Description

BACKGROUND OF THE INVENTION

1) Field of the Invention

This invention relates to novel antimycotic external imidazole preparations, and more specifically to external preparations which have reduced skin irritation, can show their effects to maximum extent and over a prolonged period of time and are physicochemically stable.

2) Description of the Related Art

Antimycotic imidazole preparations having antifungal activities against fungi and the like have already been marketed with preparation forms such as cream preparations, gel preparations and liquid preparations owing to their merits such that they have a broad antifungal spectrum and fewer resistant fungi occur clinically.

These conventional, commercial antimycotic imidazole preparations are however not fully satisfactory, because they are accompanied by drawbacks such as skin irritation and/or poor stability.

For example, liquid preparations often contain an alcohol, leading to the drawback that they have skin irritation due to the alcohol. Gel preparations also contain an alcohol or the like while cream preparations contain an emulsifier and a preservative, so that they also have the problem of skin irritation.

It is required to enhance antifungal activities so that the period of treatment can be shortened and the frequency of application can be reduced. To achieve this, it is necessary to design a base such that the effectiveness can be optimized in the treatment, for example, by improving spreadability, maintaining good releasability and enhancing retaining effects. No external preparation capable of meeting these requirements has however yet been provided.

It has hence been desired to provide an antimycotic external preparation which has low skin irritation and can fully exhibit excellent effects.

SUMMARY OF THE INVENTION

With the foregoing in view, the present inventors have proceeded with an extensive investigation. As a result, it has been found that an external preparation - which is obtained by mixing (E)-1-[2-methylthio-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazole hydrochloride, active ingredient, and a basic substance in combination an external preparation base - has low skin irritation, can continuously exhibit curative effects and is physicochemically stable, leading to the completion of the present invention.

Namely, the present invention provides an anti-mycotic external imidazole preparation comprising the following ingredients:

(a) 0.1-5 wt.% of (E)-1-[2-methylthio-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazole hydrochloride;

(b) 0.01-3 wt.% of a basic substance; and

(c) an external preparation base of an external preparation generally applied to skin surfaces selected from liquid preparations, ointment preparations and cream preparations.

Each external preparation of the present invention shows excellent pharmacological effects since (E)-1-[2-methylthio-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazole hydrochloride, the active ingredient (a), and the basic substance act synergistically and its corresponding external preparation base is combined.

When formed as external liquid preparations, they have excellent affinity with and spreadability on the skin, enhance the activities of their active ingredient and control the release of the active ingredients. Accordingly, the retainability on the skin is enhanced and curative effects can be exhibited over a prolonged period of time. Further, skin irritation is reduced.

When formed as ointment preparations, the active ingredient is dissolved to suitable extent in the base and the release of the active ingredient is controlled by the addition of the liquid oil substance. The retainability on the skin is therefore enhanced and curative effects can be exhibited over a prolonged period of time.

Further, cream preparations can control the releasability of the active ingredient, have enhanced retainability on the skin and can exhibit curative effects over a prolonged period of time, because the activities of the active ingredient are enhanced and the active ingredient is dissolved to suitable degree in the base. By the addition of a liquid oil substance, the preparations are rendered excellent not only in spreadability and percutaneous absorption but also in physicochemical stability, and their skin irritation is

reduced.

The antimycotic external imidazole preparations of the present invention have reduced skin irritation, give good feeling upon use, can exhibit superb curative effects over a prolonged period of time, and are physicochemically stable. They are therefore extremely advantageous as external antimycotic preparations for the skin or the like.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 diagrammatically shows the results of the effectiveness test conducted in Test 1 with respect to the external liquid preparations of the present invention, which illustrates their effectiveness in terms of average lesion score vs. days after infection;

FIG. 2 diagrammatically depicts the results of the effectiveness test conducted in Test 1 with respect to the ointment preparations of the present invention, which shows their effectiveness in terms of average lesion score vs. days after infection; and

FIG. 3 diagrammatically illustrates the results of the effectiveness test conducted in Test 1 with respect to the cream preparations of the present invention, which shows their effectiveness in terms of average lesion score vs. days after infection;

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The term "external preparation" as used herein embraces preparations generally applied to skin surfaces such as external liquid preparations, ointment preparations and cream preparations.

(E)-1-[2-methylthio-1-[2-(pentyloxy)phenyl]-ethenyl]-1H-imidazolehydrochloride (hereinafter called "Compound A"), ingredient (a), i.e., the active ingredient in the external preparation of this invention is a known substance having excellent antibacterial activities against bacteria, fungi and the like (EP-A-0227011).

Compound A is added in a proportion of 0.1-5 wt.% (hereinafter indicated merely by "%"), preferably 0.5-1.5% based on the whole composition.

