The pharmaceutical active ingredient azelastin (chemical name 4-(p-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone) is an asthma prophylactic and anti-allergic (see German patent 21 64 058).

It has now been found that azelastin is also effective against psoriasis and related diseases.

The invention relates to compositions for combating psoriatic diseases such as psoriasis and psoriasis-related diseases.

In terms of the invention, psoriatic diseases are understood as meaning skin diseases which accompany hyperkeratosis, such as psoriasis in particular.

Action of azelastin on psoriatic diseases and related diseases (for example psoriasis) and testing of this action.

Mice (average weight 25 g) received 1 mg/kg of azelastin daily for 7 days by oral administration. On day 8, the top layer of skin was removed with sandpaper. This mechanical irritation and removal of the uppermost layer of skin causes an acute reaction which has morphological similarities to the psoriatic reaction. The leukotriene content of the dermis and epidermis also increases. This is accompanied by a lowering of the prostaglandin concentration. These changes are also typical of psoriasis. The pretreatment with azelastin prevented these changes from occurring. Azelastin normalizes or even lowers the dermal or epidermal leukotriene concentration and raises the concentration of prostaglandins.

The current treatment of psoriasis uses mainly corticosteroids. Compared with these, azelastin only has slight or negligible side-effects and inhibits the synthesis of leukotrienes in the skin even after systemic administration; furthermore, azelastin also inhibits the formation of oedemas induced by PAF (platelet activating factor).

The pharmaceutical formulations for use on psoriatic diseases and related diseases in humans generally contain between 2 and 16 and preferably 4 to 8 mg of azelastin.

They can be administered for example in the form of tablets, capsules, pills, coated tablets, suppositories, ointments, jellies, creams, powder, dusting powder, aerosols or liquids. Examples of possible liquid forms of administration are oily or alcoholic/aqueous solutions, as well as suspensions and emulsions.

The single dose of elastin for use on psoriatic diseases and related diseases can be for example between 0.1 and 10% by weight, preferably 0.7 - 5% by weight and especially 1 - 5% by weight, in the case of pharmaceutical forms for local application to the skin and mucous membranes (for example in the form of solutions, lotions, emulsions, ointments and so on).

- (The doses are relative in each case to the free base) -

Action of azelastin on inflammatory diseases and testing of this action

The local application of azelastin causes dose-dependent inhibition of the formation of mouse ear oedema induced by the local application of 12-0-tetradecanoylphorbol acetate (TPA) or arachidonic acid (method of Young *et al.*).

Azelastin further exhibits, in a quite general way, a good anti-inflammatory action after both topical (local) and systemic administration. This action was tested for example on the carrageenin-induced rat paw oedema (method of Mörsdorf *et al.*, Arch. int. Pharmacodyn. 192 (1971) page 111) or on the chemically induced mouse ear oedema (method of Young *et al.*, Journal of Investigative Dermatology 80 (1983) page 48-52 and 82 (1984) page 367.

In the experimental model of the carrageenin-induced rat paw oedema after oral administration (Mörsdorf *et al.*, 1971), the test substances are administered orally (intragastrically) with the aid of a stomach tube 2 hours before administration of the carrageenin. The increase in paw volumes is measured one hour later. This method (shortening of the duration of action from the customary 3 hours to one hour) makes it possible to study the action of the test substances on the rapidly released mediators such as leukotrienes and PAF (platelet activating factor).

For example, in the arachidonic acid-induced mouse ear oedema, the oedema is inhibited by 28% after the oral administration of a dose of 3 mg/kg mouse body weight and by 41% after the topical application of a dose of 0.25 mg/mouse ear.

For example, in the case of the rat paw oedema (induced by carrageenin, determination of the paw volumes after one hour), the formation of oedemas is inhibited by 50% with an oral dose of 3.9 mg/kg rat.

The minimum effective dose in the animal experiments indicated above is for example 1 - 2 mg/kg in the case of oral administration and 10 mg/kg in the case of topical application (10 mg/kg correspond to about 0.25 mg/cm^2 body surface).

The general active dosage range (animal experiments as above) can be for example:
2.5 - 80 mg/kg by topical application, especially
5 - 40 mg/kg.

The single dose of azelastin for use on psoriasis can be for example between 0.1 and 10% by weight, preferably 0.7 - 5% by weight and especially 1 - 5% by weight, in the case of pharmaceutical forms for local application to the skin and mucous membranes (for example in the form of solutions, lotions, emulsions, ointments, clysmas and so on).

