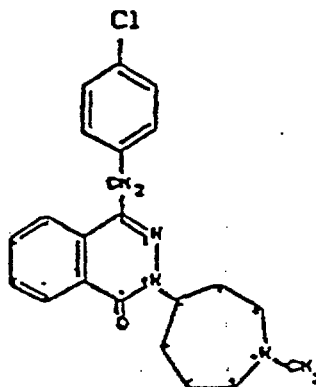


Azelastine is a phthalazinone derivative having the following structural formula:



Its chemical name is 4-(4-chlorobenzyl)-2-(perhydro-1-methylazepin-4-yl)-1-(2H)-phthalazinone. Azelastine is used in particular for the prophylaxis of asthma. Azelastine also has antiallergic and antihistaminic properties (see DE-PS 21 64 058).

One of the main disadvantages attending the application of azelastine is the side effect of tiredness. Many patients also report sleepiness, drowsiness and the like. This side effect occurs in particular in the first few days of treatment with azelastine so that patients are unable to drive vehicles or operate machines and suffer a significant reduction in their general attentiveness.

Accordingly, it would be extremely desirable and also an important medicinal advance if azelastine could be formulated in such a way that it did not induce tiredness.

Hitherto, the side effect of tiredness has normally been overcome by the development of a compound preparation from the tiredness-inducing active substance in question and caffeine. The function of the caffeine is to antagonize the sedative property of the active substance. This procedure cannot be applied in the case of azelastine because the elimination half lives $t_{1/2}$ ($t_{1/2}$ is the time in which the serum level of the active

substance in the blood falls from a certain starting value to half that value in the absence of any further supply of active substance) of azelastine and caffeine differ considerably from one another: the $t_{1/2}$ of azelastine is 20 hours while the $t_{1/2}$ of caffeine is only 3.5 hours. Accordingly, if azelastine and caffeine are administered together, the effect of the caffeine can be expected to weaken after a certain time so that the sedative effect of the azelastine reappears.

Now, the usual solution is to retard the release of the active substance caffeine in the formulation to such an extent that an extended active time is obtained. However, this approach is attended by the difficulty that the blood level profiles of the two active substances in vivo are very similar to one another. This is not possible with the techniques available at the present time on account of the considerable differences in the elimination values.

Azelastine has an extremely unpleasant taste so that, for example, liquid azelastine formulations (for example juice) in particular are refused by patients, particularly children. According to the invention, however, azelastine can now be made up into formulations with considerably improved taste.

The problem addressed by the present invention was to provide an azelastine preparation containing the active substance azelastine and a process for its production, the sedative side effect of azelastine being largely or completely suppressed.

This problem has been solved by a medicinal preparation with controlled release of its active principle containing typical auxiliaries and additives and a retard component, characterized in that the active substance azelastine or a physiologically safe salt thereof is released under control and is present in a quantity of 1

part by weight of azelastine, based on the base, to 0.004 to 800 parts by weight of the retard component, the release rate amounting to between 0.05 and 5 mg, for example to between 0.05 and 3 mg or even to between 0.05 and 1 mg of azelastine per hour.

If the azelastine is present in the form of its salt, the above-mentioned quantity of azelastine, based on the base, increases accordingly through the higher molecular weight of the salt. Throughout the present specification, all quantitative references to azelastine are always based on the base and, where a salt is present, should be increased in accordance with the higher molecular weight of the salt.

The present invention also relates to a process for the production of a medicinal preparation with controlled release of the active principle by introduction of an active substance into typical auxiliaries and additives and a retard component, characterized in that azelastine or a physiologically safe salt thereof is used as the active substance to be released under control in a ratio of 1 part by weight of azelastine, based on the base, to 0.004 to 800 parts by weight of the retard component and a release rate of 0.05 to 5 mg of azelastine per hour is adjusted.

Preferred embodiments of the invention are described in the subsidiary claims.

It was surprising to find that the addition of caffeine - whether retarded or unretarded - was not necessary to obtain an azelastine formulation which did not have the side effect of tiredness, instead it is sufficient to retard the active substance azelastine itself. If, therefore, the active substance azelastine is introduced into a formulation which releases the active substance over a prolonged period (so that the active substance is "retarded"), the side effect of

tiredness no long occurs in patients treated with this formulation. This is all the more surprising insofar as azelastine is a substance having an elimination half life of 20 hours, as mentioned above.

5 In pharmaceutical technology, the process of retarding has hitherto only been applied to substances having short half lives, for example of up to at most 10 hours. The retarding of an active substance with a half life of 20 hours has hitherto been regarded as an error in
10 pharmaceutical science.

Another surprising aspect of these formulations is that the bitter taste hitherto observed does not occur after their ingestion.

Accordingly, the present invention relates to
15 formulations characterized by controlled release of the active substance azelastine or physiologically safe salts of azelastine. Suitable salts are, for example, the chloride, acetate, maleate, lactate, citrate, tartrate, gluconate, embonate.

20 The present invention also relates to a process for the production of formulations characterized by controlled release of the active substance azelastine or physiologically safe salts of azelastine.

The azelastine release rate of 0.05 to 5 mg per hour
25 is determined in an aqueous test solution having a pH value of 1.0 and/or 6.8. The test solution in question is an aqueous solution having the pH values indicated. The pH values are adjusted by addition of acid or by addition of a typical buffer.