On the other hand, examples of the basic substance as ingredient (b) include organic amines such as alkylamines and mono-, di- and trialkanolamines; and inorganic alkalis such as alkali hydroxides and alkali carbonates. Among these, monoethanolamine, diethanolamine, triethanolamine, sodium hydroxide, potassium hydroxide and the like are particularly preferred. Ingredient (b) is added in a proportion of 0.01-3%, preferably 0.1-1% based on the whole composition.

The external preparation base as ingredient (c) can be suitably selected in accordance with the preparation form of the intended external preparation in the present invention.

To prepare an external preparation in the form of an external liquid preparation, it is preferable to use, as a base, a liquid preparation base which contains a nonionic surfactant and a liquid oil substance in proportions of 1-25% and 1-55%, respectively based on the whole composition. As the nonionic surfactant contained in the above liquid preparation base, a polyoxyalkylene ester or ether surfactant is preferred, with an ester-type surfactant between polyoxyethylene (POE) and a saturated fatty acid or an ether-type surfactant between POE and a saturated aliphatic alcohol being particularly preferred. Specific examples include POE monolaurate, POE monostearate, POE lauryl ether, POE cetyl ether, POE hydrogenated castor oil and the like. They can be added preferably in a proportion of 2-15% based on the whole composition. No particular limitation is imposed on the liquid oil substance insofar as it is liquid at room temperature. Particularly preferred are fatty acid esters, including diisopropyl adipate, diethyl sebacate and isopropyl myristate by way of example. They can be used either singly or in combination. They can be added preferably in a proportion of 5-45% based on the whole composition. Further, the external liquid preparation base can also be added with ethanol in a proportion of 5-80%, preferably 30-70% based on the whole composition. Further addition of purified water is preferred.

To prepare an external preparation in the form of an ointment preparation, it is preferable to use, as a base, an ointment base which contains a nonionic surfactant and an oleaginous ointment base in proportions of 2-5% and at least 80%, respectively based on the whole composition. As the nonionic surfactant which is contained in the above base, a polyoxyalkylene alkyl ether, polyalkylenelycol fatty acid ester, polyoxyalkylene hydrogenated castor oil, sorbitan fatty acid ester, propyleneglycol fatty acid ester or the like can be used. Specific examples include POE oleyl ether, POE monolaurate, POE hydrogenated castor oil 5, sorbitan sesquioleate, and propyleneglycol monostearate. They can be added preferably in a proportion of 2.5-3.5% based on the whole composition. On the other hand, as the oleaginous ointment base, it is preferable to use (i) a mineral oil, for example, yellow soft paraffin, white soft paraffin, paraffin,

liquid paraffin, plastibase, ZELEN 50W or silicone in combination with (ii) a liquid oil substance selected from diethyl sebacate, diisopropyl adipate, medium-chain fatty acid triglycerides and 2-octyldodecanol. These oleaginous ointment bases can be added preferably in an amount of 90-95%. Of these components, the liquid oil substance (ii) can be added preferably in a proportion of 2-15%, notably 5-10% based on the whole composition. Further, the ointment base can also be added with water in a proportion of 1-10%, preferably 2-5% based on the whole composition. In addition, it is also preferable to use, as a stabilizer, butylhydroxyanisole or dibutylhydroxytoluene (BHT) in combination with disodium edetate.

To prepare the external preparation of this invention in the form of a cream preparation, it is preferable to use a cream base which contains a non-ionic surfactant, an oil substance and water in proportions of 1-20%, 2-50% and 40-90%, respectively based on the whole composition.

Exemplary nonionic surfactants which can be contained in the above cream base include polyoxyalkylene surfactants such as polyoxyalkylene sorbitan fatty acid esters, polyoxyalkylene alkyl ethers, polyoxyalkyleneglycol fatty acid esters and polyoxyalkylene hydrogenated castor oil; and fatty acid ester surfactants such as sorbitan fatty acid esters and glycerin fatty acid esters. Specific examples include sorbitan monostearate, POE sorbitan monostearate, glyceryl monostearate, POE cetyl ether, polyethyleneglycol monostearate, and POE hydrogenated castor oil. They can be added preferably in a proportion of 2-10% based on the whole composition.

No particular limitation is imposed on the oil substance insofar as it can be used in general cream preparations. Usable exemplary oil substances include hydrocarbons such as light liquid paraffin, squalane, white soft paraffin, microcrystalline wax and ceresin; waxes such as beeswax, spermaceti and carnauba wax; fatty acid esters such as diethyl sebacate, diisopropyl adipate, cetyl lactate, cetyl palmitate and myristyl myristate; aliphatic alcohols such as stearyl alcohol, 2-octyldodecanol, 2-hexyldecanol and cetanol; triglycerides such as natural fatty acid triglyceride and medium-chain fatty acid triglycerides; fatty acids such as palmitic acid, stearic acid and myristic acid; etc. Among these, as to aliphatic compounds, saturated aliphatic compounds are particularly preferred. Described specifically, stearyl alcohol, white soft paraffin, medium-chain fatty acid triglycerides, diethyl sebacate, octyldodecanol and squalane are particularly preferred. They can be used either singly or in combination. They can be added preferably in a proportion of 10-30% based on the whole composition. Further, water can also be added preferably in a proportion of 60-80%.

