Pharmaceutical composition comprising benzydamine

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising benzydamine. More in particular, the present invention relates to a pharmaceutical cream, cream-gel or gel composition comprising benzydamine having improved tolerability and efficacy for the prevention and treatment of inflammatory and/or infective conditions mainly localized in the genital area, in particular vaginosis, vaginitis and vulvo-vaginitis.

BACKGROUND OF THE INVENTION

Infections of the female genital apparatus, vaginosis, vaginitis and vulvo-vaginitis, are one of the most widespread gynecological problems, whose incidence seems to be increasing.

Even if the causes are different and numerous, and not always of infectious origin, the majority of diagnoses identifies (i) bacterial vaginosis, i.e. polymicrobial syndromes characterized by a radical modification of the vaginal ecosystem consisting, in particular, in the replacement of the normal lactobacillar flora by pathogens (mainly anaerobes), very often caused or complicated by Gardnerella infections; (ii) Candida vaginitis and vulvo-vaginitis; (iii) Trichomonas vaginalis vaginitis.

Bacterial vaginosis is the most common vaginal and/or vulvo-vaginal infection among women in the fertile age. There are many predisposing factors for these alterations of the bacterial vaginal flora, for example: incorrect hygiene, intrauterine diaphragms, immune deficiencies, diabetes, sexual activity with more partners. The most typical symptom of bacterial vaginosis is abundant, smelly and greyish vaginal loss; itching, vaginal burning and pain during sexual intercourse can rarely be experienced. Pathogenic bacteria, generally Gardnerella vaginalis, which

almost completely replace the normal lactobacillar flora, are one of the most common causes of vaginosis.

Vaginitis is an inflammation of the vagina which can affect women of any age; it is called vulvo-vaginitis when it affects also the vulva, i.e. external genitals. In vulvo-vaginitis, fungi of the Candida genus often play a key role as infective agents.

These inflammations can be episodic, recurring (i.e. they appear again after treatment) and in some cases even chronic.

Reference and consolidated therapies (either local or systemic) for the treatment of the above conditions are based on antimycotics, antibacterials, corticosteroids, non steroidal antiinflammatories or xylocaine and derivatives thereof (when itching prevails), or antihistaminics (only orally). In episodic infections there is no need for a change in the therapy, because the advantages outweigh potential risks (side effects, undesired local toxicity reactions, sensitisation); instead, in recurring episodes prevention would undoubtedly be a successful approach.

Several patent applications disclose combinations of active ingredients useful in the treatment of vaginosis, vaginitis and vulvo-vaginitis.

EP2014295 relates to topical compositions containing Zanthoxylum bungeanum extract, 18-beta glycyrrhetic acid, Matricaria chamomilla essential oil, Melaleuca alternifolia essential oil, Curcuma longa or curcumin extract and lactic or propionic acid.

WO2007085020 relates to a pharmaceutical composition for vaginal administration comprising an. estrogen compound, a progesterone compound, and a pharmaceutically acceptable carrier for vaginal administration, wherein the composition is useful in the treatment of urogenital symptoms associated with atrophic vaginitis.

EP0389924 relates to topical dosage form for the treatment of vaginal infections containing purpuromycin.

EP0910377 relates to a pharmaceutical composition for topical administration in the treatment of vaginitis comprising one or more anti-vaginitis medicaments, such as metronidazole and miconazole, and one or more local anaesthetics, such as lidocaine or benzocaine.

EP2034984 relates to a pharmaceutical composition, such as a vaginal suppository or cream, for the treatment of symptoms associated with atrophic vaginitis comprising: a triphenylethylene derivative compound.

WO2016/113194 discloses the formulation of benzydamine hydrochloride in the form of a cream for topical administration comprising benzydamine hydrochloride in an amount of 0.12% w/w, Miglyol® 812 (caprylic/capric triglyceride) in an amount of 3% w/w, Tefose® 63 (PEG-6 and PEG-32 palmitostearate) in an amount of 18% w/w, and Labrafil® M2130CS (lauroyl macrogol-6-glycerides) in an amount of 3% w/w, together with econazole nitrate in an amount of 1% w/w.

