Medicaments containing bisphosphonic acids and derivatives thereof which are provided for preventing and treating autoimmune diseases and allergies

Field of the invention

This invention relates to pharmaceutical preparations for the prevention and treatment of autoimmune disorders and of allergies.

It is known that autoimmune disorders, such as multiple sclerosis, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, uveitis *etc.*, and allergies, in particular food allergies, nickel allergy and pollen allergies *etc.* are attributable to an inappropriate reaction by the body's immune system.

It is furthermore known that, due these inappropriate reactions of the immune system, endogenous substances (autoantigens) are perceived as foreign substances and a defence reaction develops against them which results in damage to the body's own tissue. Depending upon the organ system involved, some 40 autoimmune conditions have been identified. These defence reactions may be directed both against individual cell constituents and against entire cells or organs.

Allergies are known to be the result of hypersensitivity towards certain substances, the allergens, which gives rise to an over-reaction of the immune system. In other words, affected subjects react to certain substances (the

allergens) with specific symptoms as a defence against the allergen.

Prior art

Attempts to treat autoimmune disorders caused by inappropriate reactions of the immune system with non-specifically acting immunosuppressants have proved entirely unsatisfactory as the use of immunosuppressants brings about a general inhibition of inflammatory reactions which may go as far as to shut down large parts of the immune system, so resulting in the occurrence of many side-effects, for example toxic damage, increased susceptibility to infectious diseases and increased risk of the occurrence of malignant diseases.

The alternative approach of avoiding the side-effects associated with the use of non-specifically acting immunosuppressants by using selective suppression (*c.f. Ann. Neurol.* 37 Suppl. 1, 87-101), with action being purposefully and specifically taken against the allergens or autoantigens at various points in the defence reaction, also met with less than complete success.

One of these methods is based upon the oral or inhalatory administration of autoantigens or allergens specific to the particular disorder. While it is indeed possible in this manner to reinduce the body's resistance to these autoantigens or allergens or to enable the body to tolerate the autoantigens or allergens which have hitherto been attacked and initiate the enhanced immune response, the overall success rate of this patient desensitisation is limited because the desensitisation is inadequate (*Ann. N. Y. Acad. Sci.* 778, 1-27; *Ann. N. Y.*

Acad. Sci. 778, 243-250; *Science* 261, 1727-1730; *Annu. Rev. Med.* 48, 341-351).

The mechanism of oral reinduction of tolerance by these substances is not yet completely understood. It may, however, be assumed that in the case of oral administration a part is played both by the immune system and by the bacterial flora of the gastrointestinal tract, the T cells (T lymphocytes), in particular the γδ-T cells (*The Journal of Immunology* 158, 3610-3618; *Res. Immunol.* 147, 49-59; *Immunology Letters* 48, 97-102).

It was, however, entirely surprising that the reinduction of tolerance achieved with oral or inhalatory administration of autoantigens or allergens specific to the disorder was greatly promoted if the autoantigens or allergens were administered in combination with bisphosphonic acids or the derivatives thereof. These combinations may thus successfully be used for the prevention and treatment of autoimmune disorders or allergies.

The use of bisphosphonic acids and of some of the derivatives thereof in pharmaceutical preparations is already known. The microbiostatic action of bisphosphonic acids (DE 3611522), the action thereof in the treatment of disorders of calcium and phosphate metabolism (DE 2534390, DE 2534391, DE 3334211, DE 3434667, DE 2745083), cytostatic action (DE 3425812), the lipid-reducing action thereof (*Arzneimittelforschung* 46, 759-762) and the ability thereof to stimulate immune cells (WO 97/38696 A1) are already known. The fact that bisphosphonic acids have an immunomodulatory action (WO 97/38696 A1) is furthermore known and has been used.

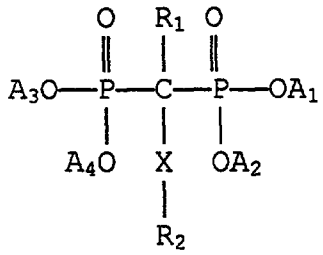
However, use of these compounds is associated with many side-effects which are determined by the mode of administration. In the case of intravenous infusion, such side-effects are fever, flu-like symptoms with violent shivering, lymphopenia and thrombocytopenia and, in the case of oral administration, they are painful swallowing, oesophagitis, oesophageal erosion, oesophageal ulceration, dyspepsia, diarrhoea *etc.*. Moreover, oral treatment with bisphosphonates, for example, requires relatively large quantities of active substance and therapeutic success is still unsatisfactory (*Drug-Saf.* 14, 158-170).