- (The doses are relative in each case to the free base) -

The pharmaceutical formulations for use in the abovementioned indications generally contain between 2 and 16 and preferably 4 to 8 mg of azelastin.

They can be administered for example in the form of tablets, capsule, pills, coated tablets, suppositories, enemas, ointments, clysmas, jellies, gels, creams, powder, dusting powder, suspensions (aerosols) or liquids. Examples of possible liquid forms of administration are oily or alcoholic/aqueous solutions, as well as suspensions and emulsions. Preferred forms of administration are tablets containing between 2 and 16 mg and preferably between 4 and 10 mg of azelastin. For example, it is possible to recommend 1 to 2 tablets containing 4 to 8 mg of azelastin, 3 times a day. The minimum daily dose for oral administration is for example 4 mg; the maximum daily dose for oral administration should not exceed 24 mg.

The acute toxicity of azelastin in the mouse (expressed as the LD_{50} mg/kg; method of Miller and Tainter: Proc. Soc. Exper. Biol. a. Med. 57 (1944) 261) is for example between 120 and 170 mg/kg for oral administration.

- (The doses are relative in each case to the free base) -

The pharmaceutical compositions or drugs contain azelastin or its physiologically acceptable salts as the active ingredient. The active ingredient is optionally present in a mixture with other pharmacologically or pharmaceutically active substances. The drugs are prepared in known manner and the known and conventional pharmaceutical adjuncts and other conventional excipients and diluents can be used.

Such excipients and adjuncts can be for example substances which are recommended or indicated in the following literature

references as adjuncts for pharmacy, cosmetics and related fields: Ullmanns Encyklopädie der technischen Chemie (Ullmanns Encyclopaedia of Chemical Technology), volume 4 (1953), page 1 to 39; Journal of Pharmaceutical Sciences, volume 52 (1963), page 918 *et seq.*; H.v. Czetsch-Lindenwald, Hilfsstoffe für Pharmazie und angrenzende Gebiete (Adjuncts for Pharmacy and Related Fields): Pharm. Ind., no. 2 (1961), page 72 *et seq.*; Dr. H.P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete (Encyclopaedia of Adjuncts for Pharmacy, Cosmetics and Related Fields), Cantor KG, Aulendorf in Württemberg, 1981.

It is also possible to add preservatives, stabilizers, buffer substances, for example calcium hydrogenphosphate, colloidal aluminium hydroxide, taste correctors, sweeteners, colours, antioxidants and complexing agents (for example ethylene-diaminetetraacetic acid) and the like. If appropriate, the pH range should be adjusted to *ca.* 3 to 7 with physiologically acceptable acids or buffers in order to stabilize the molecule of active ingredient. In general, the pH is preferably as neutral as possible to weakly acid (up to pH 5).

Formulations for dermal application can be prepared using the abovementioned substances and spreadable or liquid hydrocarbons such as liquid petrolatum or paraffin, or gels of paraffinic hydrocarbons and polyethylene, fats and oils of vegetable or animal origin, which can also be partially hydrogenated, or synthetic fats such as glycerides of C_8-C_{18} fatty acids, and also beeswax, cetyl palmitate, wool wax, wool wax alcohols, fatty alcohols such as cetyl alcohol and stearyl alcohol, polyethylene glycols with molecular weights of 200 to 20,000, liquid waxes such as isopropyl myristate, isopropyl stearate and ethyl oleate, emulsifiers such as the sodium, potassium and ammonium salts of stearic acid or palmitic acid, as well as triethanolamine stearate, alkali metal salts of oleic acid and ricinoleic acid, salts of sulphonated fatty alcohols, such as sodium laurylsulphate, sodium cetylsulphate

and sodium stearylsulphate, bile acid salts, sterols such as cholesterol, partial fatty acid esters of polyhydric alcohols, such as ethylene glycol monostearate, glycerol monostearate and pentaerythritol monostearate, partial fatty acid esters of sorbitan, partial fatty acid esters of polyethoxylated sorbitan, polyethoxylated sorbitol ethers, polyethoxylated fatty acid esters, polyethoxylated fatty alcohol ethers, fatty acid esters of sucrose, fatty acid esters of polyglycerol, and lecithin.