30 Suitable formulations are, for example, retard tablets, retard capsules, pellets, juices, implantates, injections, plasters, aqueous or oily suspensions, oily solutions, granules, pills, soft gelatin capsules, micro-capsules.

35 The preparations according to the invention may be

obtained as follows:

1. By fixing azelastine to physiologically safe cation exchangers. Suitable cation exchangers are, for example,

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acrylate and methacrylate resins with an exchangeable proton, acidic groups: $\text{COO}^\ominus$, for example Amberlite® IRP-64

10 polystyrene resins with an exchangeable Na^+ , acidic groups: $\text{SO}_3^\ominus$, for example Amberlite® IRP-69

The ion exchangers are acidic ion exchangers. The maximum ratio of azelastine to ion exchanger is approximately 1:1; the minimum ratio is approximately 1 part by weight of active substance to 800 parts by weight of ion exchanger resin. 1 To 400 parts by weight of ion exchanger are preferably used to 1 part by weight of active substance. In a particularly preferred embodiment, 1 to 100 parts by weight of ion exchanger are used to 1 part by weight of active substance.

The azelastine is fixed to the ion exchanger by passing an azelastine solution through a bed of the ion exchanger in a column or by suspending the ion exchanger in a solution of azelastine, followed after stirring by filtration and washing. The charged ion exchanger is dried at temperatures of up to about 50°C . The charged ion exchanger particles are preferably provided with a coating of the type described, for example, in US-A-4,221,776. One advantage of this additional coating is that the release rate of the active substance can be varied and influenced through the choice of the coating material. The charged ion exchanger particles provided with a coating may be dried with hot air at 70 to 90°C .

35 The charged ion exchanger particles may be packed in

hard gelatine capsules or, alternatively, a suspension may be prepared as the formulation using water and thickeners, flavourings, stabilizers and preservatives.

- 5 2. Applying a coating of the following substances to
active substance particles, granules or pellets or to
azelastine-containing tablets (the coating substances
mentioned may also be used in admixture with one another):
10 hydroxypropyl methyl cellulose phthalate or acetate
succinate; cellulose, starch and polyvinyl acetate
phthalate; carboxymethyl cellulose; polyvinyl acetate;
methyl cellulose phthalate, methyl cellulose succinate,
methyl cellulose phthalate succinate and methyl cellulose
15 phthalic acid semiester; zein; ethyl cellulose and ethyl
cellulose succinate; shellac; gluten; ethyl carboxyethyl
cellulose; ethacrylate/maleic anhydride copolymer; maleic
anhydride/vinyl methyl ether copolymer; styrene/maleic
acid copolymers; 2-ethylhexyl acrylate/maleic anhydride;
20 crotonic acid/vinyl acetate copolymer; glutamic acid/
glutamic acid ester copolymer; carboxymethyl ethyl
cellulose glycerol monooctanoate; cellulose acetate
succinate; polyarginine; fats, oils, waxes, fatty al-
cohols; anionic polymers of methacrylic acid and meth-
acrylates (Eudragit® L, Eudragit® S); copolymers of
25 acrylates and methacrylates with a small content of
ammonium groups (Eudragit® S) and copolymers of acrylates
and methacrylates and trimethyl ammonium methacrylate
(Eudragit® RL); copolymer of ethyl acrylate and methyl
methacrylate 70:30 (Eudragit® NE 30 D); copolymer of
30 acrylic acid, methacrylic acid and esters thereof (ratio
of the free carboxyl groups to the ester groups, for
example 1:1) (Eudragit® L 30 D).

The substances mentioned may additionally contain
typical plasticizers (for example dibutyl sebacate,
35 citric and tartaric acid esters, glycerol and glycerol

esters, phthalic acid esters and similar substances) and also water-soluble substances, such as polyethylene glycols, polyvinyl pyrrolidone, copolymers of polyvinyl pyrrolidone and polyvinyl acetate, hydroxypropyl cellulose, hydroxypropyl methyl cellulose. Solids, such as talcum and/or magnesium stearate, may also be included in the coating.

The pellets, granules, tablets may also contain additions of organic acids (for example citric acid, tartaric acid, maleic acid, fumaric acid, ascorbic acid).

Coating is carried out by spraying of solutions in organic solvents or suspensions of the substances mentioned in organic solvents or water. Other auxiliaries, for example surfactants, pigments, may be added to optimize processability. The solutions or suspensions are sprayed on, for example, in coating pans or in perforated pans or by the air suspension method (for example using a Glatt WLS5 fluidized bed coater). Coating may also be carried out by the coacervation method, in which case so-called microcapsules are formed.

Coating may also be carried out by the coagulation of aqueous dispersions of the substances mentioned above. In this case, the active substance is mixed with the dispersion and the water is removed by drying.

Coated active-substance particles and coated granules can be pressed to tablets while coated pellets can be packed into hard gelatine capsules.

In the coating of active-substance particles or granules containing particles of active substance, more coating material is normally used than in the coating of pellets because the surface which has to be covered is considerably larger than in the case of pellets.

0.004 to 800 parts by weight of coating material may be used per part by weight of active substance. A ratio by weight of 1 part of active substance to 0.005 - 500

parts by weight of coating material is preferred, a ratio by weight of 0.01 to 200 parts by weight of coating material to 1 part by weight of active substance being particularly preferred. The coating materials are applied at elevated temperature, preferably in an air stream. Entry air temperature for example 70 to 90°C; waste air temperature for example up to 40°C.