It was thus not in the least obvious to use this group of compounds in combination with autoantigens or allergens in order to reinduce the body's tolerance to autoantigens or allergens.

Description of the invention

The invention accordingly relates to a novel method of solving the hitherto unsolved problem of the prevention and treatment of autoimmune disorders and of allergies by means of pharmaceutical preparations, namely to use the autoantigens or allergens hitherto used to treat autoimmune disorders and allergies in combination with bisphosphonates or the derivatives thereof.

The invention relates to the use of bisphosphonic acids and the derivatives thereof for the production of pharmaceutical preparations for the prevention and treatment of autoimmune diseases or allergies, wherein the bisphosphonic acids and the derivatives thereof which are used are those of the general formula:



(I),

in which

A_1, A_2, A_3, A_4, which may be identical or different and mean hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclic residue, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

X, which may also be absent or may be alkylene, alkenylene or hydroxyalkylene,

R_1, R_2, which may be identical or different and mean H, OH, $-NH_2$, a substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heterocyclic residue or $-SR_3$, Cl and $-NR_3R_4$, in which

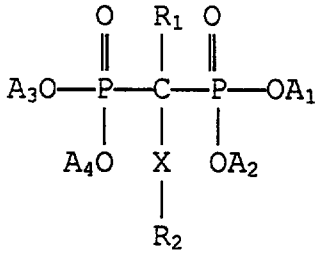
R_3, R_4, which may be identical or different and mean H, OH, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclic residue,

and the pharmaceutically compatible salts, esters thereof as well as salts of esters or compounds which, on administration, form the compounds to be administered as metabolites or catabolites, in combination with the specific autoantigens for the prevention and treatment of the particular autoimmune disorder, or in combination with the specific allergens for the prevention and treatment of the particular allergy, wherein, instead of the particular autoantigens or allergens, it is also possible to use fragments or derivatives thereof and the analogues or fragments thereof of the autoantigens or allergens, providing that these each exhibit the same immunological characteristics as the corresponding whole molecules, and
wherein the bisphosphonic acids or the derivatives thereof and the autoantigens or allergens or fragments, derivatives or analogues thereof
may be administered simultaneously or in succession.

The substances may here be administered both synchronously and with a delay by simultaneous or separate administration of the active substances.

From the group of bisphosphonic acids and the derivatives thereof of the general formula I, those bisphosphonic acids and the derivatives thereof which are preferred for

use for the prevention and treatment of autoimmune disorders or allergies are of the general formula:



(II),

in which

A_1, A_2, A_3, A_4, which may be identical or different and mean hydrogen, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, an aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

R_1, means H, OH, NH_2,

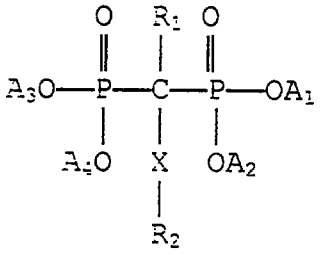
X, which may also be absent or may be alkylene, alkenylene or hydroxyalkylene, in each case having 1 to 12 carbon atoms,

R_2, means H, OH, $-NH_2$, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted

by functional groups, or $-SR_3$, Cl and $-NR_3R_4$, in which

R_3, R_4, which may be identical or different and mean H, OH, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups.