The Applicant manufactured and distributed a vaginal cream-gel for the treatment of nonspecific vaginitis containing benzydamine in an amount of 0.5% w/w based on the total weight of the cream-gel.

SUMMARY OF THE INVENTION

The Applicant faced the problem to provide a pharmaceutical composition comprising benzydamine having improved tolerability and efficacy for the prevention and treatment of inflammatory and/or infective conditions mainly localized in the genital area, in particular vaginosis, vaginitis and vulvo-vaginitis.

The Applicant has found that a pharmaceutical composition comprising (i) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (ii) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, and (iii) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid, and (iv) benzydamine in an amount equal to or lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition showed an improved tolerability.

The Applicant has also found that a similar improved tolerability is provided by a pharmaceutical composition comprising (i) at least one nonionic water-soluble hydroxyethylcellulose ether having a weight average molecular weight of one million Dalton or more, (ii) at least one polyol, and (iii) benzydamine in an amount lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition, wherein said composition is free of polyethylene glycol ethers of cetearyl and stearyl alcohol, and wherein said composition optionally comprises (iv) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (v) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, and/or (vi) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid.

Thus, in a first aspect, the present invention relates to a pharmaceutical composition comprising (i) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (ii) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, and (iii) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid, and (iv) benzydamine in an amount equal to or lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition, provided that, when benzydamine is present as benzydamine hydrochloride in an amount of 0.12% w/w, together with Miglyol® 812 in an amount of 3% w/w, Tefose® 63 in an amount of 18% w/w, and Labrafil® M2130CS in an amount of 3% w/w, the composition does not comprise econazole nitrate.

In a second aspect, the present invention relates to a pharmaceutical composition comprising (i) at least one nonionic water-soluble hydroxyethylcellulose ether having a weight average molecular weight of one million Dalton or more, (ii) at least one polyol, and (iii) benzydamine in an amount lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition, wherein said composition is free of polyethylene glycol ethers of cetearyl and stearyl alcohol, and wherein said composition optionally comprises (iv) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (v) at least one ester of polyethylene

glycol glycerides with a C_{12}-C_{14} saturated fatty acid, and/or (vi) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid.

DETAILED DESCRIPTION OF THE INVENTION

According to a first aspect, the present invention relates to a pharmaceutical composition comprising (i) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (ii) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, and (iii) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid, and (iv) benzydamine in an amount equal to or lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition, provided that, when benzydamine is present as benzydamine hydrochloride in an amount of 0.12% w/w, together with Miglyol® 812 in an amount of 3% w/w, Tefose® 63 in an amount of 18% w/w, and Labrafil® M2130CS in an amount of 3% w/w, the composition does not comprise econazole nitrate.

The pharmaceutical composition according to the present invention preferably comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount lower than 10% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount lower than 7% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount lower than 5% w/w with respect to the total weight of the pharmaceutical composition.

Preferably, the pharmaceutical composition according to the present invention comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount higher than 0.5% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount higher than 1% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount higher than 2% w/w with respect to the total weight of the pharmaceutical composition.

According to a preferred embodiment of the present invention, the pharmaceutical composition comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount ranging from 1.5% to 6% w/w with respect to the total weight of the pharmaceutical composition.

According to a more preferred embodiment of the present invention, the pharmaceutical composition comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount ranging from 2.5% to 4% w/w with respect to the total weight of the pharmaceutical composition.

Useful esters of glycerin with a C_8-C_{10} saturated fatty acid are mono-, di-, or tri-glycerides of capric acid and/or caprylic acid, and mixture thereof.

Esters of glycerin with a C_8-C_{10} saturated fatty acid are commercially available from several suppliers under different commercial names, such as for example Captex® 300 and Captex® 355 (Abitec Corporation), Myritol® 312 and Myritol® 318 (BASF), Miglyol® 810 and Miglyol® 812 (Sasol), Tegosoft® CT (Evonik), Crodamol™ GTCC (Croda), BergaBest™ MCT-Oil (Berg & Schmidt), and Dermarol™ CCT (CISME Italy).

The pharmaceutical composition according to the present invention preferably comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount lower than 10% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount lower than 7% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount lower than 5% w/w with respect to the total weight of the pharmaceutical composition.

