ANTIMYCOTIC GEL HAVING HIGH ACTIVE COMPOUND RELEASE

The present invention relates to a topically applicable antimycotic preparation having high active compound release in the form of a gel preparation which contains at least one antimycotic substance from the hydroxypyridone class and at least one hydrophilic gel-forming agent.

For the topical treatment of mycoses, especially mycoses of the skin, various preparation forms of hydroxypyridone derivatives such as solutions, ointments and powders are already known. Optimum treatment of dermatomycoses, however, using the preparation forms of hydroxy-pyridones known until now is not unrestrictedly possible for the most diverse reasons.

Topically applicable liquid preparations in general include clear aqueous or aqueous-alcoholic solutions. They are either painted onto the skin surface or used for washing or baths. In particular, they are used in any skin regions which are covered by dense hair growth, since ointments or powders are not suitable for these areas. Moreover, they are used in those skin areas for which other pharmaceutical forms are not willingly used for cosmetic reasons, e.g. on the face or on highly mobile body sites (e.g. elbows, knee etc.).

The release rate of the active compound from solutions is generally high, since after application by evaporation of the vehicle constituents a high concentration gradient between the preparation and the skin results, which in the end leads to a high absorption of active compound through the skin and thus to a high efficacy.

With respect to their applicational properties, solutions, however, are rather to be assessed as less favorable, since on account of their liquid aggregate state they can only be handled with difficulty, in particular on the face, and a specific application to restricted skin areas is not possible.

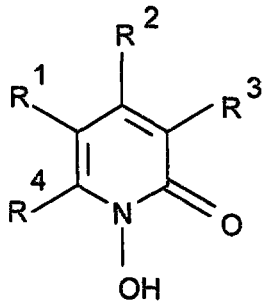
Ointments or semisolid pharmaceutical forms are administration forms which in general are spreadable in the temperature range between room temperature and skin temperature and thereby can be differentiated from the liquid administration forms and those with solid character. Based on the substance characteristics of the skin vehicle substances, ointments are in general understood as meaning anhydrous fatty bases or emulsions consisting of an oily and aqueous phase, which are stabilized by an emulsifier.

On account of their semisolid consistency, ointment preparations - in contrast to solutions - can be applied very specifically to restricted skin areas. Owing to the content of fatty constituents, however, the release of the lipophilic hydroxypyrrolidone derivatives from the ointment constituents is highly restricted. The success of treatment after ointment application is furthermore adversely affected by the fact that ointments do not usually leave behind a wipe-resistant film on the skin. On contact with the clothing or bed linen, the product applied can thus be easily removed again and is thus no longer available for successful therapy.

Powder preparations are primarily used for the adsorption of increased secretion and keeping the skin dry; a point which, in particular in the treatment of dermatomycoses, plays an important part. For practical reasons, the application of powder preparations is almost exclusively restricted to the treatment of mycosis pedis.

It has now been found that gel formulations of hydroxypyridone derivatives, which contain solvents and hydrophilic gel-forming agents and also customary formulation auxiliaries, make possible a high release of the active compound and thus an improved action due to the achievement of high concentrations of the active compound in the skin. The preparations according to the invention can furthermore be applied to the affected skin areas easily and specifically on account of their semisolid consistency and moreover exhibit the desired drying-out effect, particularly in the treatment of mycosis pedis.

The invention therefore relates to a pharmaceutical preparation comprising a hydrophilic gel-forming agent, water and a compound of the formula I



(I)

or a physiologically tolerable salt of the compound of the formula I, where R^1, R^2 and R^3, which are identical or different, are a hydrogen atom or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms.

A preferred pharmaceutical preparation is one where
R^4 is a saturated hydrocarbon having 6 to 9 carbon atoms, one of the radicals R^1 and R^3 is a hydrogen atom and the other is a hydrogen atom, methyl or ethyl and R^2 is an alkyl radical having 1 or 2 carbon atoms.

A particularly preferred pharmaceutical preparation is one wherein the compound of the formula I contains a cyclic radical in the position R^4.

Furthermore preferred is a pharmaceutical preparation wherein R^4 is a cyclohexyl radical or $-CH_2-CH(CH_3)-CH_2-(C(CH_3)_3$.

The term "saturated" in this case designates those radicals which contain no aliphatic multiple bonds, i.e. no ethylenic or acetylenic bonds.