Bisphosphonic acids and the derivatives thereof which have proved particularly effective are those of the general formula:



(III),

in which

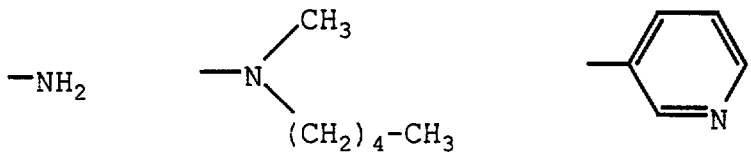
A_1, A_2, A_3, A_4, which may be identical or different and mean hydrogen, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or

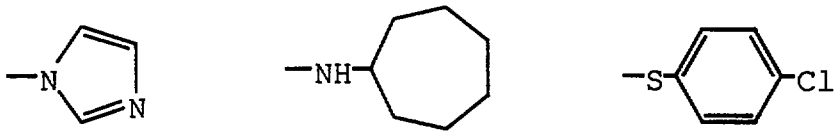
ammonium compounds derived from ethylenediamine or amino acids,

R_1, means H, OH,

X, which may also be absent or may mean $(CH_2)_{1-5}$, amidino,

R_2, may mean





Some examples of these are:

aminohydroxymethylidenebisphosphonic acid (AMP),

2-amino-1-hydroxyethylidene-1,1-bisphosphonic acid (AEP),

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronic acid),

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronic acid),

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (AHP),

amidinomethylenebisphosphonic acid (AIMP),

3-methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonic acid (ibandronic acid),

2-(3-pyridinyl)-1-hydroxyethylidenebisphosphonic acid (risedronic acid),

1-hydroxy-2-(imidazol-1-yl)-ethylidene-1,1-bisphosphonic acid (zoledronic acid),

cycloheptylaminomethylenediphosphonic acid (cimadronic acid),

4-chlorophenylthiomethylene-1,1-bisphosphonic acid
(tiludronic acid)
and the derivatives thereof.

Autoimmune disorders and allergies are prevented and treated by combined use of a bisphosphonic acid or the derivatives thereof and an autoantigen which initiates the particular autoimmune disorder, such as for example in

multiple sclerosis	with myelin basic protein (MBP), further extracts from nervous system tissue,
rheumatoid arthritis	with type I, II or III collagen,
Hashimoto thyroiditis	with thyroglobulin,
myasthenia gravis	with acetylcholine receptor protein,
lupus erythematosus	with DNA,
diabetes mellitus	with islet cell extracts, human insulin,
primary biliary cirrhosis	with liver extracts,
active chronic hepatitis	with liver cell extracts,
adrenalitis/Addison's disease	with adrenal cortex extracts,
polymyositis	with skin extracts, muscle extracts,
dermatomyositis	with muscle and/or skin extracts,
autoimmune haemolytic anaemia	with haemopoetic cell line extracts,
myocarditis myopericarditis	with heart extracts,
scleroderma	with skin extracts, skin cell extracts,

uveitis (phacouveitis, sympathetic ophthalmia)	with eye lens proteins, S-antigens, S-antigen mixtures,
pemphigus vulgaris	with skin extracts,
pemphigoid	with skin extracts,
pernicious anaemia	with gastric cell extracts, parietal cell extracts, intrinsic factor,
autoimmune atrophic gastritis	with gastric cell extracts,
Crohn's disease	with intestinal extracts,
colitis ulcerosa	with intestinal extracts
or in allergies	with the allergy-specific allergens.

Combined use is also taken to include cases in which autoantigens or allergens are already present. Such cases include, for example, Crohn's disease, in which the autoantigen is already present in the intestine as a result of the disease. In this case, in the event of oral or rectal administration, only the bisphosphonic acids or the derivatives thereof need be administered. It is also unnecessary to administer the allergen if, during treatment, the affected subject is in an environment in which the allergy-specific allergen is already present (for example pollen during the pollen release season).

Combined use may proceed not only by oral administration, for example by means of tablets *etc.*, but also, for example, by rectal, inhalatory administration, by application onto the skin or mucous membranes. Preferred administration forms are oral and inhalatory administration and application onto the skin or mucous membranes.

Of these administration forms, inhalation has proved to be particularly gentle because elevated activity is achieved with only very small quantities of autoantigen or allergen and bisphosphonic acid or the derivatives thereof and any possible side-effects of the active substances may accordingly be minimised.

The bisphosphonic acids and the derivatives thereof which are preferably used are those which are poorly resorbed, which include, for example, aminobisphosphonic acids and the derivatives thereof.