Preferably, the pharmaceutical composition according to the present invention comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount higher than 0.5% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount higher than 1% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount higher than 2% w/w with respect to the total weight of the pharmaceutical composition.

According to a preferred embodiment of the present invention, the pharmaceutical composition comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount ranging from 1.5% to 6% w/w with respect to the total weight of the pharmaceutical composition.

According to a more preferred embodiment of the present invention, the pharmaceutical composition comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount ranging from 2.5% to 4% w/w with respect to the total weight of the pharmaceutical composition.

Useful esters of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid are polyethylene glycol mono- or di-glycerides with lauric acid and/or myristic acid, and mixture thereof. The polyethylene glycol chain linked to the glyceride can have from 4 to 10 oxyethylene monomeric units, preferably from 6 to 8 monomeric oxyethylene units.

Esters of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid are commercially available from several suppliers under different commercial names, such as for example Acconon® C-44 (Abitec Corporation), Labrafil® M2130CS and Gelucire® 44/14 (Gattefossé).

The pharmaceutical composition according to the present invention preferably comprises at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid in an amount lower than 30% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid in an amount lower than 25% w/w with respect to the total weight of the pharmaceutical composition.

Preferably, the pharmaceutical composition according to the present invention comprises at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid in an amount higher than 1% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid in an amount higher than 2% w/w with respect to the total weight of the pharmaceutical composition.

According to a preferred embodiment of the present invention, the pharmaceutical composition comprises at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid in an amount ranging from 5% to 20% w/w with respect to the total weight of the pharmaceutical composition.

Useful esters of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid are esters of polyethylene glycols having from 6 to 32 oxyethylene monomeric units with palmitic acid and/or stearic acid, and mixture thereof.

Esters of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid are commercially available from several suppliers under different commercial names, such as for example Mirj™ S8, S25, S40 and S100 (Croda), Gelucire® 48/16, Tefose® 1500 CG, and Tefose 63 (Gattefossé), Simulsol™ M45PHA and M52PHA (Seppic).

Preferably, the pharmaceutical composition of the present invention does not comprise econazole nitrate when benzydamine is present together with Miglyol® 812, Tefose® 63 and Labrafil® M2130CS. More preferably, the pharmaceutical composition of the present invention does not comprise econazole nitrate.

In a second aspect, the present invention relates to a pharmaceutical composition comprising (i) at least one nonionic water-soluble hydroxyethylcellulose ether having a weight average molecular weight of one million Dalton or more, (ii) at least one polyol, and (iii) benzydamine in an amount lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition, wherein said composition is free of polyethylene glycol ethers of cetearyl and stearyl alcohol.

Useful nonionic water-soluble hydroxyethylcellulose ethers (i) have an average degree of substitution between 1 and 2 and an average degree of substituents between 2 and 3. The degree of substitution is the average number of substituted hydroxyl in the cellulose chain. The degree of substituents is the average number of ethylene oxide units linked to each glucose unit of the cellulose chain. The nonionic water-soluble hydroxyethylcellulose ethers preferably have a weight average molecular weight of from 1.0 to 1.5 x 10^6 Dalton.

Nonionic water-soluble hydroxyethylcellulose ethers are commercially available from several suppliers under different commercial names, such

as for example, Natrosol®250HHR, Natrosol®250H4R, and Natrosol®250HR (Hercules Inc.).

The pharmaceutical composition according to the present invention preferably comprises at least one nonionic water-soluble hydroxyethylcellulose ether in an amount lower than 3% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one nonionic water-soluble hydroxyethylcellulose ether in an amount lower than 2.5% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises at least one nonionic water-soluble hydroxyethylcellulose ether in an amount lower than 2% w/w with respect to the total weight of the pharmaceutical composition.

Preferably, the pharmaceutical composition according to the present invention comprises at least one nonionic water-soluble hydroxyethylcellulose ether in an amount higher than 0.5% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one nonionic water-soluble hydroxyethylcellulose ether in an amount higher than 1% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises at least one nonionic water-soluble hydroxyethylcellulose ether in an amount higher than 1.5% w/w with respect to the total weight of the pharmaceutical composition.

