e.g. miconazole nitrate), ketoconazole, clotrimazole,

isoconazole, seperconazole, econazole, oxiconazole and sulconazole. Particularly preferred for use in the invention are tioconazole or butoconazole. These agents may also be used in the form of their pharmaceutically acceptable salts.

Anti-protozoal agents for use in the invention include Paromomycin, Diclazuril (Clinacox) and Letrazuril. Preferred anti-protozoals are those which are known to be active against *Trichomonas vaginalis*. Particularly preferred anti-trichomonal drugs are those which also have anti-bacterial activity, in particular against *Gardnerella sp* and other pathogens capable of causing vaginitis, e.g. anaerobic bacteria, group B and D streptococcus and/or pathogens causing other primary or secondary vaginal/genital infections. Examples of suitable anti-protozoal agents include tinidazole, metronidazole, ornidazole, secnidazole and nimorazole. Tinidazole is particularly preferred. These agents may also be used in the form of their pharmaceutically acceptable salts.

The anti-bacterial agent for use in the invention is preferably one which is active against *Gardnerella sp* and other pathogens capable of causing vaginitis, e.g. anaerobic bacteria, group B and D streptococcus and/or pathogens causing other primary or secondary vaginal/genital infections. Broad spectrum antibiotics such as pivampicillin or clindamycin may usefully be included. Other suitable anti-bacterial agents include chlorquinaldol, diiodohydroxyquinoline, chloramphenicole and spiramycin (rovamycin).

Especially preferred formulations according to the invention are those comprising two active medicaments, i.e. a single triazole compound in combination with one additional anti-vaginitis medicament (preferably an anti-fungal or anti-protozoal compound). For example, these may comprise terconazole (triazole) in combination with tioconazole, butoconazole, tinidazole,

metronidazole or ornidazole. The invention is particularly concerned with the use of a combination of terconazole (anti-fungal) and tinidazole (anti-protozoal and antibacterial).

Combinations of two or more (e.g. three or four, preferably three) active agents may also be used in the formulations herein described. These may include, for example, a single triazole compound together with an anti-fungal (e.g. an anti-fungal imidazole) and an anti-protozoal (e.g. an anti-protozoal nitroimidazole). One example of such a combination is that comprising terconazole, tioconazole and tinidazole.

The quantity of active medicaments may be readily determined by those skilled in the art and will depend on several factors, including the nature of the medicaments and of any other non-active components, the method of application, etc. In general, the triazole derivative(s) (e.g. terconazole) may be used in amounts of from 0.1 to 5.0% by weight, preferably from 0.4 to 1.6% by weight, e.g. about 0.8 wt.%. Terconazole is conveniently used in amounts of from 50 to 250 mg, preferably 50 to 200 mg, per pessary (in an overall pessary weight of 2500 mg), more preferably from 50 to 150 mg and suitably about 80 mg.

The second anti-vaginitis medicament(s) may be present in a total amount of from 0.5 to 10% by weight, preferably from 1 to 6% by weight, e.g. about 3 wt.%. Tinidazole is conveniently used in amounts of from 50 to 500 mg per pessary (in an overall pessary weight of 2500 mg), more preferably from 100 to 200 mg and suitably about 150 mg. Tioconazole may be used in similar amounts, e.g. about 100 mg (in an overall pessary weight of 2500 mg).

Particularly preferred combinations of agents for use in the invention are those which demonstrate enhanced (e.g. synergistic) activity against one or more causative agents of vaginal infections relative to the

use of any one of the agents alone. Synergism is considered to include any one of the following: an unexpectedly faster cure rate, cure time or symptom improvement (i.e. improvement in at least one sign or key symptom of vaginitis); a reduction in the relapse rate of any given type of vaginitis (i.e. the rate of reappearance of the infection after cessation of the medicament); a broader spectrum of activity; fewer and/or reduced local or systemic side effects; and reduced toxicity associated with the use of the combined formulation compared to the expected additive effect of each individual active ingredient.

In a further aspect the invention thus provides formulations as herein described in which the active agents are present in synergistically effective amounts. In this regard, the weight ratio of triazole compound(s) to the second anti-vaginitis medicament(s) will generally be in the range of from 1:10 to 1:0.2, preferably from 1:10 to 1:0.5, e.g. about 1:2.

A further advantage associated with the use of the combination of actives herein described is that these are believed to slow down the development of resistance against at least one of the active agents present in the formulations.

A lowering of the dose of one or more of the actives (either due to the reduction in resistance and/or synergistic action) may advantageously be achieved using the combinations herein described.

It is particularly advantageous to use one or more local anaesthetics in the compositions of the invention in order to alleviate the soreness associated with vaginitis. Examples of suitable anaesthetics include aptocaine, bupivacaine, butanilicaine, carticaine, cinchocaine, clibucaine, ethyl parapiperidinoacetyl-aminobenzoate, etidocaine, lidocaine (lignocaine), mepivacaine, oxethazaine, prilocaine, pyrrocaine, ropivacaine, tolycaine, vadocaine, benzocaine, pramoxine

and mixtures thereof. The anaesthetic may also be used in the form of a salt.