3. Coating of pellets, tablets and granules containing azelastine and one or more osmotically active substances (for example mannitol, sorbitol) with a semipermeable membrane, for example of 70 to 90% by weight of cellulose acetate and hydroxypropyl methyl cellulose (30 to 10% by weight).

Other suitable osmotically active substances are organic and inorganic compounds or soluble substances which produce an osmotic pressure gradient relative to the outer liquid by way of the semipermeable wall. Osmotically active agents or osmotically active compounds include magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium hydrogen phosphate, urea, sucrose and the like. Other osmotically active agents are known from US-PS 3,854,770, 4,077,407 and 4,235,236.

Examples of semipermeable materials which are known as polymers for osmosis and reverse osmosis are cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, β -glucan acetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, polyamide, polyurethane, sulfonated polystyrene, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethyl amino acetate, cellulose acetate chloroacetate, cellulose dipalmitate, cellulose dioctanoate, cellulose dicapry-

late, cellulose dipentanoate, cellulose acetate valerate, cellulose acetate p-toluenesulfonate, cellulose acetate butyrate, ethyl cellulose, selectively permeable polymers which have been formed by the co-precipitation of a polycation and a polyanion, as described in US 3,173,876, 3,276,586, 3,541,005, 3,541,006 and 3,546,142.

Coating with semipermeable membranes may also be carried out, for example, in accordance with DE-A-33 10 081 and DE-A-33 10 096.

10 The percentage content of osmotically active substance, based on 1 part by weight of azelastine, may be from 10 to 800 parts by weight and is preferably from 20 to 600 parts by weight and, most preferably, from 50 to 400 parts by weight. The coating materials are applied
15 in such a quantity that the semipermeable membrane has a thickness of 50 to 500 μm and preferably 100 to 300 μm .

 The active substance and the osmotically active substances may be processed at temperatures between room temperature and 80°C. To adjust the release rate, a hole
20 is drilled into the membrane wall, for example by laser beam, so that after the tablets produced have been introduced into a water-containing liquid, the active substance is dissolved or suspended by liquid entering through the hole and is forced out through the hole. The
25 semipermeable membrane is applied, for example, at a feed air temperature of 70 to 90°C.

 The semipermeable membrane may optionally contain a microporous layer or microporous substances may be incorporated therein (see DE-OS 33 10 081, for example
30 pages 7 to 17).

 Materials suitable for the production of the microporous layer include, for example, polycarbonates of linear polyesters of carbonic acid in which carbonate groups recur in the polymer chain; microporous materials
35 which have been produced by phosgenation of an aromatic

dihydroxy compound, such as bisphenol; a microporous polyvinyl chloride; microporous polyamides; such as polyhexamethylene adipic acid amide; microporous modacrylic polymers; including those which have been formed from
5 polyvinyl chloride and acrylonitrile; microporous styrene/acrylic monomers and copolymers thereof; porous polysulfones characterized by diphenylene sulfone in a linear chain; halogenated polyvinylidene; polychloro-
10 ether; acetal polymers; polyesters produced by esterification of a dicarboxylic acid or an anhydride with an alkylene polyol; polyalkylene sulfides; phenolic polymers; polyesters; microporous polysaccharides containing substituted anhydroglucose units which have a decreasing permeability to water and biological liquids; asymmetrical
15 porous polymers; crosslinked olefin polymers; hydrophobic or hydrophilic microporous homopolymers; copolymers or interpolymers of reduced density and the materials described in US-PS 3,595,752; 3,643,178; 3,654,066; 3,709,774; 3,718,532; 3,803,601; 3,852,224; 3,852,388 and
20 3,853,601; in GB-PS 1,126,849 and in Chemical Abstracts, Vol. 71, 427 F, 22573F, 1969.

Other microporous materials for the production of the microporous layer include polyurethanes, crosslinked chain-extended polyurethanes, polyimides, polybenzimidazoles,
25 collodion, regenerated proteins, semisolid crosslinked polyvinyl pyrrolidone, microporous materials which have been produced by diffusion of polyvalent cations in polyelectrolyte sols, microporous derivatives of polystyrene, such as sodium polystyrene sulfonate,
30 polyvinylbenzyl trimethyl ammonium chloride, microporous cellulose acylates and similar microporous polymers are known from US-PS 3,524,753; 3,565,259; 3,276,589; 3,541,055; 3,541,006; 3,546,142; 3,615,024; 3,646,178 and 3,852,224.

35 The pore formers suitable for the production of the

microporous layer include solids and pore-forming liquids. The expression "pore formers" as used herein also encompasses substances which form micropassages and the removal of the pore formers can lead to both types. The expression "pore-forming liquids" as used herein encompasses semisolid and viscous liquids. The pore formers may be inorganic or organic and the layer-forming polymer generally contains 5 to 70% by weight and, more particularly, 20 to 50% by weight of pore former. The expression "pore former" both for solids and for liquids encompasses substances which can be dissolved out, extracted or leached out from the precursor of the microporous membrane by the liquid present in the surrounding environment to form an effective open-cell microporous layer. The pore-forming solids have a particle size of approximately 0.1 to 200 μm and include alkali metal salts, such as lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate and the like. Organic compounds, such as saccharides, including the sugars sucrose, glucose, fructose, mannitol, mannose, galactose, sorbitol and the like. Soluble polymers, such as carbowaxes, carbopol and the like, may also be used. The pore formers also include diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, poly(α,ω)-alkylenediols and the like.