According to a preferred embodiment of the present invention, the pharmaceutical composition comprises at least one nonionic water-soluble hydroxyethylcellulose ether in an amount ranging from 0.8% to 2.7% w/w with respect to the total weight of the pharmaceutical composition.

According to a more preferred embodiment of the present invention, the pharmaceutical composition comprises at least one nonionic water-soluble hydroxyethylcellulose ether in an amount ranging from 1.3% to 2.3% w/w with respect to the total weight of the pharmaceutical composition.

Useful polyols (ii) are polyalcohols having two or more hydroxy groups linked to a carbon chain having from 3 to 6 carbon atoms, such as, for example, glycerol, erythritol, arabitol, xylitol, ribitol, mannitol, sorbitol, galactitol, and inositol. Glycerol is a particularly preferred polyol useful in the present invention.

The pharmaceutical composition according to the present invention preferably comprises at least one polyol in an amount lower than 20% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one polyol in an amount lower than 18% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises at least one polyol in an amount lower than 15% w/w with respect to the total weight of the pharmaceutical composition.

Preferably, the pharmaceutical composition according to the present invention comprises at least one polyol in an amount higher than 1% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises at least one polyol in an amount higher than 3% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises at least one polyol in an amount higher

than 5% w/w with respect to the total weight of the pharmaceutical composition.

According to a preferred embodiment of the present invention, the pharmaceutical composition comprises at least one polyol in an amount ranging from 6% to 14% w/w with respect to the total weight of the pharmaceutical composition.

According to a more preferred embodiment of the present invention, the pharmaceutical composition comprises at least one polyol in an amount ranging from 8% to 12% w/w with respect to the total weight of the pharmaceutical composition.

Optionally, the composition according to the second aspect of the present invention can additionally comprise (iv) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (v) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, and/or (vi) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid in the same amounts described above.

Useful examples of esters of glycerin with a C_8-C_{10} saturated fatty acid are the same described above such as Captex® 300 and Captex® 355 (Abitec Corporation), Myritol® 312 and Myritol® 318 (BASF), Miglyol® 810 and Miglyol® 812 (Sasol), Tegosoft® CT (Evonik), Crodamol™ GTCC (Croda), BergaBest™ MCT-Oil (Berg & Schmidt), and Dermarol™ CCT (CISME Italy).

Useful examples of ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid are the same described above, such as Mirj™ S8, S25, S40 and S100 (Croda), Gelucire® 48/16, Tefose® 1500 CG, and Tefose 63 (Gattefossé), Simulsol™ M45PHA and M52PHA (Seppic).

Preferably, the pharmaceutical composition according to the present invention comprises benzydamine in an amount lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises benzydamine in an amount lower than 0.4% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises benzydamine in an amount lower than 0.3% w/w with respect to the total weight of the pharmaceutical composition.

Preferably, the pharmaceutical composition according to the present invention comprises benzydamine in an amount higher than 0.01% w/w with respect to the total weight of the pharmaceutical composition.

More preferably, the pharmaceutical composition according to the present invention comprises benzydamine in an amount higher than 0.05% w/w with respect to the total weight of the pharmaceutical composition.

Even more preferably, the pharmaceutical composition according to the present invention comprises benzydamine in an amount higher than 0.1% w/w with respect to the total weight of the pharmaceutical composition.

According to a preferred embodiment of the present invention, the pharmaceutical composition comprises benzydamine in an amount ranging from 0.03% to 0.3% w/w with respect to the total weight of the pharmaceutical composition.

According to a more preferred embodiment of the present invention, the pharmaceutical composition comprises benzydamine in an amount ranging from 0.1% to 0.25 w/w with respect to the total weight of the pharmaceutical composition.

The pharmaceutical composition according to the present invention preferably comprises an aqueous dispersion of (i) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (ii) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, (iii) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid,

and (iv) benzydamine in an amount equal to or lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition.

The pharmaceutical composition according to the present invention preferably comprises an aqueous dispersion of (i) at least one nonionic water-soluble hydroxyethylcellulose ether having a weight average molecular weight of one million Dalton or more, (ii) at least one polyol, and (iii) benzydamine in an amount lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition, wherein said composition is free of polyethylene glycol ethers of cetearyl and stearyl alcohol, and wherein said composition optionally comprises (iv) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (v) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, and/or (vi) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid.