Preferred pharmaceutical compositions are tablets, sugar-coated pills, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays. Tablets, sugar-coated pills, capsules, pills and granules may contain, apart from the active substances, conventional excipients, such as (a) fillers and extenders, for example starch, lactose, cane sugar, glucose, mannitol and silica, (b) binders, for example carboxymethyl-cellulose, alginates, gelatine, polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) suspending agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) dissolution retardants, for example paraffin and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol, glycerol monostearate, (h) adsorbents, for example kaolin and bentonite and (i) lubricants, for example talcum, calcium and magnesium stearate and solid polyethylene glycols or mixtures of the substances stated in (a) to (i).

The tablets, sugar-coated pills, capsules, pills and granules may be provided with conventional coatings and shells, which optionally contain opacifying agents, and may be of a composition such that they release the active substance, optionally with a delay, solely or preferentially in a specific part of the intestinal tract, wherein polymeric substances and waxes may, for example, be used as matrix materials.

The active substance or substances, optionally together with one or more of the above-stated excipients, may also assume microencapsulated form.

Apart from the active substance or substances, suppositories may contain conventional water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cocoa fat and higher esters (for example C_{14} alcohol with C_{16} fatty acid) or mixtures of these substances.

Apart from the active substance or substances, ointments, pastes, creams and gels may contain conventional excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth gum, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talcum and zinc oxide or mixtures of these substances.

Apart from the active substance or substances, powders and sprays may contain conventional excipients, for example lactose, talcum, silica, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays may additionally contain conventional propellants, for example chlorofluoro-carbons.

Apart from the active substance or substances, solutions and emulsions may contain conventional excipients, such as solvents, solubilising agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, peanut oil, maize oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and sorbitan fatty acid esters or mixtures of these substances.

Apart from the active substance or substances, suspensions may contain conventional excipients, such as liquid diluents, for example water, ethyl alcohol, propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth gum or mixtures of these substances.

The stated formulation forms may also contain colorants, preservatives as well as with odour- and flavour-enhancing additives, for example peppermint oil and eucalyptus oil and sweeteners, for example saccharin.

Bisphosphonic acids or the derivatives thereof of the formula (I) are suitable for simultaneous, separate or temporally staged use with the autoantigens or allergens, and these compounds should accordingly be present in the pharmaceutical preparations listed above, preferably in a concentration of approx. 0.1 to 99.5 wt.%, relative to the complete mixture. The concentration of the

autoantigens or allergens should be 0.1 to 99.5 wt.% in this case too.

Apart from the compounds of the formula (I) and the autoantigen or allergen, the pharmaceutical preparations listed above may also contain further pharmaceutical active substances.

The pharmaceutical preparations listed above are produced in the conventional manner using known methods, for example by mixing the active substance or substances with the excipient or excipients.

The stated preparations may be administered to humans or animals orally, rectally, intravaginally, topically (powders, ointments, drops) and in cavities and body cavities. Suitable preparations for oral treatment which may be considered are solutions and suspensions, gels, infusion formulations, emulsions, ointments or drops. Topical treatment may be performed using ophthalmological and dermatological formulations, silver and other salts, ear drops, eye ointments, powders or solutions. For animals, administration may be made by suitable formulation with feed or drinking water. Gels, pulverulent formulations, powders, tablets, delayed-release tablets, premixes, concentrates, granules, pellets, boli, capsules, aerosols, sprays, inhalatory preparations may also be used in humans and animals. The compounds according to the invention may furthermore be incorporated into other support materials, such as for example plastics (plastic chains for topical treatment), collagen or bone cement.

The quantities of the individual derivatives required to achieve the desired effect vary very widely. In general, it has proved advantageous in both human and veterinary medicine to administer the active substance or substances of the formula (I) in total quantities of approx. 0.5 to approx. 2000 mg per 24 hours, optionally in the form of two or more individual doses, in order to achieve the desired results. An individual dose preferably contains the active substance or substances in quantities of approx. 0.5 to approx. 2000 mg. It may, however, be necessary to deviate from the stated dosages, specifically as a function of the species and body weight of the subject to be treated, the nature and severity of the condition, the nature of the preparation and administration of the pharmaceutical preparation and the period of time or interval within which the preparation is administered.