The external preparations of the present invention can each be produced by adding the above three ingredients by a conventional method suited for the preparation form. To extent not impairing the effects of the present invention, the external preparations of the present invention can be added with various conventional additives, for example, stabilizers, perfumes, colorants, suspending agents, etc. In particular, to prepare an external preparation in the form of a cream preparation, it is desirable to add one or more conventional stabilizers, for example, an antioxidant such as butylhydroxyanisole, dibutylhydroxytoluene or propyl gallate; an antiseptic such as a paraoxybenzoic acid ester or dehydroacetic acid; and/or a chelating agent such as disodium edetate or tetrasodium edetate.

The present invention will hereinafter be described in further detail by the following examples, comparative examples and tests. It should be borne in mind however that the present invention is not limited whatsoever to or by the following examples.

Example 1

Compound A	1 g
Diethyl sebacate	15 g
POE(10) monolaurate	5 g
Triethanolamine	0.465 g
Ethanol	56 g
Purified water	q.s. to 100 m*l*.

After Compound A was dissolved in ethanol, diethyl sebacate and POE(10) monolaurate were mixed. Added next was a solution of triethanolamine in a suitable amount of purified water. Purified water was then added in an amount sufficient to produce 100 m*l*, whereby an external liquid preparation was obtained.

Example 2

Compound A	1 g
Diethyl sebacate	30 g
Diisopropyl adipate	10 g
POE(5.5) cetyl ether	5 g
Triethanolamine	0.465 g
Ethanol	35 g
Purified water	q.s. to 100 mℓ.

An external liquid preparation was prepared in a similar manner to Example 1.

Example 3

Compound A	1 g
Diethyl sebacate	30 g
POE(60) hydrogenated castor oil	5 g
Sodium hydroxide	0.115 g
Ethanol	42 g
Purified water	q.s. to 100 mℓ.

An external liquid preparation was prepared in a similar manner to Example 1.

Example 4

Compound A	1 g
Isopropyl myristate	10 g
POE(10) monolaurate	10 g
Triethanolamine	0.465 g
Ethanol	56 g
Purified water	q.s. to 100 mℓ.

An external liquid preparation was prepared in a similar manner to Example 1.

Comparative Example 1

Compound A	1 g
Diethyl sebacate	30 g
POE(10) monooleate	5 g
Ethanol	42 g
Purified water	q.s. to 100 mℓ.

An external liquid preparation was prepared in a similar manner to Example 1.

Example 5

Compound A	1 g
Diethyl sebacate	5 g
POE (5) hydrogenated castor oil	3 g
Sodium hydroxide	0.14 g
Purified water	3.86 g
BHT	0.05 g
Disodium edetate	0.05 g
White soft paraffin	86.9 g

White soft paraffin was melted at 70-80 • C, in which BHT was dissolved. The other ingredients which had been mixed at room temperature on the side were then added. The resulting mixture was stirred at 60-70 • C and then allowed to cool down to 45 • C as it was, whereby an ointment preparation was obtained.

Example 6

Compound A	1 g
Diisopropyl adipate	5 g
Sorbitan sesquioleate	3 g
Triethanolamine	0.44 g
Purified water	2.56 g
BHT	0.05 g
Disodium edetate	0.05 g
White soft paraffin	87.9 g

An ointment preparation was obtained in a similar manner to Example 5.

Example 7

Compound A	1 g
Medium-chain fatty acid triglyceride	10 g
Sorbitan sesquioleate	3 g
Diethanolamine	0.32 g
Purified water	2.68 g
BHT	0.05 g
Disodium edetate	0.05 g
White soft paraffin	82.9 g

An ointment preparation was obtained in a similar manner to Example 5.

Example 8

Compound A	1 g
2-Octyldodecanol	10 g
Sorbitan sesquioleate	3 g
Potassium hydroxide	0.16 g
Purified water	2.84 g
BHT	0.05 g
Disodium edetate	0.05 g
White soft paraffin	82.9 g

An ointment preparation was obtained in a similar manner to Example 5.

Comparative Example 2

Compound A	1 g
Diethyl sebacate	5 g
Lauromacrogol	3 g
Sodium hydroxide	0.12 g
Purified water	3.17 g
BHT	0.02 g
Disodium edetate	0.02 g
Japanese Pharmacopoeia macrogol ointment	87.67 g

Japanese Pharmacopoeia macrogol ointment was molten at 70-80 °C, to which lauromacrogol was added. BHT, disodium edetate and diethyl sebacate were added further, followed by stirring. Compound A was then added. The resultant mixture was stirred and was then allowed to cool down to 40 °C as it was, whereby an ointment preparation was obtained.