Suitable compounds of the formula I which may be mentioned, for example, are
1-hydroxy-4-methyl-6-n-hexyl-, -6-iso-hexyl-, -6-n-heptyl- or -6-isoheptyl-2-pyridone, 1-hydroxy-4-methyl-6-octyl- or -6-isooctyl-2-pyridone, in particular as 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone, 1-hydroxy-4-

methyl-6-cyclohexyl-2-pyridone, 1-hydroxy-4-methyl-6-cyclohexylmethyl- or -6-cyclohexyl-ethyl-2-pyridone, where the cyclohexyl radical can in each case also carry a methyl radical, 1-hydroxy-4-methyl-6-(2-bicyclo-[2.2.1]heptyl)-2-pyridone, 1-hydroxy-3,4-dimethyl-6-benzyl- or -6-dimethylbenzyl-2-pyridone and 1-hydroxy-4-methyl-6-(ß-phenylethyl)-2-pyridone.

The invention furthermore relates to the use of the pharmaceutical preparation for the production of a pharmaceutical for the treatment and prophylaxis of dermatomycoses.

Using the pharmaceutical according to the invention, drastic healing can be achieved in the treatment of dermatomycoses. The pharmaceutical according to the invention is also suitable for prophylactic application against dermatomycoses.

The content of the compound of the formula I in the pharmaceutical preparation according to the invention is dependent on the structure of each compound of the formula I and thus on its release from the gel, its penetration behavior in the skin and its antimicrobial properties.

In the pharmaceutical preparation according to the invention, the compound of the formula I is in general contained in an amount from 0.05 to 2 percent by weight, preferably 0.1 to 1% by weight.

Possible gel-forming agents are native substances such as gelatin, pectin, carrageenan, agar, tragacanth and alginates, semisynthetic gel-forming agents such as cellulose ethers (methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethyl-cellulose), starch derivatives and pectin derivatives and also fully synthetic gel-forming agents such as polyacrylates, polymethacrylates, polyvinyl alcohol and polyvinylpyrrolidones. Polyacrylates are particularly suitable. They are employed in amounts from 0.3 to 2.0 parts by weight to 100 parts by weight of final product.

Suitable solvents are water and also all solvents miscible with water. Those suitable are, for example, alkanols such as ethanol or isopropyl alcohol, and also propylene glycol and dimethyl sulfoxide. One or more solvents can be employed in the preparation of the formulations according to the invention.

Suitable additional solubilizers for the pharmaceutical preparation according to the invention are:
Benzyl alcohols, 2-octyldodecanol, adipates, propylene glycol and glycerol. These solubilizers are contained in the preparations according to the invention from 1 to 15 percent by weight (% by weight).

Suitable further auxiliaries are emulsifiers, wetting agents and spreading agents.

The preparations are prepared in a manner known per se by combining the individual components and - if necessary - further processing suited to the particular preparation.

The present invention is explained in greater detail by the following examples, but is not restricted to these. If not stated otherwise, the quantitative data relate to the weight.

Example 1

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)pyridone	0.50 %
Hydroxyethylcellulose	1.50 %
Polyethylene glycol-7 glycerylcocoate	5.00 %
1,2-propylene glycol	10.00 %
Isopropyl alcohol	20.00 %
Demineralized water	63.00 %

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Example 2

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	1.00 %
Polyacrylic acid polymer	
(e.g. Carbomer 934 P)	0.70 %
Sodium hydroxide	0.20 %
Sodium dioctylsulfosuccinate	0.05 %
2-octyldodecanol	7.50 %
Isopropyl alcohol	25.00 %
Demineralized water	65.55 %

Example 3

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	0.50 %
Polyacrylic acid polymer	
(e.g. Carbomer 940)	0.50 %
Sodium hydroxide	0.20 %
Polyoxyethylene(20)sorbitan monostearate	3.50 %
Isopropyl myristate	10.00 %
Ethanol	20.00 %
Demineralized water	65.30 %

Example 4

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-(2,44-trimethylpentyl)-2(1H)-pyridone	1,00 %
Hydroxypropylcellulose	1.00 %
1,2-Propylene glycol	2.50 %
Ethanol	20.00 %
Demineralized water	75.50 %

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Example 5

An ointment preparation from the prior art has the following composition:

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	1.00 %
Petroleum jelly	20.00 %
Stearyl alcohol	15.00 %
2-Octyldodecanol	10.00 %
Polyoxyethylene(20)sorbitan monostearate	3.50 %
Sorbitan monostearate	1.50 %
Demineralized water	49.00 %

Example 6

Activity testing

Testing the active compound release of the pharmaceutical preparation according to the invention in a penetration model using excised pig's skin.

The testing of the active compound release from the compositions according to the invention was carried out in a penetration model on excised pig's skin. Here, a conclusion is drawn indirectly on the active compound release from the compositions according to the invention via the determination of the penetration depth by means of a microbiological determination method:

Relatively large pieces of back skin were excised from slaughtered pigs before scalding the killed animals, wrapped with moist paper and plastic film and deep frozen at -20°C until the test.

