The medicinal agent azelastine (chemical name: 4-(p-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone) is an asthma prophylactic and antiallergenic (see DE-PS 21 64 058).

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

The present invention relates to the use of azelastine for the preparation of compositions for the treatment of psoriasis diseases, such as psoriasis, and psoriasis-related diseases.

In the context of the invention, psoriasis diseases are understood to be skin diseases which accompany hyperkeratoses, such as in particular psoriasis.

Effectiveness of azelastine against psoriasis diseases and related diseases (for example psoriasis) and testing thereof:

Mice (average weight 25 g) were given an oral daily dose of 1 mg/kg of azelastine for 7 days. On the eighth day, the upper layer of skin was removed with sandpaper. This mechanical irritation and removal of the uppermost layer of skin produces an acute reaction which bears morphological similarities to the psoriatic reaction. In addition, there is an increase in the leucotriene content of the dermis and epidermis. This is accompanied by a reduction in the concentration of prostaglandins. These changes are also typical of psoriasis. None of these changes occurred after pretreatment with azelastine. Azelastine normalizes or even reduces the dermal or epidermal leucotriene concentration and increases the concentration of prostaglandins.

At the present time, psoriasis is mainly treated with corticosteroids. In contrast to corticosteroids, azelastine has only slight or negligible side effects and inhibits leucotriene synthesis in the skin, even after

systemic administration. In addition, azelastine also inhibits the PAF-induced formation of oedema (PAF = platelet activating factor).

The pharmaceutical compositions for use in the treatment of psoriasis diseases and related diseases in human beings generally contain between 2 and 16 mg and preferably between 4 and 8 mg of azelastine.

The pharmaceutical compositions may be administered, for example, in the form of tablets, capsules, pills, dragees, suppositories, ointments, gels, creams, powders, dusting powders, aerosols or in liquid form. Suitable liquid formulations are, for example, oily or alcoholic or aqueous solutions and also suspensions and emulsions. Preferred formulations are tablets containing between 4 and 8 mg or solutions containing between 0.1 and 10% by weight of azelastine.

The individual dose of azelastine in the treatment of psoriasis and related diseases and may be, for example,

a) between 2 and 16 mg and preferably 8 mg for oral formulations;

b) between 0.1 and 10% by weight, preferably between 0.7 and 5% by weight and more preferably between 1 and 5% by weight for formulations to be locally applied to the skin and mucous membrane (for example in the form of solutions, lotions, emulsions, ointments and so on).

For example, 1 to 2 tablets containing 4 to 8 mg of azelastine may be taken 3 times a day. Where the compositions are orally administered, the minimum daily dose is, for example, 4 mg while the maximum daily dose should not exceed 24 mg (all doses apply to the free base).

Where the compositions are orally administered for example, the acute toxicity of azelastine in mice (expressed by the LD 50 mg/kg; Miller and Tainter's method: Proc. Soc. Exper. Biol. a. Med. 57 (1944) 261) is between 120 and 170 mg/kg (all doses apply to the free base).

The pharmaceutical compositions or medicaments contain azelastine or its physiologically safe salts as active substance. The active substance is optionally present in admixture with other pharmacologically or pharmaceutically active substances. The medicaments are prepared in known manner using known pharmaceutical auxiliaries and other typical excipients and diluents.

Suitable excipients and auxiliaries of the type in question are, for example, the substances recommended or described in the following literature references as auxiliaries for pharmacy, cosmetics and related fields: Ullmanns Encyklopädie der technischen Chemie, Vol. 4 (1953), pages 1 to 39; Journal of Pharmaceutical Sciences, Vol. 52 (1963), pages 918 et seq; H. v. Czetsch-Lindenwald, Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; Pharm. Ind., No. 2, 1961, pages 72 et seq; Dr. H.P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Cantor KG, Aulendorf in Württemberg, 1981.