The local anaesthetic may be used in an amount of 0.1-10.0% by weight, preferably 1.0-7.0%. The local anaesthetic is preferably lidocaine and may be used in the form of its free base (for example in an amount of 1.0-3.0%, by weight, preferably about 1.5%) or a salt such as its hydrochloride, for example 1.5-4.0% by weight, preferably about 2%. The use of the anaesthetic at these low concentrations results in the compositions being well tolerated.

The compositions may be in the form of a pessary, gel, cream, tampon or foam containing the active medicaments. Preferably, the compositions take the form of a pessary or cream.

A conventional cream base may be used, e.g. containing oily or waxy materials such as liquid paraffin, white petroleum or cetyl alcohol, water and one or more surfactants to produce a water-in-oil emulsion. A bactericide such as benzalkonium chloride is conveniently present.

When provided in the form of pessaries, these comprise a pessary base containing the active medicaments and any local anaesthetics. The pessary base may be of any conventional material for vaginal administration such as glycerol/gelatin glyco-gelatin, macrogols (polyethylene glycols), natural, synthetic or semisynthetic hard fats, and fractionated palm kernel oil. Preferred materials are hard fats which consist mainly of mixtures of the triglyceride esters of the higher saturated fatty acids along with varying proportions of mono- and diglycerides. Special grades may contain additives such as beeswax, lecithin, polysorbates, ethoxylated fatty alcohols and ethoxylated partial fatty glycerides. Examples of suitable hard fats include the range of products sold under the trade name Witepsol (e.g. Witepsol S55, Witepsol W15) by

Dynamit Nobel, Slough, England, and those sold by Gattefossé (Westwood, N.J., USA) under the trade name Suppocire. Cocoa butter-based products which include theobroma oil may also be used.

Preferably, the compositions further include a surfactant to promote dispersal of the active components and to provide for continuous penetration of the active components into the mucosal folds.

The surfactant may be a cationic, non-ionic, anionic or amphoteric surfactant although non-ionic surfactants are preferred. Anionic surfactants include salts of long chain alkyl sulphonate esters such as sodium lauryl sulphate, sodium cetostearyl sulphate and sodium tetradecyl sulphate; salts of long chain carboxylic acids such as stearates.

Cationic surfactants include quaternary ammonium or pyridinium compounds such as benzalkonium chloride (a mixture of benzyl alkyl dimethyl chlorides, the alkyl chain ranging from C_8 to C_{18}), tetradecyltrimethyl ammonium bromide and cetylpyridinium chloride.

Amphoteric surfactants include lauryl 1-carboxy glycine and lecithins such as soya lecithin.

Non-ionic surfactants include glycol and glycerol esters such as glyceryl monostearate; macrogol esters and ethers such as cetomacrogol; sorbitan and mannitan esters such as sorbitan tristearate; and polyoxyethylene derivatives of such sorbitan esters, for instance polyoxyethylene (20) sorbitan mono-oleate.

The level of surfactant required in the pessary formulation will be readily determined by those skilled in the art and will depend on the specific surfactant and the nature of the pessary base; conveniently it is in the range 0.1 to 10 percent by weight, preferably 1 to 5 percent.

One or more wound healing or skin protectant agents may also be present in the compositions. These may be selected from demulcents, absorbents and emollients and

include dimethicone (demulcent), allantoin (absorbent), sucralfate and glycerin (absorbent, demulcent and emollient). Examples of other suitable emollients include cocoa butter, white petrolatum and shark liver oil. Dimethicone has been found to be particularly advantageous in facilitating healing of the vaginal mucosa and is therefore particularly preferred for use in the formulations herein described. Since a film of dimethicone permits the passage of oxygen molecules, this effectively allows the skin to breathe whilst acting to repel water. Through this mechanism, dimethicone can exert its skin protective properties, thereby reducing maceration and damage to the vaginal mucosa. Due to its surface active properties, dimethicone is also believed to facilitate the spread of the active components around and into the folds of the vaginal mucosa where causative organisms of vaginitis tend to bury themselves (this is thought to be a significant factor in the high recurrence rates for vaginal infections).

It is also proposed that the formulations might provide for delayed (sustained) release of one or more of the active agents. This may, for example, be achieved using any of the methods described in WO 97/44032, the entire contents of which are incorporated herein by reference. A preferred system may comprise a delayed (sustained) release agent which provides for continuous delivery of the active medicament(s) over time. In general, the delayed (sustained) release of one or more of the active agents can be expected to affect, preferably reduce, the degree of systemic absorption of at least one active agent thereby providing reduction of any systemic side effect/toxicity profile. Dimethicone is particularly suitable for use in this regard.

In order to counter the inflammation and itching associated with vaginitis, it may be beneficial to

include an anti-inflammatory and/or anti-pruritic agent such as hydrocortisone, hydrocortisone acetate, methylprednisolone acepronate, betamethasone valerate, or the like, a weak topical steroid and/or chamomille.

Boric acid and/or lactic acid may also advantageously be included as a further active ingredient and may be used to adjust the pH of the final formulation close to that found in the vaginal mucosa under normal physiological conditions, e.g. in the range 3.8 to 4.2. The compositions may also include chlorophyll as a deodorant.

Other active components which may be present include estrogens such as estriol, conjugated estrogens and promestrien. Anti-viral agents such as acyclovir, penciclovir, trifluridine, afovirsen, arildone, brivudine, 1-docosanol, edoxudine, ganciclovir, idoxuridine, moroxydine, tromantadine and valacyclovir may also be present.