Comparative Example 3

Compound A	1 g
Diethyl sebacate	5 g
Cetyl lactate	2 g
Lauromacrogol	3 g
Sodium hydroxide	0.14 g
Purified water	3.46 g
BHT	0.05 g
Disodium edetate	0.05 g
Japanese Pharmacopoeia macrogol ointment	85.3 g

An ointment preparation was obtained in a similar manner to Comparative Example 2.

Comparative Example 4

Compound A	1 g
Diethyl sebacate	5 g
Propylene glycol	3 g
Lauromacrogol	3 g
Diethanolamine	0.32 g
Purified water	2.68 g
Japanese Pharmacopoeia macrogol ointment	85 g

An ointment preparation was obtained in a similar manner to Comparative Example 2.

Comparative Example 5

Compound A	1 g
Diethyl sebacate	5 g
Sorbitan sesquioleate	3 g
Purified water	3 g
BHT	0.05 g
Disodium edetate	0.05 g
White soft paraffin	87.9 g

An ointment preparation was obtained in a similar manner to Comparative Example 2.

Example 9

Compound A	1.0 g
Stearyl alcohol	4.0 g
White soft paraffin	5.0 g
Medium-chain fatty acid triglyceride	12.0 g
Glyceryl monostearate	3.0 g
POE (25) cetyl ether	2.0 g
Methyl paraoxybenzoate	0.2 g
Butyl paraoxybenzoate	0.1 g
Disodium edetate	0.02 g
Triethanolamine	0.465 g
Purified water	q.s. to 100 g

The oil-phase ingredients were melted at 60-70 °C, to which Compound A dissolved in a portion of purified water was added under stirring. An aqueous solution of the other ingredients in the remaining portion of the purified water was added. The resulting mixture was emulsified at 70-75 °C and then allowed to cool down to room temperature, whereby a cream preparation was obtained.

Example 10

Compound A	1.0 g
Cetanol	5.0 g
White soft paraffin	6.0 g
Diethyl sebacate	12.0 g
Glyceryl monostearate	4.0 g
POE (25) cetyl ether	2.0 g
Methyl paraoxybenzoate	0.2 g
Butyl paraoxybenzoate	0.1 g
Disodium edetate	0.02 g
Triethanolamine	0.465 g
Purified water	q.s. to 100 g

A cream preparation was prepared in a similar manner to Example 9.

Example 11

Compound A	1.0 g
Stearyl alcohol	4.0 g
White soft paraffin	5.0 g
2-Octyldodecanol	15.0 g
Sorbitan monostearate	2.0 g
POE (20) sorbitan monostearate	3.0 g
Methyl paraoxybenzoate	0.2 g
Butyl paraoxybenzoate	0.1 g
Disodium edetate	0.02 g
Sodium hydroxide	0.115 g
Purified water	q.s. to 100 g

A cream preparation was prepared in a similar manner to Example 9.

Example 12

Compound A	1.0 g
Cetanol	5.0 g
White soft paraffin	6.0 g
White beeswax	2.0 g
Squalane	10.0 g
Glyceryl monostearate	3.2 g
POE (25) cetyl ether	1.8 g
Methyl paraoxybenzoate	0.2 g
Butyl paraoxybenzoate	0.1 g
Disodium edetate	0.02 g
Triethanolamine	0.465 g
Purified water	q.s. to 100 g

A cream preparation was prepared in a similar manner to Example 9.

Example 13

Compound A	1.0 g
Cetanol	5.0 g
White soft paraffin	6.0 g
Medium-chain fatty acid triglyceride	10.0 g
Diethyl sebacate	5.0 g
Glyceryl monostearate	4.0 g
POE (25) cetyl ether	2.0 g
Methyl paraoxybenzoate	0.2 g
Butyl paraoxybenzoate	0.1 g
Disodium edetate	0.02 g
Triethanolamine	0.465 g
Purified water	q.s. to 100 g

A cream preparation was prepared in a similar manner to Example 9.

Comparative Example 6

Compound A	1.0 g
Stearyl alcohol	4.0 g
White soft paraffin	5.0 g
Oleic acid	10.0 g
Glyceryl monostearate	3.0 g
POE (25) cetyl ether	2.0 g
Methyl paraoxybenzoate	0.2 g
Butyl paraoxybenzoate	0.1 g
Propylene glycol	5.0 g
Disodium edetate	0.02 g
Purified water	q.s. to 100 g

A cream preparation was prepared in a similar manner to Example 9.

Test 1 (Effectiveness Test)

A *Trichophyton* infection treatment test of certain external preparations according to this invention was conducted by the following method:

Hair was pulled out at four parts on the back of each guinea pig. Those parts were infected with a culture of *Trichophyton mentagrophytes* TIMM 1189 strain. From the fifth day after the infection to the fungus, a test preparation was applied once a day for straight 14 days. The lesion score was ranked in accordance with the following standard. The smaller the lesion score, the higher the effectiveness.