4. Encapsulation of azelastine active substance or fixing to the following substances or mixtures thereof:

- digestible fats, for example triglycerides of saturated fatty acids $\text{C}_8\text{H}_{16}\text{O}_2$ to $\text{C}_{18}\text{H}_{36}\text{O}_2$ and mixtures thereof, peanut oil and hydrogenated peanut oil, castor oil and hydrogenated castor oil, olive oil,

- 5 sesame oil, cottonseed oil and hydrogenated cottonseed oil, corn oil, wheat germ oil, sunflower seed oil, cod-liver oil, mixtures of mono-, di- and triesters of palmitic and stearic acid with glycerol, glycerol trioleate, diglycol stearate, stearic acid.
- 10 - Non-digestible fats and fat-like substances, for example 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), carnauba wax, beeswax, fatty alcohols (linear or branched) with a chain length of $C_8H_{17}OH$ to $C_{30}H_{61}OH$ and, more particularly, from $C_{12}H_{25}OH$ to $C_{24}H_{49}OH$.
- 15 - Polymers, such as polyvinyl alcohol, polyvinyl chloride, polyacrylic acid (Carbopol®); anionic polymers of methacrylic acid and methacrylates (Eudragit® L, Eudragit® S), acrylate and methacrylate copolymers with trimethyl ammonium methacrylate (Eudragit® RL, Eudragit® RS);
- 20 copolymers of acrylates and methacrylates (Eudragit® NE 30 D) and of acrylic acid, methacrylic acid and esters thereof (ratio of the free carboxyl groups to the ester groups 1:1) (Eudragit® L 30 D), polyethylene, polyglycolic acid, polyhydroxybutyric acid, polylactic acid, copolymers of lactic acid and glycolic acid (manufacturer: Boehringer Ingelheim),
- 25 copolymers of lactic acid and ethylene oxide, copolymers of glycolic acid and ethylene oxide, copolymers of lactic acid and hydroxybutyric acid, hydroxypropyl methyl cellulose phthalate or acetate succinate; cellulose acetate phthalate, starch
- 30 acetate phthalate and polyvinyl acetate phthalate;
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- 5 carboxymethyl cellulose; methyl cellulose phthalate, succinate, phthalate succinate, methyl cellulose phthalic acid semiester; zein; ethyl cellulose; shellac, gluten; ethylcarboxyethyl cellulose; ethacrylate/maleic anhydride copolymer; maleic anhydride/vinylmethylether copolymer; styrene/maleic acid copolymers; 2-ethylhexyl acrylate maleic anhydride; crotonic acid/vinyl acetate copolymers; glutamic acid/glutamic acid ester copolymers; 10 carboxymethyl cellulose glycerol monooctanoate; cellulose acetate succinate; polyarginine; cross-linked alginate; crosslinked gelatine;
- 15 - swelling agents, such as methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose (Pharmacoat, Methocel E = propylene glycol ether of methyl cellulose), alginic acid and salts thereof (Na, Ca salt, also mixtures of sodium alginate and calcium salts, for example CaHPO_4), starch, carboxy- 20 methyl starch, carboxymethyl cellulose and salts thereof (for example Na salt), galactomannan, gum arabic, karaya gum, ghatti gum, agar agar, carrageen, xanthan gum, guar gum and derivatives thereof, carob bean flour, propylene glycol alginate, 25 pectin, tragacanth.

Formulations of this type may be prepared as follows:

- 30 a) by dissolving or dispersing azelastine or salts thereof in the fats or fat-like substances mentioned or mixtures thereof, even with melting of the substances mentioned and subsequent recooling, size reduction, optionally adding other substances, such as for example the water-soluble or water-swella- 35 ble

- substances mentioned, and pressing to tablets. The cooling of the melt and size reduction may even be carried out in a single step by dispersing the melt in cold water or subjecting it to spray solidification. Where the oils mentioned above are used as retarding agents, azelastine or a salt thereof is dissolved or suspended in the oil and, optionally after the addition of up to 2% of aluminium monostearate, the solution or suspension is introduced into ampoules and subsequently sterilized or, optionally after the addition of flavourings and/or sedimentation retarders, such as highly dispersed silicon dioxide (for example Aerosil®), is homogenized and poured into bottles;
- b) by mixing azelastine with the above-mentioned fats, polymers or swelling agents or mixtures thereof, optionally in the presence of heat, and pressing the mixtures to form tablets or pellets, optionally after the addition of other auxiliaries;
- c) by mixing azelastine with solutions of the above-mentioned fats or polymers in water or organic solvents, such as for example ethanol, ethyl acetate, acetone or isopropanol, optionally mixing with carrier materials, such as celluloses, and subsequent evaporation of the solvents and mixing the active-substance encapsulation obtained with other auxiliaries and processing to tablets or pellets for example;
- d) by moistening a mixture of azelastine and the swelling agents mentioned with organic solvents, such as ethanol, ethyl acetate, acetone or isopropanol, optionally with addition of binders, such as

polyvinyl pyrrolidone or copolymers of polyvinyl pyrrolidone and polyvinyl acetate, granulating the mixture obtained, subsequent drying, adding other auxiliaries and pressing the mixture to tablets;

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- e) by mixing azelastine with a solution of natural or synthetic resins, such as shellac or polyvinyl acetate in polyethylene glycol with a molecular weight of 200 to 1500, optionally adding other auxiliaries, such as for example stearates or swelling agents, and introducing the material obtained into soft gelatine or hard gelatine capsules.