Conventional microbicides capable of preventing HIV and/or other sexually transmitted infections may also be included in the formulations herein described. Examples of such agents include those which disrupt or otherwise disable HIV, such as surfactants, e.g. menfegol, benzalkonium chloride, docosanol, C31G (Savvy, nonoxynol-9, sodium cholate), polybiguanides, sodium dodecyl sulphate; antibiotics, e.g. gramicidin, magainins, defensins, protegrins; acidifying agents, e.g. Buffer Gel, Acidform, Lactobacillus crispatus; oxidising agents, e.g. chlorhexidine, povidone iodine, hydrogen peroxide/peroxidase gel; antibodies, e.g. anti-HIV antibodies; long-chain anionic polymers, e.g. cellulose acetate phthalate; reverse transcriptase inhibitors, e.g. UC-781, loviride, tenofovir; agents which block HIV attachment/fusion, such as long-chain anionic polymers, e.g. dextrin-2-sulphate, naphtalene sulphonate polymer (Pro 2000), carrageenan, polystyrene sulphonate, cellulose sulphate, cellulose acetate

phthalate, polymeric dimandelic acid ether (SAMMA); dendrimers, e.g. SPL7013, HIV-binding peptides/proteins, e.g. cyanovirin; T-20; lipid membrane modifiers, e.g. beta-cyclodextrin; anti-CD4 antibodies, e.g. B-12; agents which prevent intracellular HIV replication (e.g. nepirapine 16); reverse transcriptase inhibitors (e.g. UC-781, loviride, tenofovir); and plant products (e.g. Praneem, gossypol, pokeweed antiviral protein), etc.

In a further aspect of the invention the compositions herein described may be formulated for rapid or delayed (sustained) release, or preferably both, of the local anaesthetic(s). Any suitable method, such as those described in WO 97/44032, may be used to provide rapid and/or delayed release of this substance(s).

In a preferred system, rapid and delayed (sustained) release may be achieved using a local anaesthetic in two or more different forms having different solubilities, for example in hydrophobic and hydrophilic forms. An anaesthetic such as lidocaine may, for example, be provided in both salt and free base forms which result in differing rates of release of the anaesthetic, thus providing both immediate and sustained action. Such compositions can for example contain 0.1-3.5% (preferably about 2.0%) by weight of lidocaine HCl and 0.1-3.0% (preferably about 1.5%) by weight of lidocaine. The total amount of lidocaine and its hydrochloride is preferably not more than 5% by weight. The relative amounts of the free base and the salt used can be varied depending on the nature of the pessary or cream base, in particular according to the lipophilic and hydrophilic properties of the base. However, in general the composition can contain 20-80% of the free base form of the anaesthetic and 80-20% of the salt form, on the basis of the total weight of the two forms.

A lidocaine salt such as the hydrochloride can be included in a pessary base (e.g. a cocoa butter-based

material) as a suspension or, preferably, dissolved in the base with the aid of a surfactant (particularly a non-ionic surfactant such as referred to above). The free base can be dissolved directly in the pessary base.

Similar techniques can be used to include the anaesthetics in a cream formulation. Thus the salt form can be mixed with the aqueous phase ingredients of the cream and the free base form with the oily phase ingredients. The two phases can then be mixed together to form a cream emulsion containing the two forms of the anaesthetic in the different phases. Since it is possible to vary the lipophilicity of the oil phase, the release rate of the lidocaine from this phase can therefore be adjusted to enable a slow but continuous release of lidocaine from the oil phase. Conversely, the hydrophilicity and the pH of the aqueous phase can be changed to vary the release of lidocaine from the aqueous phase. In this manner it is possible to tailor the release rate profiles of lidocaine from the two phases so that they complement each other, resulting in prolonged release of lidocaine from the cream base containing the emulsion of the two phases.

In a preferred embodiment, the pharmaceutical compositions herein described may contain a bioadhesive agent, in particular a mucoadhesive agent, to promote adhesion and thus prolonged contact of the composition to the mucosa membranes, e.g. the vaginal epithelium. This has the desired effect of retaining sufficient amounts of the active agents at the target site for sufficient time to be effective. For example, the formulations may remain attached to the epithelial surfaces for a period of at least about 24 hours. In some cases, the use of a bioadhesive may also provide for controlled, e.g. delayed or sustained, release of the active agents from the formulation which can reduce the need for frequent administration. Compositions containing a bioadhesive agent are novel and form a

further aspect of the invention.

Viewed from a further aspect the invention thus provides a pharmaceutical composition comprising at least one triazole compound active against *Candida albicans*, in combination with at least one additional anti-vaginitis medicament, wherein said composition further comprises at least one physiologically tolerable bioadhesive (e.g. a mucoadhesive).

Bioadhesive (i.e. mucoadhesive) agents which may be used in compositions of the invention may be natural or synthetic, polyanionic, polycationic or neutral, water-soluble or water-insoluble, but are preferably large (e.g. having a molecular weight of 500 to 3000 kDa, e.g. 1000 to 2000 kDa), water-insoluble cross-linked (e.g. containing 0.05 to 2%, e.g. 0.75 to 1.5% cross-linker by weight of the total polymer, prior to any hydration), water-swellable polymers capable of forming hydrogen bonds. Preferably the bioadhesives have a mucoadhesive force greater than 100, especially preferably greater than 120, particularly greater than 150, as assessed according to the method of Smart et al., 1984, J. Pharm. Pharmacol., 36, p295-299, expressed as a percent relative to a standard *in vitro*.