+1: A small number of tiny erythema and/or erythematous papule are observed in a state scattered like isles, or the lesion is convalescing and new body hair has been growing.

+2: Erythema has spread all over the infected parts with separation of epidermis.

+3: Severe inflammation such as flare and swelling are locally observed with occurrence of substantial scales.

+4: Formation of thickened crust is observed.

The results of the above test are shown in FIG. 1 through FIG. 3.

As will become apparent from the respective figures, each of the external preparations of the present invention was recognized to have high effectiveness.

Test 2 (Safety Test)

A skin irritation test of certain external preparations according to this invention was conducted by the following method:

Pieces of a commercial patch test adhesive plaster (product of Torii & Co., Ltd.) were coated with the individual test preparations and were applied for 48 hours on a lower middle back area of each of 28-30 normal volunteers. Upon elapsed time of 1 hour and 24 hours after the removal of the adhesive plaster pieces, the degree of erythema (i.e., the degree of irritation to the skin) at the part coated with the preparation was determined.

Mild erythema and distinct erythema were indicated by ± and +, respectively. The degree of erythema was indicated by the percentage of erythema-bearing sections based on the entire area.

The results of the above test are summarized in Table 1 through Table 3.

Table 1

Unit: %

	Determined 1 hour later		Determined 24 hours later	
	≥±	≥+	≥±	≥+
Example 1	3.6	0	3.6	0
Example 2	1.8	0	1.8	0
Example 3	3.6	0	1.8	0
Example 4	3.6	0	3.6	0
Comp.Ex. 1	30.3	23.2	26.8	17.9

Table 2

Unit: %

	1 hour later		24 hours later	
	≥±	≥+	≥±	≥+
Example 5	0	0	0	0
Example 6	0	0	0	0
Example 7	0	0	0	0
Example 8	1.7	0	0	0
Comp.Ex. 2	3.3	0	0	0
Comp.Ex. 3	5.0	0	1.7	0
Comp.Ex. 4	3.3	0	0	0
Comp.Ex. 5	10.0	1.7	3.3	0

Table 3

Unit: %

	1 hour later		24 hours later	
	≥±	≥+	≥±	≥+
Example 9	0	0	0	0
Example 10	3.6	0	0	0
Example 11	7.1	0	3.6	0
Example 12	0	0	0	0
Example 13	0	0	0	0
Comp.Ex. 6	19.6	8.9	8.9	5.4

As is envisaged clearly from each table, each of the external preparations of the present invention had extremely low skin irritation.

Test 3 (Stability Test)

A stability test of the external liquid preparations out of the external preparations according to this invention was conducted by the following method:

Each external liquid preparation was stored for 6 months in a constant-temperature chamber controlled at 40°C and was tested for variations in external appearance and the content of the active ingredient

(percent remainder). The results are summarized in Table 4.

Table 4

Item tested Preparation	Variations in external appearance	Percent remainder (%)
Example 1	-	99.7
Example 2	-	99.8
Example 3	-	99.8
Example 4	-	99.6
Comp.Ex. 1	+	94.4

Variations in external appearance:
(-) No variation.
(+) Slight yellowing.

As is apparent from Table 4, the external liquid preparations of the present invention had excellent stability in both the physical properties and the active ingredient.

Test 4 (Stability Test)

A stability test of the ointment preparations out of the external preparations according to this invention was conducted by the following method:

Each ointment preparation was stored for 6 months in a constant-temperature chamber controlled at 40°C and was tested for discoloration, bleeding and the content of the active ingredient (percent remainder). The results are summarized in Table 5.

Table 5

Item tested Preparation	Discoloration	Bleeding	Percent remainder (%)
Example 5	-	-	99.5
Example 6	-	-	99.4
Example 7	-	-	99.7
Example 8	-	-	99.8
Comp.Ex. 2	+	-	96.4
Comp.Ex. 3	-	-	99.1
Comp.Ex. 4	+	-	90.3

Table 5 (Cont'd)

Item tested Preparation	Discoloration	Bleeding	Percent remainder (%)
Comp.Ex. 5	+	+	98.9

Discoloration: (-) no change, (+) slight yellowing.
Bleeding: (-) no bleeding, (+) slight bleeding.

As is clear from Table 5, the ointment preparations of the present invention underwent neither discoloration nor bleeding and the contents of the active ingredient remained substantially unchanged. They were hence recognized stable.

Test 5 (Stability Test)

A stability test of the cream preparations out of the external preparations according to this invention was conducted by the following method:

Each cream preparation was stored for 6 months in a constant-temperature chamber controlled at 45°C and was tested for discoloration, separation and the content of the active ingredient (percent remainder). The results are summarized in Table 6.