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Broadly speaking, the medicinal preparations are prepared by methods known per se using known pharmaceutical auxiliaries and other typical carriers and diluents in addition to the retard components; the auxiliaries mentioned as retard components may also perform other functions, for example as mould release agents or as disintegrating agents. Suitable carriers and auxiliaries of this type are, for example, the substances recommended or mentioned in the following literature references as auxiliaries for use in pharmacy, cosmetics and related fields: Ulmanns 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 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, 2nd Edition, Editio Cantor, Aulendorf in Württemberg 1981. Examples of typical auxiliaries, carriers and diluents are gelatine, natural sugars, such as cane sugar or lactose, lecithin, pectin, starch (for example cornstarch) and starch

derivatives, cyclodextrins and cyclodextrin derivatives, polyvinyl pyrrolidone, gelatine, gum arabic, alginic acid, tylose, talcum, lycopodium, silica (for example colloidal silica), levulose, tragacanth, sodium chloride, 5 stearates, magnesium and calcium salts of C_{12-22} fatty acids, more particularly saturated fatty acids (for example stearates), polyethylene glycol having an average molecular weight of 200 to 20,000, preferably 200 to 5,000 and more preferably 200 to 1,000 or mixtures 10 thereof and/or polymers of vinyl pyrrolidone and/or copolymers of vinyl pyrrolidone and vinyl acetate, 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) 15 or polyhydric alcohols, such as glycols, glycerol, diethylene glycol, pentaerythritol, sorbitol, mannitol, etc., which may even be etherified, benzyl benzoate, dioxolanes, glycerol formals, tetrahydrofurfuryl alcohol, polyglycol ethers with C_{1-12} alcohols, dimethyl acetamide, 20 lactamides, lactates, ethyl carbonates, silicones (more particularly medium-viscosity polydimethyl siloxanes), calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, magnesium carbonate, gum arabic, alginic acid, stearates, fats and similarly acting 25 substances.

In addition, the formulations may contain interfacially active substances, for example alkali metal soaps, such as alkali metal salts of higher fatty acids (for example Na palmitate, Na stearate) or derivatives 30 thereof (for example Na ricinoleate sulfuric acid ester); sulfurized compounds or sulfonated compounds which are obtained by reaction of higher fatty alcohols with sulfuric acid or chlorosulfonic acid and which are used, for example, in the form of the sodium salts (for example 35 sodium lauryl sulfate, sodium cetyl sulfate, sodium

stearyl sulfate, sodium cetyl sulfonate); salts of galenic acids; saponins; quaternary ammonium compounds; partial fatty acid esters of sorbitan; partial fatty acid esters and fatty acid esters of polyoxyethylene sorbitan; 5 sorbitol ethers of polyoxyethylene; fatty acid esters of polyoxyethylene; fatty alcohol ethers of polyoxyethylene; fatty acid esters of sucrose; fatty acid esters of polyglycerol; proteins; lecithins.

The formulations may also contain celluloses, 10 particularly where compacts are to be produced. Suitable celluloses are purified cellulose (commercially available, for example, as Elcema®) or microcrystalline cellulose commercially available, for example, as Avicel®. However, other binding fillers, such as calcium hydrogen 15 phosphate, lactose, starches (for example potato starch, cornstarch, modified starches, such as Starch ST 1500/Colorcon), glucose, mannitol, sucrose, may also be used.

In addition, the formulations may contain sedimentation retarders such as, for example, highly disperse 20 silicas with a specific surface of 50 to 500 m²/g and, more particularly, 100 to 400 m²/g (as determined by the BET method). Such silicas are commercially available, for example, as Aerosil®.

In addition, the formulation may usefully contain 25 mould release agents, such as talcum or siliconized talcum, calcium and magnesium stearate, stearic acid, paraffin, hydrogenated fats and oils, silicone oil emulsion.

Other suitable auxiliaries are substances which 30 promote disintegration (so-called disintegrating agents), such as crosslinked polyvinyl pyrrolidone, sodium carboxymethyl starch, sodium carboxymethyl cellulose, formaldehyde gelatine, formaldehyde casein, polyacrylic acid and ultra-amylopectin.

35 Solutions and suspensions may be prepared, for

example, using water or physiologically safe organic solvents, such as for example ethanol, 1,2-propylene glycol, polyglycols and derivatives thereof. Injectable solutions or suspensions may be prepared using, for example, 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.

10 Stabilizers, dyes, antioxidants and complexing agents (for example ethylenediamine tetraacetic acid) and the like and acids, such as citric acid, tartaric acid, maleic acid, fumaric acid, may also be added.

15 Suitable antioxidants are, for example, sodium metabisulfite, cysteine, ascorbic acid and esters thereof (for example palmitate), flavonoids, gallic acid, gallic acid alkyl ester, butyl hydroxyanisole, nordihydroguaiaretic acid, tocopherols and tocopherols + synergists (substances which complex heavy metals, for example 20 lecithin, ascorbic acid, citric acid, phosphoric acid).

25 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.