Appropriate bioadhesives include, but are not limited to, poly(carboxylic acid-containing) based polymers, such as poly(acrylic, maleic, itaconic, citraconic, hydroxyethyl methacrylic, methoxyethyl methacrylic, methoxyethoxyethyl methacrylic or methacrylic) acid which have strong hydrogen-bonding groups, or derivatives thereof such as salts and esters. Examples of such polymers include the EUDRAGIT® polymers available from Röhm GmbH, Germany, in particular the EUDRAGIT® grades for sustained release which are based on copolymers of acrylate and methacrylates with quaternary ammonium groups as functional groups as well as ethylacrylate methylmethacrylate copolymers with a neutral ester group. These polymers are insoluble and

permeable and their release profiles can be altered by varying mixing ratios and/or film thickness. Suitable EUDRAGIT® polymers include the EUDRAGIT® RL-types which are highly permeable, the EUDRAGIT® RS-types which are poorly permeable and the EUDRAGIT® NE-types which are swellable and permeable. EUDRAGIT® RL-types, e.g. EUDRAGIT® RL-100, are preferred.

Alternatively, as bioadhesives, cellulose derivatives may be used such as methyl cellulose, ethyl cellulose, methylethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl ethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose or cellulose esters or ethers or derivatives or salts thereof, e.g. hydroxypropyl methyl cellulose-E15 (HPMC E-15) or Sodium carboxymethyl cellulose-H (Sodium CMC-H). Optionally, these may be used together with a plasticizer. Combinations of two or more cellulose derivatives may also be employed, for example HPMC E-15 and Sodium CMC-H.

Other naturally occurring or synthetic polymers may also be used such as gums, e.g. acacia gums, xanthan gum, guar gum, locust bean gum, tragacanth gums, karaya gum, ghatti gum, cholla gum, psillium seed gum and gum arabic; clays such as manomorillonite clays, e.g. Veegum, attapulgite clay; polysaccharides such as dextran, pectin, amylopectin, agar, carrageenan, mannan or polygalactonic acid or starches such as hydroxypropyl starch or carboxymethyl starch; lipophilic formulations containing polysaccharides, e.g. Orabase (Bristol Myers Squibb); carbohydrates such as polysubstituted with groups such as sulphate, phosphate, sulphonate or phosphonate, e.g. sucrose octasulphate; polypeptides such as casein, gluten, gelatin, fibrin glue; chitosan (chloride salt, lactate or glutamate) or carboxymethyl chitin; glycosaminoglycans such as hyaluronic acid; metals or water soluble salts of alginic acid such as

sodium alginate or magnesium alginate; schleroglucan; adhesives containing bismuth oxide or aluminium oxide; atherocollagen; polyvinyl polymers such as polyvinyl alcohols, polyvinylmethyl ethers, polyvinylpyrrolidone, polycarboxylated vinyl polymers (such as polyacrylic acid as mentioned above); polysiloxanes; polyethers; polyalkylene oxides and glycols, e.g. polyethylene oxides and glycols; polyalkoxys and polyacrylamides and derivatives and salts thereof; polyglycolic and polylactic acid homopolymers and copolymers; glycolide and lactide copolymers, e.g. poly-L-(lactide co-glycolide).

The above described polymeric bioadhesives may also be cross-linked and may be in the form of copolymers. Where present, any cross-linking agent should be provided in an amount to provide sufficient bioadhesion, i.e. to allow the system to remain attached to the target epithelial surfaces for a sufficient time to allow the desired dosing to take place. Preferably, poly(acrylic acid) polymers (or copolymers, e.g. with di- or poly functional allyl ethers or acrylates to make the polymer insoluble), which have preferably been cross-linked, e.g. using a polyalkenyl polyether, are employed which have a high molecular weight and are thixotropic. Appropriate bioadhesives having this form are available commercially (e.g. from Goodrich) as Polycarbophil, e.g. Noveon AA-1, Carbomer (Carbopol), e.g. Carbopol EX165, EX214, 434, 910, 934, 934P, 940, 941, 951, 971, 974P, 980, 981, 1342 and 1382.

Chitosans are a class of preferred mucoadhesives for use in the invention. In addition to their bioadhesive properties, these also exhibit antifungal and antimicrobial effects. Their bioadhesive properties, due essentially to their molecular weight and salt type, can be varied by the use of cross-linking agents, e.g. tripolyphosphate (TPP), dialdehydes, epichloridrine, etc.

Hydrophilic pressure sensitive materials can provide high adhesive strength towards both dry and moistened substrates and are also suitable for use in the invention. The Corplex adhesive hydrogels are one example of such materials (see Controlled Release Society 30th Annual Meeting PROCEEDINGS, 2003: #123). These are prepared by non-covalent (H-bond) cross-linking of a film-forming hydrophilic polymer (e.g. PVP) with a short-chain plasticizer (typically PEG) bearing complementary reactive OH groups at its chain ends. These hydrogels make up the Corplex-100 series. Also suitable for use as adhesive hydrogels are the Corplex-200 series which are obtained by additional cross-linking of a film-forming polymer in the Corplex-100 hydrogels by a hydrophilic polymer that contains the complementary reactive groups in the repeating units of the backbone and forms an H-bonded interpolymeric complex.