It may accordingly be sufficient in some cases to use less than the above-stated quantity of active substance, while in other cases the active substance must be used in a quantity greater than that stated above. The person skilled in the art will establish the optimum dosage and mode of administration of the active substances in each case on the basis of his/her expertise.

When treating animals, the compounds to be used according to the invention may be given in the conventional concentrations and preparations together with feed or with feed preparations or with drinking water.

Examples

Tablets are produced in a manner known *per se* using a mixture of

1.	3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt	600	mg
	Bovine collagen, type II	10	mg
	Mannitol	400	mg
	Starch	50	mg
	Magnesium stearate	10	mg
2.	4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$	26	mg
	Bovine collagen, type II	10	mg
	Mannitol	400	mg
	Starch	50	mg
	Magnesium stearate	10	mg
3.	3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$	1.125	mg
	Bovine collagen, type II	10	mg
	Mannitol	400	mg
	Starch	50	mg
	Magnesium stearate	10	mg
4.	3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt	600	mg
	Myelin basic protein (MBP)	8	mg
	Mannitol	400	mg
	Starch	50	mg
	Magnesium stearate	10	mg

5.	4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$	26	mg
	Myelin basic protein (MBP)	8	mg
	Mannitol	400	mg
	Starch	50	mg
	Magnesium stearate	10	mg
6.	3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$	1.125	mg
	Myelin basic protein (MBP)	8	mg
	Mannitol	400	mg
	Starch	50	mg
	Magnesium stearate	10	mg

Capsules are produced in a manner known *per se* using

7.	3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt	600	mg
	Myelin basic protein (MBP)	8	mg
	Proteolipid protein	15	mg
	Magnesium stearate	15	mg
8.	4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$	26	mg
	Myelin basic protein (MBP)	8	mg
	Proteolipid protein	15	mg
	Magnesium stearate	15	mg

9.	3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$	1.125	mg
	Myelin basic protein (MBP)	8	mg
	Proteolipid protein	15	mg
	Magnesium stearate	15	mg
10.	3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt	600	mg
	Bovine collagen, type II	10	mg
	Magnesium stearate	15	mg
11.	4-Amino-1-hydroxypropylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$	26	mg
	Bovine collagen, type II	10	mg
	Magnesium stearate	15	mg
12.	3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$	1.125	mg
	Bovine collagen, type II	10	mg
	Magnesium stearate	15	mg

wherein the above constituents are mixed together and then introduced in conventional manner into a hard gelatine capsule.

A preparation for inhalation for a 2 ml dose is produced using:

13.	4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$	1.3	mg
	Myelin basic protein	15	mg
	β-Cyclodextrin hydrate	7	mg
	pH 7.2 phosphate buffer	0.2	ml
	water for injection;		
14.	3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt	30	mg
	Myelin basic protein	15	mg
	β-Cyclodextrin hydrate	7	mg
	pH 7.2 phosphate buffer	0.2	ml
	water for injection;		
15.	3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$	0.25	mg
	Myelin basic protein	15	mg
	β-Cyclodextrin hydrate	7	mg
	pH 7.2 phosphate buffer	0.2	ml
	water for injection;		
16.	4-Amino-1-hydroxybutylidene-1,1-bisphosphonate (monosodium salt), $3H_2O$	1.3	mg
	Bovine collagen, type II	10	mg
	β-Cyclodextrin hydrate	7	mg
	pH 7.2 phosphate buffer	0.2	ml
	water for injection;		

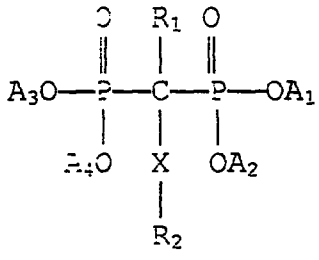
17.	3-Amino-1-hydroxypropylidene-1,1-bisphosphonate, disodium salt	30	mg
	Bovine collagen, type II	10	mg
	β-Cyclodextrin hydrate	7	mg
	pH 7.2 phosphate buffer	0.2	ml
	water for injection;		
18.	3-Methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonate, monosodium salt, $1H_2O$	0.25	mg
	Bovine collagen, type II	10	mg
	β-Cyclodextrin hydrate	7	mg
	pH 7.2 phosphate buffer	0.2	ml
	water for injection.		