Examples of antioxidants used are sodium metabisulphite, ascorbic acid, gallic acid, alkyl gallates, butylhydroxy-anisole, nordihydroguaiaretic acid, tocopherols and tocopherols + synergistic agents (substances which bind heavy metals by complexation, for example lecithin, ascorbic acid, phosphoric acid). The addition of synergistic agents considerably increases the antioxidizing action of the tocopherols.

Examples of possible preservatives are sorbic acid, p-hydroxybenzoic acid esters (for example lower alkyl esters), benzoic acid, sodium benzoate, trichloroisobutyl alcohol, phenol, cresol, benzethonium chloride and formalin derivatives.

The pharmaceutical and galenical manipulation of the compounds according to the invention is in accordance with the conventional standard methods. For example, active ingredient(s) and adjuncts and/or excipients are thoroughly mixed by stirring or homogenization (for example by means of conventional mixers), this operation generally being carried out at temperatures between 20 and 80°C, preferably of 20 to 50°C and especially at room temperature. Reference is also made to the following standard work: Sucker, Fuchs, Speiser, Pharmazeutische Technologie (Pharmaceutical Technology), Thieme-Verlag Stuttgart, 1978.

The compounds can be administered to the skin or mucous membrane or intracorporeally, for example orally, enterally, pulmonarily, rectally, nasally, vaginally, lingually, intravenously, intraarterially, intracardially, intramuscularly, intraperitoneally, intradermally or subcutaneously. The parenteral formulations are especially sterile or sterilized products.

For the treatment of psoriasis, azelastin is used locally, for example in the form of solutions, tinctures, suspensions, emulsions, ointments, gels, creams, pastes, lotions or shampoos. It is preferable to use anhydrous formulations, which makes it possible to use salicylic acid and/or urea simultaneously. Such formulations, which can also be rendered washable by the addition of surfactants, are described for example in German Offenlegungsschrift 36 03 859. The urea can be present either as a surfactant/urea inclusion compound or else in the free form. It is of course also possible to use formulations which contain neither urea nor salicylic acid.

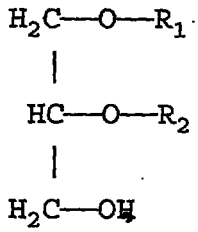
The use concentrations of azelastin here are for example 0.1 to 10% (weight/weight), preferably 0.5 to 8% and especially 1 to 5%. The use concentrations of salicylic acid are for example 0.1 to 10%, preferably 0.2 to 8% and especially 0.5 to 5%. The use concentrations of urea are for example 1 to 20%, preferably 3 to 18% and especially 5 to 15%.

For topical application, as well as for formulation as a drug for other modes of administration, it has proved advantageous for example to use the azelastin together with at least one alkylglycerol having 2 to 12 carbon atoms in the alkyl radical, which can be present in the form of an ether group bonded to one of the primary or secondary OH groups of the glycerol. Such alkylglycerols increase or improve the action of the azelastin. It is preferable here to use alkylglycerols having 3 to 9 C atoms, by themselves or in a mixture.

A drug which contains

a) azelastin and

b) an alkylglycerol of general formula I:



in which one of the radicals R_1 and R_2 is an alkyl group having 2 to 12 C atoms and the other radical is an H atom,

and optionally other conventional pharmacological additives and diluents, therefore has particularly advantageous effects.

It is preferable to use a mixture of water and an alkyl-glycerol mixture of nonyl- or octyl-glycerol, hexyl- or pentyl-glycerol and propyl- or ethyl-glycerol. An appropriate formulation for topical application contains for example 1 to 100 mg of azelastin per ml of alkylglycerol of formula I or a corresponding mixture of alkylglycerol with water.

Such a mixture is also designated hereafter as a cascade.

The content of azelastin in mg/ml cascade is denoted by a following index, so that, for example, a cascade mixture containing 40 mg/ml azelastin is designated as cascade 40 and a mixture containing 60 mg of azelastin per ml of cascade is designated as cascade 60.