The pharmaceutical composition of the present invention in the form of aqueous dispersion comprises water in an amount higher than 40% w/w, preferably higher than 50% w/w, and more preferably higher than 60% w/w with respect to the total weight of the composition. Most preferably, water is comprised in an amount higher than 70% w/w with respect to the total weight of the pharmaceutical composition.

Preferably, the pharmaceutical composition according to the present invention is for topical use.

Preferably, the pharmaceutical composition according to the present invention is prepared in suitable dosage forms, such as creams, ointments, lotions, cream-gels, gels, foams, vaginal douches, or solutions for external use.

More preferably, said dosage form is cream, cream-gel, gel, vaginal douche or solution for external use.

Even more preferably, said dosage form is cream, cream-gel, or gel.

Most preferably, the pharmaceutical composition according to the first aspect of the present invention is in the form of a cream, and the

pharmaceutical composition according to the second aspect of the present invention is in the form of a gel or a cream-gel.

The pharmaceutical composition according to the present invention may comprises other pharmaceutically acceptable excipients.

Useful pharmaceutically acceptable excipients can be selected from the group comprising emollients, thickeners, preservative, stabilizers, buffers, and the like.

Advantageously, the pharmaceutical composition comprises at least one preservative, such as, for example, benzoic acid, ascorbic acid, and/or propyl gallate.

Advantageously, the pharmaceutical composition comprises at least one stabilizer, such as, for example, ethylenediaminetetraacetic acid (EDTA), N-(hydroxyethyl)-ethylenediaminetriacetic acid (HEDTA), nitrilotriacetic acid (NTA), and/or diethylenetriaminepentaacetic acid (DTPA).

The examples that follow are intended for further illustration of the present invention, though without limiting it.

EXAMPLES

Tolerability test 1

An in vitro test on vaginal mucosa cells was conducted by using cream-gels and aqueous solutions of benzydamine at different concentrations. A placebo cream-gel free of benzydamine hydrochloride was also tested. The base cream-gel had composition reported in the following table 1. The samples under investigation had the benzydamine hydrochloride concentration as reposted in the following table 2.

TABLE 1

INGREDIENT	% W/W
Sodium Citrate	0.45
Citric Acid	0.07

Ceteareth 20	2.0
Neutral oil	2.5
HEC	1.8
Propylenic glycol	8.0
Benzoic acid	0.2
Water q.s.	100

Ceteareth-20 is the polyethylene glycol ether of cetearyl and stearyl alcohol, where 20 indicates the average number of ethylene oxide residues in the polyoxyethylene chain.

HEC is a nonionic water-soluble hydroxyethylcellulose ether having a weight average molecular weight of about 1.3×10^6 Dalton.

Neutral oil is a mixture of esters of glycerin with a caprylic and capric fatty acid.

TABLE 2

SAMPLE	COMPOSITION	% W/W
1	Aqueous solution	0.06
2	Aqueous solution	0.12
3	Aqueous solution	0.25
4	Aqueous solution	0.50
5	Cream-gel	0.12
6	Cream-gel	0.25
7	Cream-gel	0.50
PL	Cream-gel	-

The cell viability was measured after 1 hour and after 24 hour from application of the sample to the vaginal mucosa and the results were normalized to an untreated sample of vaginal mucosa (CONTROL).

The results are reported in the following table 3.

TABLE 3

SAMPLE	VIABILITY AFTER 1 HOUR	VIABILITY AFTER 24 HOUR
CONTROL	100.00	100.00
1	106.59	101.61
2	106.20	93.03
3	110.87	78.23
4	60.46	21.24
5	0.84	0.53
6	1.16	0.59
7	0.78	0.65
PL	0.81	0.60

The data clearly showed that benzydamine aqueous solution up to 0.25% w/w are very well tolerated by vaginal mucosa, while a concentration of 0.50% w/w started to show a lower tolerability.

On the other hand, the cream-gel formulations of benzydamine were not tolerated at any concentration, but this was due to the composition of the cream-gel rather than to the benzydamine, as demonstrated by the placebo sample.

Tolerability test 2

Different formulations were prepared and tested for their tolerability as illustrated in the tolerability test 1.