Examples of such substances are gelatine, natural sugars such as sucrose or lactose, lecithin, pectin, starch (for example cornstarch), cyclodextrins and cyclodextrin derivatives, polyvinyl pyrrolidone, polyvinyl acetate, gelatine, gum arabic, alginic acid, tylose, talcum, lycopodium, silica (for example colloidal silica), cellulose, cellulose derivatives (for example cellulose ethers in which the cellulose hydroxy groups are partly etherified with lower saturated aliphatic alcohols and/or lower saturated aliphatic hydroxy-alcohols, for example methyl hydroxypropyl cellulose,

methyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose phthalate); fatty acids and magnesium, calcium or aluminium salts of C_{12-22} fatty acids, more particularly saturated types (for example stearates), emulsifiers, oils and fats, more particularly vegetable oils and fats (for example peanut oil, castor oil, olive oil, sesame oil, cottonseed oil, corn oil, wheat germ oil, sunflower oil, cod liver oil, even in hydrogenated form; mono-, di- and triglycerides of saturated fatty acids $C_{12}H_{24}O_2$ to $C_{18}H_{36}O_2$ and mixtures thereof), pharmaceutically safe monohydric and polyhydric alcohols and polyglycols, such as polyethylene glycols and derivatives thereof, esters of aliphatic saturated or unsaturated fatty acids (2 to 22 carbon atoms, more particularly 10 to 18 carbon atoms) with monohydric aliphatic alcohols (1 to 20 carbon atoms) or polyhydric alcohols, such as glycols, glycerol, diethylene glycol, pentaerythritol, sorbitol, mannitol, etc., which may even be etherified, esters of citric acid with primary alcohols, acetic acid, benzyl benzoate, dioxolanes, glycerol formals, tetrahydrofurfuryl alcohol, polyglycolethers with C_{1-12} alcohols, dimethyl acetamide, lactamides, lactates, ethyl carbonates, silicones (more particularly medium-viscosity polydimethyl siloxanes), calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, magnesium carbonate and the like.

Other suitable auxiliaries are substances which promote disintegration (so-called disintegrating agents), such as crosslinked polyvinyl pyrrolidone, sodium carboxymethyl starch, sodium carboxymethyl cellulose or microcrystalline cellulose. Known shell-forming substances may also be used. Suitable shell-forming substances are, for example, polymers and copolymers of acrylic acid and/or methacrylic acid and/or esters thereof; copolymers of acrylates and methacrylates with

a small content of ammonium groups (for example Eudragit® RS), copolymers of acrylates and methacrylates and trimethylammonium methacrylate (for example Eudragit® RL); polyvinyl acetate; fats, oils, waxes, fatty alcohols; hydroxypropyl methyl cellulose phthalate or acetate succinate; cellulose, starch and polyvinyl acetate phthalate; carboxymethyl cellulose; methyl cellulose phthalate, succinate, phthalate succinate and phthalate acid semiester; zein; ethyl cellulose and succinate; shellac, gluten; ethyl carboxyethyl cellulose; ethacrylate/maleic anhydride copolymer; maleic anhydride/vinylmethyl ether copolymer; styrene/maleic acid copolymers; 2-ethylhexyl acrylate maleic anhydride; crotonic acid/vinyl acetate copolymer; glutamic acid/glutamic acid ester copolymer; carboxymethyl ethyl cellulose glycerol monooctanoate; cellulose acetate succinate; polyarginine.

Suitable plasticizers for shell-forming materials include the following: citric and tartaric acid esters (acetyltriethyl, acetyltributyl, tributyl, triethyl citrate); glycerol and glycerol esters (glycerol diacetate, triacetate, acetylated monoglycerides, castor oil); phthalic acid esters (dibutyl, diamyl, diethyl, dimethyl, dipropyl phthalate), D-(2-methoxy or -ethoxyethyl)-phthalate, ethylphthalyl, butylphthalyl ethyl and butyl glycolate; alcohols (propylene glycol, polyethylene glycol of various chain lengths), adipates (diethyl adipate, di-(2-methoxy- or -ethoxyethyl adipate); benzophenone; diethyl or dibutyl sebacate, succinate, tartrate; diethylene glycol dipropionate; ethylene glycol diacetate, dibutyrate, dipropionate; tributyl phosphate, tributyrin; polyethylene glycol sorbitan monooleate (polysorbates, such as Polysorbat 80); sorbitan monooleate.