30 Suitable plasticizers for coating materials are citric acid and tartaric acid esters (acetyl triethyl, acetyl tributyl, tributyl, triethyl citrate); glycerol and glycerol esters (glycerol diacetate, triacetate, acetylated monoglycerides, castor oil); phthalic acid esters (dibutyl, diamyl, diethyl, dimethyl, dipropyl, D-(2-methoxy or ethoxyethyl)-phthalate, ethyl phthalyl and butyl phthalyl ethyl and butyl glycolate); alcohols (propylene glycol, polyethylene glycols of different 35 chain lengths), adipates (diethyl, di-(2-methoxy or

ethoxyethyl)-adipate); benzophenone; diethyl and dibutyl sebacate, succinate, tartrate; diethylene glycol dipropionate; ethylene glycol diacetate, dibutyrate, dipropionate; tributyl phosphate, tributyrin; polyethylene glycol sorbitan monooleate; sorbitan monooleate.

The retard components or coating materials may be applied using solvents from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatic, aromatic, heterocyclic solvents and mixtures thereof. Typical solvents are inter alia acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethyl glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diethylene glycol dimethyl ether, water and mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol and ethylene dichloride and methanol and mixtures thereof. These solvents are removed in the course of the coating process. Irrespective of the method used for their production, the formulations according to the invention are characterized in that they release or give off the active substance azelastine or physiologically safe salts thereof to body fluids at a rate of 0.05 to 5 mg per hour.

Dosages always apply to azelastine as base; where salts of azelastine are used, the dosages should be modified in accordance with the molecular weight.

The azelastine contents of the preparations accord-

ing to the invention are as follows:

- 5 a) in the case of oral formulations 0.1 mg to 50 mg, preferably 0.2 mg to 30 mg and more preferably 0.5 mg to 20 mg of azelastine active substance. The individual doses mentioned may be applied 1 to 5 times a day, preferably 1 to 3 times a day and more preferably 1 to 2 times a day;
- 10 b) in the case of parenteral formulations (intravenous, intramuscular, subcutaneous, intraperitoneal): 0.1 mg to 500 mg, preferably 0.2 mg to 400 mg and more preferably 0.5 to 250 mg azelastine active substance. The individual doses mentioned may be
- 15 administered once a month (for example in the case of subcutaneous implantates) to three times a day, preferably once a month to twice daily and, more particularly, once a month to once a day;
- 20 c) in the case of dermal formulations (for example plasters) 5 mg to 5000 mg, preferably 10 mg to 3000 mg and more preferably 30 mg to 2000 mg of azelastine active substance. The individual doses mentioned may be administered once a day to once a
- 25 month, preferably once every three days to once every three weeks and, more preferably, weekly to every two weeks.

Particularly preferred retard components are:

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- a) cation exchangers
Poly(styrene divinylbenzene)sulfonic acid sodium salt (for example Amberlite® IRP 69). For example, 3 to 10 parts of Amberlite® IRP 69 are used to 1
- 35 part azelastine (base).

b) Coating materials

Hydroxypropyl methyl cellulose phthalate

1.5 to 3 parts of hydroxypropyl methyl cellulose phthalate 55 are used to 1 part of azelastine.

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Ethyl cellulose

0.1 to 1 part of ethyl cellulose to 1 part of azelastine

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Eudragit resins such as Eudragit® RS for example

0.01 to 0.1 part of Eudragit® RS to 1 part of azelastine.

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c) Semipermeable membranes with an osmotically active core containing the active substance and an outlet opening:

coating with a 100 to 300 μ m thick layer of 82% of cellulose acetate and 18% of hydroxypropyl methyl cellulose.

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d) Encapsulating substances

hydrocolloids, for example hydroxypropyl methyl cellulose:

2 to 10 parts of hydrocolloid to 1 part of azelastine.

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Eudragit® RS:

10 to 15 parts of Eudragit® RS to 1 part of azelastine.

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Glycerol ditripalmitostearate (for example Precirol Ato 5)

1 to 10 parts of Precirol Ato 5 to 1 part of azelastine.

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The required release rate of 0.05 to 5 mg per hour is established by the measures defined in the process claim in conjunction with the corresponding disclosures in the specification. If a certain release rate is to be established within the range mentioned, the following steps for example may be taken:

1. Producing the coating or encapsulating the active substance in the manner described above.
2. Testing the release of active substance from the formulation using 0.1 N HCl (2 hours) and phosphate buffer pH 6.8 (thereafter) as the release medium.
3. a) If the release rate is too high:
the content of retard component should be increased and/or the content of water-soluble auxiliaries should be reduced; the content of osmotically active substance should be increased.
- b) If the release rate is too low:
the content of retard component should be reduced and/or the content of water-soluble auxiliaries should be increased; the content of osmotically active substance should be increased.

In general, a release rate of 1 mg of azelastine per hour is desirable.

Example 1:

100 g of azelastine hydrochloride are mixed with 960 g of hydroxypropyl methyl cellulose (viscosity of a 2% aqueous solution: 4000 mPa.s (4000 cP) (commercial

product: for example Methocel K4M Premium), 1320 g of spray-dried lactose and 20 g of magnesium stearate are mixed and the resulting mixture is pressed to tablets with a weight of 120 mg, a diameter of 6 mm and a radius of curvature of 6 mm.

The tablets may then be conventionally coated with a film which is soluble in or permeable to or resistant to gastric juices.

To produce a coating resistant to gastric juices, 1000 g of tablets are sprayed, for example in a coating pan, with approximately 1000 g of the following suspension:

63 g of cellulose acetate phthalate are dissolved in 480 g of acetone. 21 g of diethyl phthalate, 30 g of dichloromethane and 131 g of methanol are introduced into the resulting solution. 4.4 g of titanium dioxide are uniformly suspended in the solution obtained.