To aid in processing, the polymeric bioadhesives herein described may be used in combination with additional excipients. For example, plasticizers such as glycerol, propylene glycol, diethyl phthalate, dibutyl phthalate, etc., may be added.

Preferred bioadhesives for use in the compositions of the invention are those which are able to release the active substances into the vaginal epithelium without affecting the normal vaginal flora and which cause minimal irritation. These include polyacrylic hydrogels, polyvinyl alcohol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, xanthan gum and chitosan.

In situ-gelling mucoadhesive polymer vehicles may also be used in delivery of the pharmaceutical compositions herein described. One example of such a system is based on the use of Polycarbophil as a mucoadhesive polymer in combination with poloxamers which are used to confer in situ-gelling

thermosensitivity to the system (see Controlled Release Society 30th Annual Meeting PROCEEDINGS, 2003: #902). Such systems offer high vaginal retention and are described, for example, in US 2003/0091642 the contents of which are incorporated herein by reference. A preferred example of such a vehicle is that comprising Lutrol F127 in combination with Carbopol 5984.

Glyceryl Monooleate (GMO) behaves in a manner similar to certain polymers in that, in excess water it swells and forms a physically stable viscous gel that is capable of releasing a dissolved or dispersed active (drug) by slow diffusion. GMO has been classified as having moderate to excellent bioadhesive properties. Unswollen GMO has the greatest mucoadhesion, followed by the partly swollen lamellar phase and the fully swollen cubic phase. Glyceryl Monooleate-based systems are thus capable of undergoing an *in-situ* transformation to a semi-solid system on contact with the vaginal mucosa and may therefore find use as a suitable bioadhesive in the compositions herein described. The drug release profile of GMO systems can be controlled by varying the surface-to-volume ratio, the drug loading, and the water content and by the addition of salt, glycerin, propylene glycol or any similar amphiphilic substance of low molecular weight. One drawback of using a GMO system based in the cubic phase can be its stiffness. In order to overcome this problem a solvent can be utilized. Another approach is the addition of a vegetable or animal oil. Both approaches can be used successfully for sustained release of biologically active materials such as those described herein. The GMO system provides good adhesion to mucosa and enables controlled release of the active medicaments from the formulation. GMO/water liquid crystalline gels may also be suitable for vaginal delivery of the drugs herein described.

Thermoreversible gels which have a very low viscosity at ambient temperature (allowing them to be

considered a liquid) and which are viscous at body temperature may also be used to deliver the compositions in accordance with the invention. The liquid form of such materials prior to application facilitates an even distribution on the vaginal mucosa whilst the more viscous form permits better adherence to the mucosa by limiting its flow. Poloxamers such as Lutrol F127 and Lutrol F68 are block copolymers that form thermoreversible gels and these are particularly suitable for use in the invention. These materials form gels which exhibit maximum viscosity in the range from 30 to 60°C. The sol-gel transition temperatures and the viscosity of aqueous solutions vary with the concentration. However, by varying the concentration between 16-25 wt.%, gel viscosities ranging from 1200 to 2600 mPa at 37°C may be achieved. Gels formed from mixtures of Lutrol F127 and/or Lutrol F68 have the additional advantage that these exhibit no reduction in viscosity with increasing temperature over a wide range.

Thermoreversible gels derived from starch may also be used in the formulations of the invention. Such materials may be derived from starch by enzymatic treatment, e.g. using glucosyltransferases such as phosphorylases or α-1,4-α-1,4 glucosyltransferases such as amylomaltase (AMase). One example of such a product is AMAZ (available from TNO Nutrition and Food Research, The Netherlands).

The ability to control the rate of release of one or more the active agents from the formulations herein described is particularly desirable. Controlled release includes rapid release as well as prolonged or sustained release. One way in which controlled release may be achieved is by appropriate selection of a bioadhesive, for example by selecting a bioadhesive which is capable of providing delayed (sustained) release of one or more components of the formulation. Bioadhesive systems suitable for use in this regard are generally known and

described in the art and include, in particular, the polymeric bioadhesives herein described. Such systems can be adjusted to control the release rate of active by varying the amount of cross-linking agent in the polymer. A particularly preferred polymer for use in this regard is Polycarbophil which is commercially available from B. F. Goodrich under the tradename NOVEON®-AA1. Polycarbophil is a polyacrylic acid cross-linked with divinyl glycol.

Solid Lipid Nanoparticles (SLNs) may also be used to provide controlled release of one or more the active agents herein described. In such systems the lipid phase of an emulsion (or a portion thereof) is exchanged with a solid lipid (i.e. a lipid which is solid at room temperature and also at body temperature). The solid lipids can be obtained by high-pressure homogenization or by microemulsion techniques. One or more of the active agents described herein can be solubilized or molecularly dispersed into the solid lipid particles (the particles obtained are normally in the range of 200 nm to 2 μm and are thus termed nanoparticles). The structure obtained is typically a function of (1) the formulation composition; lipids, active ingredients, surfactants etc.; (2) the production conditions; hot or cold homogenization; and (3) the interaction between the various ingredients. One example of such a system is a matrix composed of Compritol and Poloxamer 188. By varying the production temperature (from 40-90°C) and the concentration of Poloxamer (from 0 to 2.5 wt.%) a series of bi-phasic profiles can be obtained with an initial burst release of active followed by a prolonged release. This system is ideal for a vaginal product since some of each drug is released immediately and the rest of the actives released over time.