Solutions or suspensions may be prepared, for example, with water or physiologically safe organic

solvents such as, for example, ethanol, propanol, isopropanol, 1,2-propylene glycol, polyglycols and derivatives thereof, dimethyl sulfoxide, fatty alcohols, triglycerides, partial esters of glycerol; paraffins and the like.

Injectable solutions or suspensions may be prepared, for example, with nontoxic parenterally safe diluents or solvents such as, for example, water, 1,3-butanediol, ethanol, 1,2-propylene glycol, polyglycols in admixture with water, Ringer's solution, isotonic sodium chloride solution or even hydrogenated oils, including synthetic mono- or diglycerides or fatty acids, such as oleic acid.

Solubilizers and emulsifiers known per se may be used in the preparation of the compositions. Examples of solubilizers and emulsifiers are polyvinyl pyrrolidone, sorbitan fatty acid esters, such as sorbitan trioleate, phosphatides, such as lecithin, acacia, tragacanth, polyethoxylated sorbitan mono-oleate and other ethoxylated fatty acid esters of sorbitan, polyethoxylated fats, polyethoxylated oleotriglycerides, linolised oleotriglycerides, polyethylene oxide condensation products of fatty alcohols, alkyl phenols or fatty acids or even 1-methyl-3-(2-hydroxyethyl)-2-imidazolidone. Polyethoxylated in this context means that the substances in question contain polyoxyethylene chains of which the degree of polymerization is generally between 2 and 40 and more particularly between 10 and 20.

These polyethoxylated materials may be obtained, for example, by reaction of hydroxyfunctional compounds (for example mono- or diglycerides or unsaturated compounds such as, for example, those containing oleic acid functions) with ethylene oxide (for example 40 moles ethylene oxide per mole glyceride). Examples of oleotriglycerides are olive oil, peanut oil, castor oil, sesame oil, cottonseed oil, corn oil (see also Dr. H.P. Fiedler "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und

angrenzende Gebiete" 1971, pages 191-195).

In addition, preservatives, stabilizers, buffers, for example calcium hydrogen phosphate, colloidal aluminium hydroxide, flavour correctants, sweeteners, dyes, antioxidants and complexing agents (for example ethylenediaminetetraacetic acid) and the like, may be added. The compositions may have to be adjusted to a pH of around 3 to 7 with physiologically safe acids or buffers in order to stabilize the active substance molecule. A neutral to mildly acidic pH value (up to 5) is generally preferred.

Dermal compositions may be prepared using the above-mentioned substances and spreadable or liquid hydrocarbons, such as vaseline or paraffin, or gels of paraffin hydrocarbons and polyethylene, fats and oils of vegetable or animal origin, which may even be partly hydrogenated, or synthetic fats, such as glycerides of C_{8-18} fatty acids, beeswax, cetyl palmitate, wool wax, wool wax alcohols; fatty alcohols, such as cetyl alcohol, stearyl alcohol, polyethylene glycols with molecular weights of 200 to 20,000; liquid waxes, such as isopropyl myristate, isopropyl stearate, ethyl oleate; emulsifiers, such as sodium, potassium and ammonium salts of stearic acid or palmitic acid and also triethanolamine stearate, alkali metal salts of oleic acid, ricinoleic acid, salts of sulfurized fatty alcohols, such as sodium lauryl sulfate, sodium cetyl sulfate, sodium stearyl sulfate, salts of galenic acid, sterols, such as cholesterol, partial fatty acid esters of polyhydric alcohols, such as ethylene glycol monostearate, glycerol monostearate, pentaerythritol monostearate, partial fatty acid esters of sorbitan, partial fatty acid esters of polyoxyethylene sorbitan, sorbitol ethers of polyoxyethylene, fatty acid esters of polyoxyethylene, fatty alcohol ethers of polyoxyethylene, fatty acid esters of sucrose, fatty acid esters of polyglycerol, lecithin.