The preparation of the alkylglycerols is known for example from DE-OS 33 43 530.8. For instance, preferred alkyl-glycerol/water mixtures are those containing for example

nonylglycerol, octylglycerol, hexylglycerol, pentylglycerol, propylglycerol and ethylglycerol. Such aqueous mixtures preferably contain 3 of said glycerol ethers and specifically one lower ether (ethyl, propyl), one intermediate ether (pentyl, hexyl) and one higher ether (octyl, nonyl), the amount by weight of the lower ether being about as large as the sum of the amounts by weight of the other two glycerol ethers. The amount of water is about the same as the amount of the lower glycerol ether and is for example half the total amount of the glycerol ethers present. Examples of such glycerol ether/water mixtures are tabulated below:

	Water	Glycerol propyl ether	Glycerol hexyl ether	Glycerol nonyl ether
Parts by weight	2 :	2 :	1 :	1

	Water	Glycerol ethyl ether	Glycerol pentyl ether	Glycerol octyl ether
Parts by weight	2 :	2 :	1 :	1

The drugs containing the alkylglycerols of formula I are particularly suitable for topical application. To treat psoriasis and related diseases, for example, the affected areas of skin are rubbed for example with cascade 1 to cascade 100 two to three times a day. No harmful side-effects have yet been observed.

However, topical treatment with an azelastin cascade mixture can also be used to treat internal inflammatory diseases, for

example, by rubbing said mixture into a large area of skin, therapeutically active blood levels being attained *via* absorption through the skin. This mode of application has the advantage that the cascade formulations are perfectly tolerated by the skin.

The type of azelastin formulation in the form of the cascade (for example in the form of the solutions cascade 1 to cascade 100) is also suitable for the preparation of suppositories for rectal insertion. This represents another good method of treating internal inflammatory diseases.

A particularly advantageous excipient mixture for the azelastin consists of a mixture of about 4 parts by weight of water, 4 parts by weight of propylglycerol and 2 parts by weight each of hexylglycerol and nonylglycerol.

To prepare the drugs containing the azelastin in the presence of a glycerol ether of formula I or a mixture of such glycerol ethers of formula I, the azelastin is used for example with 10,000 to 0.05, for example 1000 to 5 or 700 to 7 and preferably 30 to 10 parts by weight (based in each case on one part by weight of azelastin) of at least one glycerol ether of formula I or a mixture of such glycerol ethers, and optionally 10,000 to 0.05, for example 400 to 2 and preferably 20 to 3 parts by weight of water (also based on one part by weight of azelastin). When the corresponding drugs are prepared, this mixing with the glycerol ethers can take place at the beginning or else optionally at a later stage of the preparation.

Examples

1. Example of a formulation for the topical treatment of psoriasis

This involves a solution of 8.8% of azelastin hydrochloride in a solvent mixture called cascade 0 (azelastin 8%).

Preparation of cascade 0

1000 g of water, 1000 g of glycerol 1-n-propyl ether, 500 g of glycerol 1-n-hexyl ether and 500 g of glycerol 1-n-nonyl ether are mixed in a suitable vessel.

Preparation of the azelastin solution

About 2.5 litres of cascade 0 are placed in a suitable vessel and 264 g of azelastin hydrochloride are dissolved in this solvent mixture.

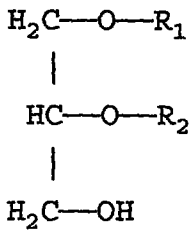
The volume is then made up to 3 litres with cascade 0.

The density of the solution is 1.023 g/ml at 22°C. This solution is sterile-filtered under aseptic conditions into a sterile receiver through a membrane filter with a pore size of 0.2 µm and filled into sterile 10 ml dropping bottles.
1 ml of solution contains 80 mg of azelastin (corresponding to 88 mg of azelastin·HCl).

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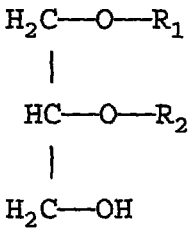
Claims

1. Use of azelastin and an alkylglycerol or a mixture of alkylglycerols of general formula I:



for the preparation of a composition for the treatment of psoriatic diseases.

2. A process for the preparation of a drug according to Claim 1, characterized in that an alkylglycerol of formula I:



in which one of the radicals R_1 and R_2 is an alkyl group having 2 to 12 C atoms and the other radical is an H atom, or a mixture of such alkylglycerols, and optionally water are additionally used in the preparation, 10,000 to 0.05 parts by weight of alkylglycerol of formula I, or appropriate mixture of alkylglycerols, and optionally 10,000 to 0.05 parts by weight of water being used, based in each case on one part by weight of azelastin.