The tablets are sprayed discontinuously, heated drying air being blown onto the tablets between the spraying phases.

One retard tablet contains 5 mg of azelastine hydrochloride.

Example 2:

12 g of azelastine hydrochloride, 20 g of Eudragit® RS PM, 250 g of talcum and 200 g of lactose are mixed and the resulting mixture is moistened with approximately 140 g of a mixture of 12.7 g of glycerol triacetate (commercially available, for example, as triacetin) and 127.3 g of Eudragit® RS 12.5. The moist material is conventionally granulated through a 1 mm mesh sieve and, after drying at room temperature, a mixture of 909 g of Eudragit® RS 12.5 and 91 g of triacetin is sprayed on by spray gun in a coating pan. The dried granules obtained are then pressed in the absence of further auxiliaries to

form biconvex tablets with a weight of 300 mg and a diameter of 10 mm.

One tablet contains 5 mg of azelastine hydrochloride in retarded form.

5

Example 3:

50 g of azelastine HCl are made into a paste with 100 g of tartaric acid, 250 g of lactose, 10 g of micro-crystalline cellulose (Avicel PH 101) and 7 g of hydroxy-propyl cellulose (viscosity of a 5% solution: 75 to 150 mPa·s (commercially available, for example, as Klucel LF)). The paste formed is pressed through a perforated plate (perforation diameter 1 mm) and the strands formed are conventionally size-reduced and rounded off (spheron-izer disc). The pellets obtained are dried and sieved. 300 g of pellets with a particle size of 800 to 1200 μm are conventionally coated with a solution of 42.5 g of ethyl cellulose (commercially available as Ethocel Type N 22) and 37.5 g of polyethylene glycol 1500 (commercially available, for example, as Carbowax 1540) in 720 g of chloroform by spraying in a fluidized bed.

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20

50 mg of the coated pellets obtained as described above are packed into size 3 hard gelatine capsules.

One hard gelatine capsule contains 4.4 mg of azelastine hydrochloride in retarded form.

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Example 4:

The preparations according to the invention are produced by encapsulation in swelling substances:

The following ingredients are mixed (quantities in grams):

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		Formulation		
		1	2	3
	Azelastine hydrochloride	50	50	50
	Hydroxypropyl methyl cellulose			
5	(Methocel K 4 M)	480	192	96
	Lactose	660	948	1044
	Magnesium stearate	10	10	10

10 The mixtures are pressed in a tablet press to form flat tablets with a weight of 120 mg and a diameter of 6 mm.

The tablet thicknesses in mm are as follows:

		3.25	3.15	3.05
	Breaking strength (N)	47	48	50
15	(Heberlein breaking strength tester)			

One tablet contains 5 mg of azelastine HCl.

20 The release of active substance as measured in a USP XXI apparatus (Dissolution Tester, Apparatus 2, dissolution medium: 500 ml 0.1 N HCl, rotational speed: 120 r.p.m.) is as follows:
Release rate in %:

		Formulation		
		1	2	3
25	After 5 mins.	4	31	50
	60 mins.	20	76	100
	120 mins.	36	96	
	180 mins.	55		
30	240 mins.	74		
	300 mins.	86		
	360 mins.	93		

Example 5:

35 100 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 paste is pressed through a perforated plate (perforation diameter 1 mm) and the strands formed are conventionally size-reduced and spheronized. The pellets obtained are dried and sieved.

1000 g of pellets with a particle size of 800 to 1250 μ m 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 solution. 800 g of a 30% aqueous dispersion of a copolymer of acrylates and methacrylates with a small content of trimethyl ammonium ethacrylate chloride (= Eudragit® RS 30 D) are added to the emulsion obtained which is then stirred 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 resulting suspension is stirred into the dispersion obtained as described above.

The lacquering suspension obtained is conventionally applied to the pellets, for example using a fluidized bed spray granulator (feed air temperature 40-50°C, waste air temperature max. 40°C). The pellets are dried under the same conditions.

The lacquering suspension described above is sprayed on until the dried pellets have a total weight of 1042 g.

The lacquered pellets are packed in quantities of 78.1 mg in size 3 hard gelatine capsules. One hard gelatine capsule contains 5 mg of azelastine hydrochloride in retarded form. The release rate of the active substance from a capsule in the USP XXI Apparatus (Dissolution Tester, Apparatus 2, dissolution medium: 500 ml 0.1 N HCl, rotational speed: 120 r.p.m.) is

3.0 mg $\hat{=}$ 60% after 1 hour

4.5 mg $\hat{=}$ 90% after 2 hours.

Accordingly, the release rate is 3 mg of active substance
5 per hour.

Example 6:

The procedure is as described in Example 5 except
that the lacquering suspension mentioned in that Example
10 is sprayed onto the pellets until the dried pellets have
a total weight of 1127 g. The lacquered pellets are then
packed in quantities of 84.5 mg into size 3 hard gelatine
capsules. One hard gelatine capsule contains 5 mg of
azelastine hydrochloride in retarded form. The release
15 rate of the active substance from a capsule in the USP
XXI apparatus (test conditions as in Example 5) is

0.25 mg $\hat{=}$ 5% after 1 hour

0.50 mg $\hat{=}$ 10% after 2 hours.

20

Accordingly, the release rate is 0.25 mg of active
substance per hour.