Table 6

Item tested Preparation	Discoloration	Separation	Percent remainder(%)
Example 9	-	-	99.8
Example 10	-	-	99.6
Example 11	-	-	99.6
Example 12	-	-	99.0
Example 13	-	-	99.4
Comp.Ex. 6	+	+	95.7

Discoloration: (-) no change, (+) slight yellowing.
Separation: (-) no separation, (+) separated.

As is apparent from Table 6, the cream preparations of the present invention underwent neither discoloration nor separation and the contents of the active ingredient remained substantially unchanged. They were hence recognized stable.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. An antimycotic external imidazole preparation comprising the following ingredients:
   (a) 0.1-5 wt.% of (E)-1-[2-methylthio-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazole hydrochloride;
   (b) 0.01-3 wt.% of a basic substance; and
   (c) an external preparation base of an external preparation generally applied to skin surfaces selected from liquid preparations, ointment preparations and cream preparations.

Table 5 (Cont'd)

Item tested Preparation	Discoloration	Bleeding	Percent remainder (%)
Comp.Ex. 5	+	+	98.9

Discoloration: (-) no change, (+) slight yellowing.
Bleeding: (-) no bleeding, (+) slight bleeding.

As is clear from Table 5, the ointment preparations of the present invention underwent neither discoloration nor bleeding and the contents of the active ingredient remained substantially unchanged. They were hence recognized stable.

Test 5 (Stability Test)

A stability test of the cream preparations out of the external preparations according to this invention was conducted by the following method:

Each cream preparation was stored for 6 months in a constant-temperature chamber controlled at 45°C and was tested for discoloration, separation and the content of the active ingredient (percent remainder). The results are summarized in Table 6.

Table 6

Item tested Preparation	Discoloration	Separation	Percent remainder(%)
Example 9	-	-	99.8
Example 10	-	-	99.6
Example 11	-	-	99.6
Example 12	-	-	99.0
Example 13	-	-	99.4
Comp.Ex. 6	+	+	95.7

Discoloration: (-) no change, (+) slight yellowing.
Separation: (-) no separation, (+) separated.

As is apparent from Table 6, the cream preparations of the present invention underwent neither discoloration nor separation and the contents of the active ingredient remained substantially unchanged. They were hence recognized stable.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. An antimycotic external imidazole preparation comprising the following ingredients:
   (a) 0.1-5 wt.% of (E)-1-[2-methylthio-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazole hydrochloride;
   (b) 0.01-3 wt.% of a basic substance; and
   (c) an external preparation base of an external preparation generally applied to skin surfaces selected from liquid preparations, ointment preparations and cream preparations.

* C L M S *

2. The preparation of claim 1, wherein the external preparation base, ingredient (c), contains 1-25 wt.% of a nonionic surfactant, 1-55 wt.% of a liquid oil substance, 5 - 80 % of ethanol, and purified water and is in the preparation form of an external liquid preparation.

3. The preparation of claim 2, wherein the liquid oil substance is a saturated fatty acid ester.

4. The preparation of claim 2 or 3, wherein the nonionic surfactant is an ester-type nonionic surfactant between polyoxyethylene and a saturated fatty acid or an ether-type nonionic surfactant between polyoxyethylene and a saturated aliphatic alcohol.

5. The preparation of claim 1, wherein the external preparation base, ingredient (c), contains 2-5 wt.% of a nonionic surfactant, at least 80 wt.% of an oleaginous ointment base and 1 - 10 wt. % of water and is in the preparation form of an ointment preparation.

6. The preparation of claim 1, wherein the external preparation base, ingredient (c), contains 1-20 wt.% of a nonionic surfactant, 2-50 wt.% of an oil substance and 40-90 wt.% of water and is in the preparation form of a cream preparation.

Claims for the following Contracting State : ES

1. Process for the preparation of an antimycotic external imidazole preparation, which comprises: mixing the following ingredients in the indicated amounts:
   (a) 0.1-5 wt.% of (E)-1-[2-methylthio-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazole hydrochloride,
   (b) 0.01-3 wt.% of a basic substance, and
   (c) an external preparation base of an external preparation generally applied to skin surfaces selected from liquid preparations, ointment preparations and cream preparations; and sufficiently homogenizing all the ingredients in such a way that the final composition obtained has homogeneity sufficient for use over the skin.

2. Process according to claim 1, wherein the external preparation base, the ingredient (c), comprises:
   1-25 wt.% of a nonionic surfactant,
   1-55 wt.% of a liquid oil substance, and
   5-80 wt.% of ethanol and purified water.

3. Process according to claim 2, wherein the liquid oil substance is a saturated fatty acid ester.

4. Process according to claim 2 or 3, wherein the nonionic surfactant is an ester-type nonionic surfactant between polyoxyethylene and a saturated fatty acid or an ether-type nonionic surfactant between polyoxyethylene and a saturated aliphatic alcohol.