The compositions of the base formulations are illustrated in the following table 4. All amounts are expressed in percent by weight based on the weight of the total composition.

TABLE 4

Composition	21	22	23	24	25	26	27	28
Benzoic acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium Citrate	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Citric Acid	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
HEC	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Ceteareth 20	2.0	1.0	1.0	2.0	--	2.0	--	--
Neutral oil	2.5	1.25	2.5	2.5	--	2.5	2.5	1.25
Emulsifier	--	--	--	--	--	--	5.0	2.5
Surfactant	--	--	--	--	--	--	2.5	1.25
Propylenic glycol	--	--	--	--	--	8	--	--
Glycerol	10	10	10	--	10	--	10	10
Water q.s.	100	100	100	100	100	100	100	100

Ceteareth-20 is the polyethylene glycol ether of cetearyl and stearyl alcohol, where 20 indicates the average number of ethylene oxide residues in the polyoxyethylene chain.

HEC is a nonionic water-soluble hydroxyethylcellulose ether having a weight average molecular weight of about one million Dalton.

Neutral oil is a mixture of esters of glycerin with a caprylic and capric fatty acid.

Emulsifier is a mixture of PEG-6 stearate and PEG-32 stearate.

Surfactant is a mixture of lauroyl macrogol-6 glycerides.

The test results, normalized to an untreated sample of vaginal mucosa (CONTROL), are reported in the following table 5.

TABLE 5

SAMPLE	VIABILITY AFTER 1 HOUR	VIABILITY AFTER 24 HOUR
CONTROL	100.00	100.00
21	0.78	0.74
22	3.82	0.75
23	3.19	0.69
24	0.83	0.72
25	86.75	84.28
26	1.08	075
27	98.40	90.43
28	94.96	95.49

The results surprisingly showed that the removal of Ceteareth-20 strongly improved the tolerability of the formulation 25 (having the consistency of a gel) on the mucosa vaginal cells, which was further even improved by the use of the mixture of emulsifier and surfactant of samples 27 and 28 (having the consistency of a cream-gel).

Tolerability test 3

Formulation 25 and a formulation 54 having a composition similar to that of formulation 27, containing different concentrations of benzydamine hydrochloride, were prepared and tested for their tolerability as illustrated in the tolerability test 1.

The compositions of the formulations are illustrated in the following table 6. All amounts are expressed in percent by weight based on the weight of the total composition.

TABLE 6

	Gel formulations					Cream formulations				
	25	50	51	52	53	54	55	56	57	58
Glycerol	10	10	10	10	10	--	--	--	--	--
Benzoic acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium Citrate	0.45	0.45	0.45	0.45	0.45	0.40	0.40	0.40	0.40	0.40
Citric Acid	0.07	0.07	0.07	0.07	0.07	0.2	0.2	0.2	0.2	0.2
HEC	1.8	1.8	1.8	1.8	1.8	--	--	--	--	--
Neutral oil	--	--	--	--	--	3.0	3.0	3.0	3.0	3.0
Emulsifier	--	--	--	--	--	18.0	18.0	18.0	18.0	18.0
Surfactant	--	--	--	--	--	3.0	3.0	3.0	3.0	3.0
Benzydamine hydrochloride	--	0.50	0.25	0.12	0.06	--	0.50	0.35	0.25	0.12

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The test results, normalized to an untreated sample of vaginal mucosa (CONTROL), are reported in the following table 7.

TABLE 7

SAMPLE	VIABILITY AFTER 24 HOUR
CONTROL	100.00
25	79.20
50	0.80

51	22.90
52	81.70
53	92.30
54	42.40
55	55.63
56	59.90
57	50.30
58	69.20

The results clearly showed that the formulations in the form of cream were tolerated at any tested concentration of benzydamine, with optimal results for sample 58 having a concentration of benzydamine hydrochloride of 0.12 % w/w.

Further, the results also showed that the formulations in the form of gels, having a higher release speed, were tolerated up to a concentration of benzydamine hydrochloride of 0.12 % w/w.