Before the test, the skin surface was freed from fatty tissue, shaved and treated with isopropanol for 60 minutes for disinfection purposes. For each test batch a separate piece of skin (about 2 x 3 cm) was used. The skin surface was treated with preparations containing various compounds of the formula I. After the end of the various action times (0.5, 1 and 4 hours), the products were removed from the skin surface by washing. In order to

investigate the different penetration power of the active compounds - or the different release power of the preparations - the pieces of skin were stripped off 2 x, 6 x and 10 x using Scotch film on, in each case, three adjacent tracks. Each track was then inoculated 10 x in a punctiform manner with a suspension of Trichophyton mentagrophytes 100/25 (about 200 microconidia per inoculation point). The pieces of skin were then incubated at 28°C for 7 days on water and agar with penicillin, streptomycin and cycloheximide addition. From the 4th day of incubation onwards, the result was daily read off macroscopically.

Results:

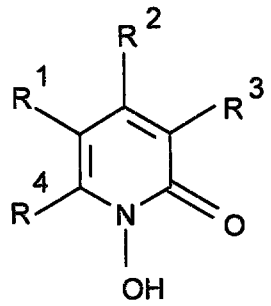
After a time of action of the active compound-containing gel preparations, according to Examples 1 to 4, of 4 hours, the pieces of skin are macroscopically fungus-free on all sections - in contrast to the corresponding placebo preparations.

For the active compound-containing ointment preparation not according to the invention, according to Example 5, which was prepared according to the prior art, the time of action of 4 hours is not sufficient to kill the macroconidia on the inoculated segments.

THIS SHEET HAS BEEN REPLACED

Patent claims:

1. A pharmaceutical preparation comprising a hydrophilic gel-forming agent, water and a compound of the formula I



(I)

or a physiologically tolerable salt of the compound of the formula I, where R^1, R^2 and R^3, which are identical or different, are a hydrogen atom or alkyl having 1 to 4 carbon atoms, and R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms.

2. A pharmaceutical preparation as claimed in claim 1, wherein R^4 is a saturated hydrocarbon having 6 to 9 carbon atoms, one of the radicals R^1 and R^3 is a hydrogen atom and the other is a hydrogen atom, methyl or ethyl and R^2 is an alkyl radical having 1 or 2 carbon atoms.

3. A pharmaceutical preparation as claimed in claim 1 or 2, wherein the compound of the formula I contains a cyclic radical in the position R^4.

4. A pharmaceutical preparation as claimed in claim 3, wherein R^4 is a cyclohexyl radical or $-CH_2-CH(CH_3)-CH_2-C(CH_3)_3$.

5. A pharmaceutical preparation as claimed in one or more of claims 1 to 4, wherein the hydrophilic gel-forming agents employed are native substances such as gelatin, pectin, tragacanth, agar, carrageenan or alginate, semisynthetic compounds such as cellulose ethers, e.g.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose or sodium carboxymethylcellulose, starch derivatives or pectin derivatives and also fully synthetic gel-forming agents such as polyacrylates, polymethacrylates, polyvinyl alcohol or polyvinylpyrrolidones or mixtures of the hydrophilic gel-forming agents.

6. The pharmaceutical preparation as claimed in claim 5, wherein polyacrylate is employed as the hydrophilic gel-forming agent.

7. The pharmaceutical preparation as claimed in one or more of claims 1 to 6, wherein solubilizers from the group consisting of benzyl alcohol, 2-octyldodecanol, propylene glycol, adipates and glycerol are additionally employed.

8. The pharmaceutical preparation as claimed in one or more of claims 1 to 7, wherein a water-miscible solvent such as an alkanol, e.g. ethanol and/or isopropyl alcohol and also propylene glycol or dimethyl sulfoxide is additionally employed.

9. The pharmaceutical preparation as claimed in one or more of claims 1 to 8, wherein the compound of the formula I is contained in an amount from 0.05 to 2 percent by weight, preferably from 0.1 to 1% by weight, and the hydrophilic gel-forming agent is contained in an amount from 0.3 to 2% by weight.

10. The use of the pharmaceutical preparation as claimed in one or more of claims 1 to 9 for the production of a pharmaceutical for the treatment and prophylaxis of dermatomycoses.

11. A process for the production of a pharmaceutical preparation as claimed in one or more of claims 1 to 9, which comprises mixing a compound of the formula I, one or more hydrophilic gel-forming agents and water, and also other components customary for the

This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

preparation of gels.

This Sheet Has Been Replaced