Where at least one of the active agents herein described is present in salt form, ion exchange systems based on the interaction between soluble polymers and

oppositely charged drugs may provide for controlled release. Examples of such systems include Carbopol in combination with chondroitin 6-sulphate or lambda carrageenan (see Controlled Release Society 30th Annual Meeting PROCEEDINGS, 2003: #392).

Other examples of bioadhesives which may be used to give controlled and prolonged release of one or more actives to the vaginal mucosa are described in US-A-6,306,914, the contents of which are incorporated herein by reference. A yet further example of such a system is an agent which comprises a graft copolymer of a poly-α-glycoside and at least a graft copolymerizable α,β-ethylenically unsaturated monocarboxylic acid or acid derivative as described in WO 00/47644, the entire contents of which are also incorporated herein by reference.

Other systems which are able to release an active agent in a controlled manner for an extended period in the vaginal cavity are described in US-A-4,551,148, the contents of which are incorporated herein by reference. Such systems comprise liquid or semi-solid adjacent unit cells having common lipoidal external phases, non-lipoidal internal phases and emulsifiers. The external and internal phases of these systems comprise an emulsion, emulsion/dispersion, double emulsion, suspension within an emulsion or mixture. Typically, the active agent or agents will be contained within the non-lipoidal phases. One example of such a system is that marketed under the tradename VagiSite® (KV Pharmaceutical Company, Mo, USA). The VagiSite® system is a high internal phase ratio water-in-oil emulsion system that exhibits bioadhesive properties to mucosal tissues. The biphasic system is composed of a drug laden internal phase and a water-insoluble external phase. Not only does this system result in less product leakage from the vagina, but also provides for a controlled delivery and release of the active drug or

drugs over several days. This therefore reduces the number of doses of the product required for therapeutic effectiveness which contributes to improved patient compliance.

Combinations of two or more of the bioadhesive technologies herein desribed may be used in the formulations of the invention. One example of such a combination is that based on GMO, block copolymers and solid lipid nanoparticles. The mucoadhesive properties of GMO may, for example, be enhanced with any of the block copolymers herein described, e.g. GMO may be combined with a Lutrol block copolymer to provide a programmed release of active(s) over a period of time. A dilution-thickening effect can further be achieved by mixing in specific amounts block copolymers and a mesomorphic GMO phase. GMO in the cubic phase may also be used as the solid lipid phase of a solid lipid nanoparticle (SLN). Programmed drug release can further be achieved by incorporating a block copolymer into a molten GMO of the lipid phase of a solid lipid nanoparticle matrix.

The bioadhesives described herein may be prepared using standard processes and procedures well-known in the art, although many are available commercially, e.g. from Goodrich, BDH, Hercules, Dow Chemical Co., KV Pharmaceutical Co., etc.

The desired concentration range of any particular bioadhesive present in the formulations of the invention will depend on the chosen bioadhesive and its desired effect (i.e. the desired release rate of active or actives) and can be readily determined by those skilled in the art. Suitable concentrations may, for example, fall within the range of 5 to 90% by weight, preferably 5 to 80% by weight, e.g. 5 to 40% by weight.

It will be appreciated from the discussion herein that the bioadhesive agent may itself comprise the carrier or excipient in any pharmaceutical formulation

and thus in those cases, a further carrier or excipient need not necessarily be present.

The compositions herein described are suitable for the treatment and/or prevention of primary and/or secondary vaginal infections, e.g. mixed vaginal infections such as those associated with acute and recurrent vulvovaginal candidiasis, bacterial vaginosis and trichomonal vaginitis. These are also considered to be effective in treating any secondary candidial, bacterial and/or trichomonal infections which might result from treatment of such causative agents. Vaginal infections due to group B and D streptococcus and the like, infections due to microorganisms causing vulvitis and vulvovaginitis, and other vaginal infections (e.g. atrophic vaginitis, allergic or irritant vulvo vaginitis, genital psoriasis (with or without clinically relevant infection), vulvitis due to Lichen sclerosis, etc.) may also be usefully treated using the compositions herein described.

Although primarily described for use in treating vaginal infections, the compositions in accordance with the invention may also find more general use in treating primary and/or secondary genital infections in both men and women, including sexually transmitted infections, e.g. infections due to chlamydia; balanitis; penile dermatitis; herpes genitalis; gonorrhea; etc.

The pessaries may be manufactured by conventional methods, for instance by admixture of the active ingredients in the molten pessary base and pouring the resulting mixture into chilled moulds.

The pessaries may be presented in a pack to provide a complete course of treatment, for example with some of the pessaries containing a combination of actives in accordance with the invention for initial use (e.g. over the first three days) and some containing only a single anti-vaginitis medicament for use when the symptoms have begun to subside. For example, a 7-day regimen of

treatment using pessaries containing the actives terconazole and tioconazole might comprise a combination of these two actives for the first three days and tioconazole alone for the remaining four days.