Suitable antioxidants are, for example, sodium metabisulfate, ascorbic acid, gallic acid, gallic acid alkyl ester, butyl hydroxyanisole, nordihydroguaiaretic acid, tocopherols and tocopherols + synergists (substances which complex heavy metals, for example lecithin, ascorbic acid, phosphoric acid). The addition of the synergists enhances the antioxygenic effect of the tocopherols to a considerable extent.

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

The compounds according to the invention are pharmaceutically and galenically handled by standard methods. For example, active substance(s) and auxiliaries or excipients are thoroughly mixed by stirring or homogenizing (for example by means of standard mixers), generally at temperatures of 20 to 80°C, preferably at temperatures of 20 to 50°C and more preferably at room temperature. Further relevant particulars can be found in the following standard work: Sucker, Fuchs, Speiser, Pharmazeutische Technologie, Thieme-Verlag Stuttgart, 1978.

The compositions may be applied to the skin or mucous membrane or internally, for example by oral, enteral, pulmonal, rectal, nasal, vaginal, lingual, intravenous, intraarterial, intracardial, intramuscular, intraperitoneal, intracutaneous and subcutaneous administration. The parenteral formulations are in particular sterile or sterilized products.

In the treatment of psoriasis, azelastine is locally applied, for example in the form of solutions, tinctures, suspensions, emulsions, ointments, gels, creams, pastes, lotions or shampoos. Water-free compositions are preferably used so that salicylic acid and/or urea may be

applied at the same time. Compositions such as these, which can even be formulated for removal by washing through the addition of surfactants, are described for example in DE-OS 36 03 859. The urea may be present either as a surfactant/urea inclusion compound or even in free form. Compositions containing neither urea nor salicylic acid may of course also be used.

The azelastine is used in concentrations of, for example, 0.1 to 10% (weight/weight), preferably 0.5 to 8% and more preferably 1 to 5%. The salicylic acid is used in concentrations of, for example, 0.1 to 10%, preferably 0.2 to 8% and more preferably 0.5 to 5%. The urea is used in concentrations of, for example, 1 to 20%, preferably 3 to 18% and, more preferably, 5 to 15%.

1. Azelastine film tablets for oral application

Production of the tablets

A premix is prepared from 440 g of azelastine HCl, 360 g of microcrystalline cellulose and 200 g of talcum. This premix and also 6000 g of lactose monohydrate, 2870 g of microcrystalline cellulose and 100 g of highly disperse silicon dioxide are passed through a sieve and homogenized in a suitable mixer. 30 g of magnesium stearate are added to the mixture obtained through a sieve and the whole is homogenized once more. The material obtained is pressed to tablets with a weight of 100 mg, a diameter of 6 mm and a radium of curvature of 5.5 mm.

Production of the film tablets:

The tablets are continuously sprayed with 1.2 kg of a film suspension in an apparatus of the type typically used for this purpose:

To prepare the film suspension, 60 g of polyethylene

glycol 6000, 12 g of Polysorbat 80 and 9.6 g of carboxymethyl cellulose sodium are dissolved in 787.2 g of water. 120 g of talcum, 120 g of titanium dioxide and 1.2 of Simethicone (a mixture of polydimethyl siloxane (predominantly 90 to 99% by weight) and silicon dioxide (for example 4 to 7% by weight); US Pharmacopoeia, 21st Edition) are dispersed in the resulting solution and 90 g of a copolymer based on dimethylaminoethyl methacrylate and neutral methacrylates in the form of a 30% aqueous dispersion (Eudragit® E 30 D) are added to the dispersion with gentle stirring. One film tablet contains 4 mg of azelastine (corresponding to 4.4 mg of azelastine hydrochloride).