5. Process according to claim 1, wherein the external preparation base, the ingredient (c), contains 2-5 wt.% of a nonionic surfactant, at least 80 wt.% of an oleaginous ointment base and 1-10 wt.% of water and is in the preparation form of an ointment preparation.

6. Process according to claim 1, wherein the external preparation base, the ingredient (c), contains 1-20 wt.% of a nonionic surfactant, 2-50 wt.% of an oil substance and 40-90 wt.% of water and is in the preparation form of a cream preparation.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Antimycotische, Imidazol enthaltende, äußere Zubereitung, umfassend nachstehende Bestandteile:
   (a) 0,1 bis 5 Gew.-% (E)-1-[2-Methylthio-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazolhydrochlorid;
   (b) 0,01 bis 3 Gew.-% eines basischen Stoffes und
   (c) eine Grundlage für eine äußere Zubereitung, nämlich für eine äußere Zubereitung, die im allgemeinen auf die Hautoberfläche aufgetragen wird, ausgewählt aus Flüssigzubereitungen, Salbenzubereitungen und Cremezubereitungen.

2. Zubereitung nach Anspruch 1, wobei die äußere Grundlage für eine Zubereitung, Bestandteil (c), 1 bis 25 Gew.-% eines nichtionischen Tensids, 1 bis 55 Gew.-% eines flüssigen öligen Stoffes, 5 bis 80 % Ethanol und gereinigtes Wasser enthält und in der Zubereitungsform einer äußeren, flüssigen Zubereitung vorliegt.

3. Zubereitung nach Anspruch 2, wobei der flüssige, ölige Stoff ein gesättigter Fettsäureester ist.

4. Zubereitung nach Anspruch 2 oder 3, wobei das nichtionische Tensid ein nichtionisches Tensid vom Estertyp ist zwischen Polyoxyethylen und einer gesättigten Fettsäure oder ein nichtionisches Tensid vom Ethertyp zwischen Polyoxyethylen und einem gesättigten aliphatischen Alkohol ist.

5. Zubereitung nach Anspruch 1, wobei die Grundlage für eine äußere Zubereitung, Bestandteil (c), 2 bis 5 Gew.-% eines nichtionischen Tensids, mindestens 80 Gew.-% einer öligen Salbengrundlage und 1 bis 10 Gew.-% Wasser enthält und in der Zubereitungsform einer Salbenzubereitung vorliegt.

6. Zubereitung nach Anspruch 1, wobei die Grundlage für eine äußere Zubereitung, Bestandteil (c), 1 bis 20 Gew.-% eines nichtionischen Tensids, 2 bis 50 Gew.-% eines öligen Stoffes und 40 bis 90 Gew.-% Wasser enthält und in der Zubereitungsform einer Cremezubereitung vorliegt.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer antimycotischen, Imidazol enthaltenden, äußeren Zubereitung, umfassend:
   Vermischen der nachstehenden Bestandteile in den ausgewiesenen Mengen:
   (a) 0,1 bis 5 Gew.-% (E)-1-[2-Methylthio-1-[2-(pentyloxy)phenyl]ethenyl]-1H-imidazolhydrochlorid;
   (b) 0,01 bis 3 Gew.-% eines basischen Stoffes und
   (c) eine Grundlage für eine äußere Zubereitung, nämlich eine äußere Zubereitung, die allgemein auf die Hautoberfläche aufgetragen wird, ausgewählt aus Flüssigzubereitungen, Salbenzubereitungen und Cremezubereitungen und
   ausreichendes Homogenisieren aller Bestandteile derart, daß das fertige Mittel ausreichende Homogenität zur Verwendung auf der Haut erhält.

2. Verfahren nach Anspruch 1, wobei die Grundlage für eine äußere Zubereitung, Bestandteil (c), umfaßt:
   1 bis 25 Gew.-% eines nichtionischen Tensids,
   1 bis 55 Gew.-% eines flüssigen, öligen Stoffes und
   5 bis 80 Gew.-% Ethanol und gereinigtes Wasser.

3. Verfahren nach Anspruch 2, wobei der flüssige ölige Stoff ein gesättigter Fettsäureester ist.

4. Verfahren nach Anspruch 2 oder 3, wobei das nichtionische Tensid ein nichtionisches Tensid vom Estertyp zwischen Polyoxyethylen und einer gesättigten Fettsäure oder ein nichtionisches Tensid vom Ethertyp zwischen Polyoxyethylen und einem gesättigten aliphatischen Alkohol ist.

5. Verfahren nach Anspruch 1, wobei die Grundlage für eine äußere Zubereitung, Bestandteil (c), 2 bis 5 Gew.-% eines nichtionischen Tensids, mindestens 80 Gew.-% einer öligen Salbengrundlage und 1 bis 10 Gew.-% Wasser enthält und in der Zubereitungsform einer Salbenzubereitung vorliegt.