Alternatively, a "Combi-pack" may comprise one or more pessaries together with a cream for external use to provide a particular course of treatment in which at least one pessary and/or the cream comprises a combination of actives as herein described. For example, a pack of pessaries may be provided in which one or more pessaries contains a combination of actives in accordance with the invention, the pack further comprising a cream containing either a single anti-vaginitis medicament or a combination of active agents in accordance with the invention intended for a full course of treatment (e.g. 3, 5 or 7 days). Also provided are "Combi-packs" containing at least one pessary which contains either a single anti-vaginitis medicament or a combination of medicaments in accordance with the invention for the first day (single dose treatment) or for a course of 3, 5 or 7 days, together with a cream for external use containing a combination of actives as herein described.

Packs of pessaries which include at least one pessary containing a combination of actives as herein described are considered to form part of the invention.

A pack comprising one or more pessaries and/or a cream in which at least one pessary or said cream comprises a combination of active agents as herein described also forms part of this invention.

It is common practice in vaginitis therapy that oral treatment is combined with topical treatment, particularly in resistant cases, in non-responders or in the treatment of recurrent conditions, e.g. vulvovaginal candidiasis or trichomoniasis. Accordingly, it is possible that the topical formulations herein described may be used in conjuction with oral therapy, for example

in combination with oral administration of conventional agents having any combination of anti-fungal, anti-protozoal and antibacterial properties.

The following Examples are given by way of illustration only:

Example 1 - Pessary

Terconazole	100
Tinidazole	150
Suppocire A	2250
	2500 mg per pessary

The two active ingredients are mixed into the molten Suppocire and the resulting mixture is poured into pre-cooled moulds. The moulds are passed through a cooling tunnel at -10°C, the pessaries are removed from the moulds and packaged.

Example 2 - Cream

	% by weight
Purified Water	63.16
Benzalkonium Chloride 50%	0.10
Polawax	15.00
Isopropyl Myristate	10.00
Mineral Oil NF, 70	5.00
Propyl Gallate	0.10
Monobasic Sodium Phosphate	1.30
Dibasic Sodium Phosphate	0.09
Phenoxyethanol (&) Methylparaben (&) Ethylparaben (&) Butylparaben (&) Propylparaben (&) Isopropylparaben	0.25
Terconazole	2.00
Tinidazole	3.00
	100.00

The oily phase components are mixed at 60°C. The aqueous phase comprising the remaining components is also blended at 60°C and the two phases combined and blended.

Example 3 - Pessary

Terconazole	100
Tinidazole	150
Tioconazole	100
Suppocire A	2150
	2500 mg per pessary

Pessaries are prepared analogously to Example 1.

Example 4 - Cream

	% by weight
Glyceryl Monooleate	37.0
Poloxamer 407	16.5
Poloxamer 188	5.90
Citric Acid (10% soln.)	1.20
Sodium Citrate (10% soln.)	0.20
Preservative	0.50
Terconazole	2.00
Tinidazole	3.00
Water	q.s. to 100%

Mix Water and Glyceryl Monooleate until homogenous and heat to 75°C.
Begin cooling to 37°C while mixing.
Separately co-blend Poloxamers and add to main batch.
Adjust pH to 4.0.
Add preservative.
Uniformly disperse active ingredients at 33°C.
Cool to 25°C.

Claims:

1. A pharmaceutical composition for topical administration comprising at least one triazole compound active against *Candida albicans*, in combination with at least one additional anti-vaginitis medicament.

2. A composition as claimed in claim 1, wherein said triazole compound is additionally active against one or more non-albicans *Candida* species.

3. A composition as claimed in claim 2, wherein said triazole compound is terconazole.

4. A composition as claimed in any one of claims 1 to 3, wherein said anti-vaginitis medicament comprises one or more of the following agents:

(a) an anti-fungal agent;

(b) an anti-protozoal compound; and

(c) an anti-bacterial agent.

5. A composition as claimed in claim 4, wherein said anti-fungal agent is an imidazole compound.

6. A composition as claimed in claim 5, wherein said imidazole compound is tioconazole, butoconazole, miconazole, ketoconazole, clotrimazole, isoconazole, seperconazole, econazole, oxiconazole or sulconazole.

7. A composition as claimed in any one of claims 4 to 6, wherein said anti-protozoal compound further exhibits anti-bacterial activity.

8. A composition as claimed in claim 7, wherein said anti-protozoal compound is a nitroimidazole.

9. A composition as claimed in claim 8, wherein said

anti-protozoal compound is tinidazole, ornidazole or metronidazole.

10. A composition as claimed in any one of claims 4 to 9, wherein said anti-bacterial agent is pivampicillin, clindamycin, chlorquinaldol, diiodohydroxyquinoline or chloramphenicole.

11. A composition as claimed in claim 1 in which the triazole compound is terconazole and the anti-vaginitis medicament is tioconazole and/or tinidazole.

12. A composition as claimed in claim 1 in which the triazole compound is terconazole and the anti-vaginitis medicament is butoconazole.

13. A composition as claimed in any preceding claim further comprising one or more local anaesthetics.

14. A composition as claimed in claim 13, wherein said anaesthetic is lidocaine or benzocaine.

15. A composition as claimed in any preceding claim which includes a surfactant.

16. A composition as claimed in any preceding claim which includes one or more wound healing or skin protectant agents, e.g. dimethicone.

17. A composition as claimed in any preceding claim which further comprises at least one bioadhesive agent, e.g. a mucoadhesive.