Stability test

Different cream formulations based on formulation 58 were tested for stability by storing them at temperature of 40°C for two months. After storage, the emulsion was visually inspected for detecting any phase separation or granule formation, chemically analyzed for detecting the presence of benzydamine N-oxide, and tested for their tolerability as illustrated in the tolerability test 1.

The composition of the tested formulations is illustrated in the following tables 8A and 8B. All amounts are expressed in percent by weight based on the weight of the total composition.

TABLE 8A

Composition	60	61	62	63	64	65	66	67
Benzydamine hydrochloride	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Neutral oil	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Emulsifier	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
Surfactant	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Benzoic acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium Citrate	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40
Citric Acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
BHA	0.05	-	-	-	0.01	-	0.01	
Pyruvic acid	-	0.085	0.128	-	-	-	-	-
Vitamin E	-	-	-	0.05	0.05	0.05	0.05	
Ascorbyl palmitate	-	-	-	-	-	0.05	0.05	0.05
Propylgallate	-	-	-	-	-	-	-	-
EDTA	-	-	-	-	-	-	-	-
Water q.s.	100	100	100	100	100	100	100	100

TABLE 8B

Composition	68	69	70	71	72	73	74
Benzydamine hydrochloride	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Neutral oil	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Emulsifier	18.0	18.0	18.0	18.0	18.0	18.0	18.0
Surfactant	3.0	3.0	3.0	3.0	3.0	3.0	3.0

Benzoic acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium Citrate	0.4	0.4	-	-	-	-	-
Citric Acid	0.2	0.2	-	-	-	-	-
BHA	-	-	-	-	-	-	-
Pyruvic acid	-	-	-	-	-	-	-
Vitamin E	-	-	-	-	-	-	-
Ascorbyl palmitate	-	-	-	-	-	-	-
Propylgallate	0.05	0.1	0.05	0.1	0.1	0.1	0.1
EDTA	-	-	-	-	0.025	0.05	0.1
Water q.s.	100	100	100	100	100	100	100

The test results are reported in the following table 9. The stability and tolerability were evaluated by using the following score:

1 Bad

2 Sufficient

3 Good

4 Very good

TABLE 9

SAMPLE	EMULSION STABILITY	CHEMICAL STABILITY	TOLERABILITY
60	3	3	1
61	3	3	1
62	3	3	1
63	3	1	-

64	3	1	-
65	3	1	-
66	3	1	-
67	3	1	-
68	3	2	2
69	3	2	2
70	2	3	2
71	2	3	3
72	3	3	4
73	4	3	4
74	4	4	4

Formulations 60 to 62 containing BHA or pyruvic acid were sufficiently stable, but showed a very bad tolerability.

Formulations 63 to 67 containing Vitamin E and/or ascorbyl palmitate, also in combination with BHA were found not chemically stable, with formation of benzydamine N-oxide (the test of tolerability was not even made for these compositions).

Formulations 68 and 69 were stable, but with formation of black dots and a yellowish color after storage. The removal of the buffer system (Sodium Citrate / Citric Acid), as in formulations 70 and 71, improved this defect, but worsened the emulsion stability.

Formulations 72 to 74, wherein the buffer system has been removed and a stabilizer EDTA was added, surprisingly provided the best results.

In vivo preclinical test

Female New Zealand White rabbits were treated once a day by intravaginal route with 1 ml of Placebo Vaginal Cream or Benzydamine

Hydrochloride Vaginal Cream (6 animals/group of treatment + 2 for recovery) for 4 weeks with an interim sacrifice at 2 weeks.

The composition of Placebo Vaginal Cream or Benzydamine Hydrochloride Vaginal Cream are illustrated in the following table 10. All amounts are expressed in percent by weight based on the weight of the total composition.

TABLE 10

Composition	Placebo Vaginal Cream	Benzydamine Hydrochloride Vaginal Cream
Benzydamine hydrochloride	-	0.12
Neutral oil	3.0	3.0
Emulsifier	18.0	18.0
Surfactant	3.0	3.0
Benzoic acid	0.2	0.2
Propylgallate	0.1	0.1
EDTA	0.1	0.1
Water q.s.	100	100

At the end of the treatment period, all animals were sacrificed except recovery animals, which were kept for a 2-week treatment-free period.

The results of the test are summarized hereinbelow.