6. Verfahren nach Anspruch 1, wobei die Grundlage für eine äußere Zubereitung, Bestandteil (c), 1 bis 20 Gew.-% eines nichtionischen Tensids, 2 bis 50 Gew.-% eines öligen Stoffes und 40 bis 90 Gew.-% Wasser enthält und in der Zubereitungsform einer Cremezubereitung vorliegt.

Revendications
Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Préparation antimycotique, contenant un imidazole, pour application externe, comprenant les ingrédients suivants :
   (a) 0,1 - 5% en poids de chlorhydrate de (E)-1-[2-méthylthio-1-[2-(pentyloxy)phényl]éthényl]-1H-imadazole ;

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(b) 0,01 - 3% en poids d'une substance basique ; et
(c) une base de préparation pour application externe, pour une préparation pour application externe généralement appliquée à des surfaces de la peau, choisie parmi des préparations liquides, des préparations en pommades et des préparations en crème.

2. Préparation selon la revendication 1, dans laquelle la base pour préparation pour application externe, à savoir l'ingrédient (c), contient 1 - 25% en poids d'un agent tensio-actif non-ionique, 1 - 55% en poids d'une substance liquide de type huile, 5 - 80% d'éthanol, et de l'eau purifiée, et se trouve sous la forme de préparation d'une préparation liquide pour application externe.

3. Préparation selon la revendication 2, dans laquelle la substance liquide de type huile est un ester d'acide gras saturé.

4. Préparation selon la revendication 2 ou 3, dans laquelle l'agent tensio-actif non-ionique est un agent tensio-actif non-ionique de type ester formé entre le polyoxyéthylène et un acide gras saturé ou un agent tensioactif non-ionique de type éther formé entre le polyoxyéthylène et un alcool aliphatique saturé.

5. Préparation selon la revendication 1, dans laquelle la base pour préparation pour application externe, à savoir l'ingrédient (c), contient 2 - 5% en poids d'un agent tensio-actif non-ionique, au moins 80% en poids d'une base oléagineuse de pommade et 1 - 10% en poids d'eau, et se trouve sous la forme de préparation d'une préparation en pommade.

6. Préparation selon la revendication 1, dans laquelle la base pour préparation pour application externe, à savoir l'ingrédient (c), contient 1 - 20% en poids d'un agent tensio-actif non-ionique, 2 - 50% en poids d'une substance de type huile et 40 - 90% en poids d'eau, et se trouve sous la forme de préparation d'une préparation en crème.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'une préparation antimycotique, contenant un imidazole, pour application externe, lequel comprend les opérations consistant à :
   - mélanger les ingrédients suivants dans les quantités indiquées :
     (a) 0,1 - 5% en poids de chlorhydrate de (E)-1-[2-méthylthio-1-[2-(pentyloxy)phényl]éthényl]-1H-imidazole;
     (b) 0,001 - 3% en poids d'une substance basique ; et
     (c) une base de préparation pour application externe, pour une préparation pour application externe généralement appliquée à des surfaces de la peau, choisie parmi des préparations liquides, des préparations en pommades et des préparations en crèmes; et
   - homogénéiser de façon suffisante tous les ingrédients d'une telle manière que la composition finale obtenue présente une homogénéité suffisante en vue d'une utilisation sur la peau.

2. Procédé selon la revendication 1, dans lequel la base pour préparation pour application externe, à savoir l'ingrédient (c), comprend :
   - 1 - 25% en poids d'un agent tensio-actif non-ionique,
   - 1 - 55% en poids d'une substance liquide de type huile, et
   - 5 - 80% en poids d'éthanol et d'eau purifiée.

3. Procédé selon la revendication 2, dans lequel la substance liquide de type huile est un ester d'acide gras saturé.

4. Procédé selon la revendication 2 ou 3, dans lequel l'agent tensio-actif non-ionique est un agent tensioactif non-ionique de type ester formé entre le polyoxyéthylène et un acide gras saturé ou un agent tensioactif non-ionique de type éther formé entre le polyoxyéthylène et un alcool aliphatique saturé.

5. Procédé selon la revendication 1, dans lequel la base pour préparation pour application externe, à savoir l'ingrédient (c), contient 2 - 5% en poids d'un agent tensioactif non-ionique, au moins 80% en

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poids d'une base oléagineuse de pommade et 1 - 10% en poids d'eau, et se trouve sous la forme de préparation d'une préparation en pommade.

6. Procédé selon la revendication 1, dans lequel la base pour préparation pour application externe, à savoir l'ingrédient (c), contient 1 - 20% en poids d'un agent tensio-actif non-ionique, 2 - 50% en poids d'une substance de type huile et 40 - 90% en poids d'eau et se trouve sous la forme de préparation d'une préparation en crème.