Example 7:

25 The procedure is as described in Example 6.

If 16.9 mg of the pellets obtained in Example 6 are
packed into size 3 hard gelatine capsules, 1 hard gela-
tine capsule contains 1 mg of azelastine hydrochloride in
retarded form. The release rate of the active substance
30 from a capsule in the USP XXI apparatus (test conditions
as in Example 5) is:

0.05 mg $\hat{=}$ 5% after 1 hour

0.10 mg $\hat{=}$ 10% after 2 hours.

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Accordingly, the release rate is 0.05 mg of active substance per hour.

Example 8:

- 5 Capsules containing 6 mg of azelastine or suspensions containing 6 mg of azelastine in 5 ml - in each case bound to strongly acidic cation exchanger.

8.48 g of azelastine hydrochloride are dissolved in 4 litres of purified water. 71.5 g of styrene sulfonic acid/divinyl benzene copolymer (degree of crosslinking 8%) (commercially available, for example, as Amberlite® IR 120) are suspended in the resulting solution and the suspension formed is stirred for 3 hours. The suspension is then filtered through a glass filter nutsch and the filter cake obtained is washed twice with 300 ml of purified water and the washing water is removed by filtration under suction.

- 5 g of gelatine (isoelectric point 6 - 7.6; molecular weight 25,000 - 35,000; commercially available as Gelita® Collagel from Deutsche Gelatinefabriken, Eberbach/Neckar) are dissolved in a solution of 5 g of 1 N hydrochloric acid in 800 g purified water in a glass beaker. The filter cake mentioned above is suspended in the solution and the suspension is stirred for 1 hour. The suspension is then filtered through a glass filter nutsch and the filter cake obtained is washed twice with 200 ml of purified water and the washing water is removed by filtration under suction.

- The filter cake is dried at 60°C. The dried product is packed in quantities of 62 mg into size 4 hard gelatine capsules.

One hard gelatine capsule contains 6 mg of azelastine bound to strongly acidic cation exchanger.

- A juice containing 6 mg azelastine bound to ion exchanger in 5 ml is obtained as follows:

7.4 kg of purified water are heated to 90 - 95°C and 0.002 kg of propyl-4-hydroxybenzoate and 0.013 kg of methyl-4-hydroxybenzoate are dissolved therein. 0.020 kg of hydroxyethyl cellulose (average degree of polymerization: 250) and 3.0 kg of sucrose are dissolved in the solution cooled to 70°C.

After cooling to 25°C, 3 g of raspberry flavouring and 0.2 kg of modified starch (Starch 1500®/Colorcon) are dissolved or suspended with stirring in the solution formed. 124 g of the dried ion exchanger charged with azelastine are stirred into the suspension. The suspension is then made up to 11.0 kg (corresponding to 10 litres) with purified water.

The release rate of the active substance from a capsule or 5 ml of suspension in the USP XXI apparatus (Dissolution Tester, Apparatus 2, dissolution medium 500 ml sodium chloride 0.9%, rotational speed: 100 r.p.m.) is 25% after 1 hour, 40% after 2 hours, 50% after 3 hours, 58% after 4 hours, 65% after 5 hours, 69% after 6 hours, 72% after 7 hours and 75% after 8 hours. The dissolution medium is renewed every hour; the release values obtained are added up.

**CLAIMS**

1. Azelastine-containing medicinal preparations with controlled release of the active principle using a retard component, 0.004 to 800 parts of the retard component being used to one part by weight azelastine (based on the base), the azelastine optionally being present in the form of its physiologically acceptable salts and the release rate of the azelastine being between 0.05 and 5 mg per hour, the release rate being determined in an aqueous test solution of pH 1.0 and/or pH 6.8.
2. A medicinal preparation as claimed in claim 1, characterized in that the active principle azelastine or its physiologically acceptable salts is/are
- a) coated with one or more retard components or
 - b) fixed to a cation exchanger or
 - c) mixed with one or more osmotically active substances and covered with a semipermeable membrane and a hole is drilled or
 - d) is/are encapsulated in, or fixed to, one or more substances from the group consisting of digestible fats, indigestible fats or fat-like substances, polymers or swellable substances,
- optionally with addition of other typical auxiliaries and additives for controlled release.
2. A medicinal preparation as claimed in claim 1, characterized in that the formulations for oral administration contain 0.1 to 50 mg, those for parenteral administration 0.1 to 500 mg and those for dermal application 5 to 5000 mg azelastine.
4. A process for the production of a medicinal preparation containing the active principle azelastine with controlled release thereof, characterized in that one part by weight azelastine (based on the base) is proces-



sed with 0.004 to 800 parts by weight of a retard component and optionally other typical pharmaceutical auxiliaries and additives and a release rate of 0.05 to 5 mg azelastine/

5 hour is adjusted.

5. A process for the production of a medicinal preparation as claimed in claim 4, characterized in that the active principle azelastine or its physiologically acceptable salts is/are

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- a) coated with one or more retard components or
- b) fixed to a cation exchanger or
- c) mixed with one or more osmotically active substances and covered with a semipermeable membrane and a hole
- 15 is drilled or
- d) is/are encapsulated in, or fixed to, one or more substances from the group consisting of digestible fats, indigestible fats or fat-like substances, polymers or swellable substances,

20

other typical auxiliaries and additives optionally being additionally used in the steps mentioned above.

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6. A process for the production of a medicinal preparation as claimed in claim 4 and/or 5, characterized in that the formulations for oral administration contain 0.1 to 50 mg, those for parenteral administration 0.1 to 500 mg and those for dermal application 5 to 5000 mg azelastine.