2. Azelastine 8 mg film tablets

Production of film tablets

88g of azelastine hydrochloride, 701 g of lactose monohydrate and 701 g of microcrystalline cellulose are sieved, mixed and moistened with 1440 g of a pH-immune acrylic resin lacquer which forms substantially impermeable coatings (Eudragit® RS 12.5). The moist material is granulated through a sieve and dried. The dry granules, 100 g of talcum and 30 g of magnesium stearate are resieved and homogenized in a suitable mixer. The resulting material is pressed to tablets with a weight of 180 mg, a diameter of 8 mm and a radius of curvature of 6 mm. To produce the film tablets, the tablets are sprayed with a film suspension prepared as follows in an apparatus of the type typically used for this purpose: 18 g of magnesium stearate are dispersed with stirring in 664 g of isopropanol; 18 g of 1,2-propylene glycol and 800 g of an anionic polymer of methacrylic acid and methacrylates which contains a plasticizer, is resistant to gastric juices and only dissolves beyond pH 7 (Eudra-

git S 12.5) are subsequently incorporated in the resulting suspension.

One film tablet contains 8 mg of azelastine (corresponding to 8.8 mg of azelastine hydrochloride).

3. Azelastine 8 mg capsules

100 g of azelastine hydrochloride, 200 g of tartaric acid, 500 g of lactose and 700 g of microcrystalline cellulose are mixed and made into a paste with approximately 700 g of purified water. The moist material is passed through a perforated plate with a perforation diameter of 1 mm and the resulting strands are size-reduced and rounded in the usual way on a Spheronizer disc. The pellets obtained are dried and sieved.

1000 g of pellets (sieve fraction 800 to 1250 µm) are sprayed with a suspension prepared as follows:

0.6 g of Polysorbat 80 are dissolved in 190 g of purified water and 40 g of triethyl citrate are emulsified in the resulting solution. 800 g of a 30% aqueous dispersion of a copolymer of acrylates and methacrylates with a small content of trimethylammonium methacrylate chloride (= Eudragit® RS 30 D) are added to the emulsion obtained, followed by stirring for about 10 minutes.

109.2 g of talcum and 0.2 g of silicone antifoam oil (Simethicone) are suspended in 860 g of purified water. The suspension obtained is stirred into the dispersion obtained as described above.

The lacquering suspension thus obtained is applied to the pellets in the usual way, for example using a fluidized-bed spray granulator (inflowing air temperature 40 to 50°C, exit air temperature max. 40°C). The pellets are dried under the same conditions.

The lacquering suspension mentioned above is sprayed on until the dried pellets have a total weight of 1127 g.

The lacquered pellets are packed in size 1 hard gelatine capsules in a quantity of 148.7 mg. One hard gelatine capsule contains 8.8 mg of azelastine hydrochloride, corresponding to 8 mg of azelastine in the form of a retard formulation. The release of azelastine hydrochloride from this formulation is tested by the method according to the US Pharmacopoeia, 21st Edition (USP XXI), using the apparatus for the dissolution test, apparatus 2. The release of azelastine hydrochloride is determined in 500 ml of test solution at 37°C at a rotational speed of the paddles of 100 revolutions per minute. For the first 2 hours, the test solution consists of 0.1 molar hydrochloric acid, after which the pellets are transferred to phosphate buffer solution, pH 6.8 (European Pharmacopoeia). The release of the azelastine hydrochloride is measured from the test solutions. The results obtained are as follows:

after 1 hour	5.5%	→ in 0.1 M HCl
after 2 hours	8.4%	
after 3 hours	11.2%	→ in phosphate buffer pH 6.8
after 4 hours	14.3%	
after 5 hours	21.7%	
after 6 hours	31.7%	
after 7 hours	39.2%	
after 8 hours	48.5%	
after 9 hours	56.1%	
after 10 hours	64.0%	
after 11 hours	74.5%	
after 12 hours	81.2%	

CLAIM

The use of azelastine or therapeutically useful salts thereof for the preparation of a medicament for treating psoriasis diseases.