Once daily intravaginal administration of BHV Cream, to female New Zealand White rabbits, for 2 or 4 weeks, resulted in very limited systemic exposure. There were no mortalities, adverse clinical signs or local

reactions, and no macroscopic changes among examined parameters were considered to be related to BHV Cream.

Histologically, ulcerative changes along with inflammation, cellular debris/inflammatory cells in the lumen and decreased amount of mucus were observed in both groups of animals treated with the placebo or the BHV cream. Following the 2-week treatment-free period, only minor changes were seen in the vagina indicating a clear recovery process.

In conclusion, the BHV Cream is considered a well tolerated product for the treatment of inflammatory and/or infective conditions mainly localized in the genital area, in particular vaginosis, vaginitis and vulvo-vaginitis.

CLAIMS

1. A pharmaceutical composition comprising (i) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (ii) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, and (iii) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid, and (iv) benzydamine in an amount equal to or lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition,

provided that, when benzydamine is present as benzydamine hydrochloride in an amount of 0.12% w/w, together with Miglyol® 812 in an amount of 3% w/w, Tefose® 63 in an amount of 18% w/w, and Labrafil® M2130CS in an amount of 3% w/w, said composition does not comprise econazole nitrate.

2. The pharmaceutical composition according to claim 1, wherein said composition comprises benzydamine in an amount higher than 0.01% w/w with respect to the total weight of the pharmaceutical composition.

3. The pharmaceutical composition according to claim 1, wherein said composition comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount lower than 10% w/w with respect to the total weight of the pharmaceutical composition.

4. The pharmaceutical composition according to claim 1, wherein said composition comprises at least one ester of glycerin with a C_8-C_{10} saturated fatty acid in an amount higher than 0.5% w/w with respect to the total weight of the pharmaceutical composition.

5. The pharmaceutical composition according to claim 1, wherein said composition comprises at least one ester of polyethylene glycol

glycerides with a C_{12}-C_{14} saturated fatty acid in an amount lower than 10% w/w with respect to the total weight of the pharmaceutical composition.

6. The pharmaceutical composition according to claim 1, wherein said composition comprises at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid in an amount higher than 0.5% w/w with respect to the total weight of the pharmaceutical composition.

7. The pharmaceutical composition according to claim 1, wherein said composition comprises at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid in an amount lower than 30% w/w with respect to the total weight of the pharmaceutical composition.

8. The pharmaceutical composition according to claim 1, wherein said composition comprises at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid in an amount higher than 1% w/w with respect to the total weight of the pharmaceutical composition.

9. The pharmaceutical composition according to any one of the preceding claims, wherein said composition comprises an aqueous dispersion of (i) at least one ester of glycerin with a C_8-C_{10} saturated fatty acid, (ii) at least one ester of polyethylene glycol glycerides with a C_{12}-C_{14} saturated fatty acid, (iii) at least one ester of polyethylene glycol with a C_{16}-C_{18} saturated fatty acid, and (iv) benzydamine in an amount equal to or lower than 0.5% w/w with respect to the total weight of the pharmaceutical composition.

10. The pharmaceutical composition according to claim 9, wherein said composition comprises water in an amount higher than 40% w/w with respect to the total weight of the pharmaceutical composition.

11. The pharmaceutical composition according to any one of the preceding claims, wherein said composition is for topical use.

12. The pharmaceutical composition according to claim 11, wherein said composition is prepared in a dosage form selected from the group comprising creams, ointments, lotions, cream-gels, gels, foams, vaginal douches, or solutions for external use.

13. The pharmaceutical composition according to claim 12, wherein said dosage form is cream, cream-gel, or gel.

14. The pharmaceutical composition according to any one of the preceding claims, wherein said composition comprises at least one preservative selected from the group comprising benzoic acid, ascorbic acid, propyl gallate, and mixture thereof.

15. The pharmaceutical composition according to any one of the preceding claims, wherein said composition comprises at least one stabilizers selected from the group comprising ethylenediaminetetraacetic acid (EDTA), N-(hydroxyethyl)-ethylenediaminetriacetic acid (HEDTA), nitrilotriacetic acid (NTA), diethylenetriaminepentaacetic acid (DTPA), and mixture thereof.