18. A composition as claimed in claim 17, wherein said bioadhesive agent is selected from poly(carboxylic acid-containing) based polymers, cellulose derivatives, gums, clays, polysaccharides, carbohydrates, polypeptides,

chitosan, glycosaminoglycans, salts of alginic acid, schleroglucan, polyvinyl polymers, polysiloxanes, , polyethers, polyalkylene oxides and glycols, polyalkoxys and polyacrylamides, chitosans, and derivatives and salts thereof.

19. A composition as claimed in claim 17, wherein said bioadhesive agent is selected from polyacrylic hydrogels, polyvinyl alcohol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, xanthan gum and chitosan.

20. A composition as claimed in claim 17, wherein said bioadhesive agent comprises an *in situ*-gelling mucoadhesive, e.g. an *in situ*-gelling mucoadhesive polymer, or a thermoreversible gel.

21. A composition as claimed in claim 20, wherein said *in situ*-gelling mucoadhesive comprises glyceryl monooleate.

22. A composition as claimed in claim 20, wherein said thermoreversible gel comprises enzymatically treated starch.

23. A composition as claimed in any preceding claim which is formulated for controlled, e.g. rapid and/or delayed (sustained), release of the active medicaments.

24. A composition as claimed in claim 23 in which controlled release is provided by solid lipid nanoparticles.

25. A composition as claimed in any preceding claim in the form of a pessary.

26. A pack comprising a plurality of pessaries, at

least one of which is a pessary as defined in claim 25.

27. A composition as claimed in any one of claims 1 to 24 in the form of a cream.

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003972

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/4196 A61K31/4166 A61K31/4168 A61K31/4174
A61K9/00 A61P15/02 A61P31/04 A61P33/02

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/55333 A (LABORATOIRE INNOTHERA ; MEIGNANT, CATHERINE; VIEILLARD-BARON, CORINNE;) 4 November 1999 (1999-11-04) page 2, lines 27-31; claims 1-3 page 1, line 34 - page 2, line 16 page 7, lines 9-20 page 7, lines 23-28 page 8, lines 5-9	1-5,8,9, 15-20
X	WO 96/03149 A1 (WARNER-LAMBERT COMPANY) 8 February 1996 (1996-02-08) page 84, paragraph 2; claims 1,3,19-21 page 83, lines 14-20 page 82, line 24 - page 83, line 3 page 9, paragraph 3	1-4,17, 18

-/--

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

[X] Patent family members are listed in annex.

° 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 reason (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 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2005	11/02/2005

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	Kanbier, D

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003972

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 2003/073646 A1 (MILANKOVITS MARTON) 17 April 2003 (2003-04-17) paragraphs '0006!, '0014!, '0019!, '0021!, '0065!; claims 1,3-6,16; examples 7,13	1-10
A	WO 95/17175 A1 (THE PROCTER & GAMBLE COMPANY) 29 June 1995 (1995-06-29) page 13, lines 26,27; claims 1,3 page 4, lines 9-11	1-7, 13-15
A	WO 02/03896 A (UMD, INC) 17 January 2002 (2002-01-17) page 3, line 30 - page 4, line 10 page 7, lines 16-35; example 6 page 9, line 6 - page 11, line 23 page 17, line 30 - page 18, line 10 page 32, lines 10-14; claims 1,2,12,13	1-10, 15-19, 24-27
A	FARAH C A ET AL: "TINIDAZOLE-TIOCONAZOLE COMBINATION IN THE TREATMENT OF VAGINAL INFECTION DUE TO TRICHOMONAS GARDNERELLA-VAGINALIS OR CANDIDA-ALBICANS" BIOLOGICAL ABSTRACTS. - MICROFILMS, BIOSIS. PHILADELPHIA, PA, US, vol. 84, 1987, page COMPLETE01, XP002091996 ISSN: 0192-6985 the whole document	1,2,11, 27

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB2004/003972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955333 A	04-11-1999	FR 2777783 A1	29-10-1999
		AU 3427199 A	16-11-1999
		CA 2329762 A1	04-11-1999
		EP 1071421 A1	31-01-2001
		WO 9955333 A1	04-11-1999
		JP 2002512961 T	08-05-2002
WO 9603149 A1	08-02-1996	US 5663208 A	02-09-1997
		AU 701179 B2	21-01-1999
		AU 3004295 A	22-02-1996
		CA 2191603 A1	08-02-1996
		EP 0773795 A1	21-05-1997
		JP 10503200 T	24-03-1998
		NZ 290029 A	23-02-2001
		PH 31465 A	03-11-1998
		ZA 9506117 A	21-04-1997
US 2003073646 A1	17-04-2003	NONE	
WO 9517175 A1	29-06-1995	AT 199215 T	15-03-2001
		CA 2177682 A1	29-06-1995
		DE 69426727 D1	29-03-2001
		EP 0735866 A1	09-10-1996
		JP 9507073 T	15-07-1997
		US 5686088 A	11-11-1997
WO 0203896 A	17-01-2002	US 6416779 B1	09-07-2002
		AU 8128701 A	21-01-2002
		BR 0112571 A	27-05-2003
		CA 2416050 A1	17-01-2002
		EP 1301150 A1	16-04-2003
		JP 2004508296 T	18-03-2004
		MX PA02012819 A	22-09-2003
		WO 0203896 A1	17-01-2002