The bisphosphonate (for example alendronate) and the autoantigen (for example MBP) are dissolved in a phosphate buffer solution and the β-cyclodextrin hydrate is dissolved therein. The solution is made up to the desired volume with water for injection, sterilised by filtration and aseptically packaged in containers suitable for inhalation by atomisation.

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Claims

1. Use of bisphosphonic acids and the derivatives thereof for the production of pharmaceutical preparations for the prevention and treatment of autoimmune diseases or allergies, characterised in that the bisphosphonic acids and the derivatives thereof which are used are those of the general formula:



(I),

in which

A_1, A_2, A_3, A_4, which may be identical or different and mean hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclic residue, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

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X, which may also be absent or may be alkylene, alkenylene or hydroxyalkylene,

R_1, R_2, which may be identical or different and mean H, OH, $-NH_2$, a substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heterocyclic residue or $-SR_3$, Cl and $-NR_3R_4$, in which

R_3, R_4, which may be identical or different and mean H, OH, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclic residue,

and the pharmaceutically compatible salts, esters thereof as well as salts of esters or compounds which, on administration, form the compounds to be administered as metabolites or catabolites,

in combination with the specific autoantigens for the prevention and treatment of the particular autoimmune disorder, or

in combination with the specific allergens for the prevention and treatment of the particular allergy,

wherein, instead of the particular autoantigens or allergens, it is also possible to use fragments or derivatives thereof and the analogues and fragments

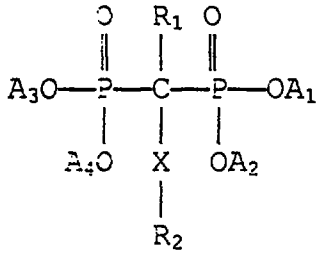
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thereof of the autoantigens or allergens, providing that these each exhibit the same immunological characteristics as the corresponding whole molecules, and

wherein the bisphosphonic acids or the derivatives thereof and the autoantigens or allergens or fragments, derivatives or analogues thereof may be administered simultaneously or in succession.

2. Pharmaceutical composition for use for the prevention and treatment of autoimmune conditions or allergies according to claim 1, characterised in that, as bisphosphonic acids and the derivatives thereof, it contains those of the general formula:



(II),

in which

A_1, A_2, A_3, A_4, which may be identical or different and mean hydrogen, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as

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well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

R_1, means H, OH, NH_2,

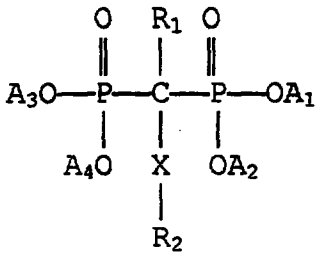
X, which may also be absent or may be alkylene, alkenylene or hydroxyalkylene, in each case having 1 to 12 carbon atoms,

R_2, means H, OH, $-NH_2$, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups, or $-SR_3$, Cl and $-NR_3R_4$, in which

R_3, R_4, which may be identical or different and mean H, OH, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups.

3. Pharmaceutical composition for use for the prevention and treatment of autoimmune conditions or allergies according to claim 1, characterised in that, as bisphosphonic acids and the derivatives thereof, it contains those of the general formula:

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(III),

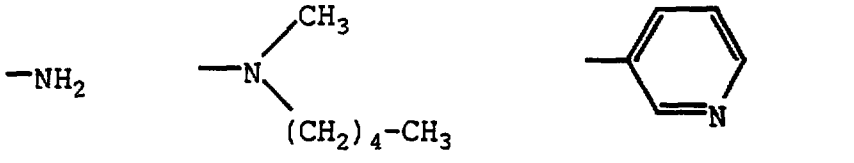
in which

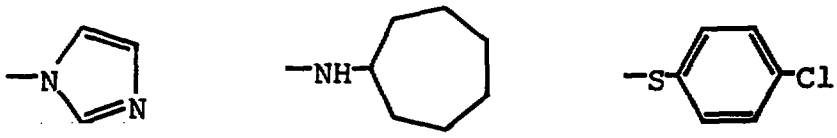
A_1, A_2, A_3, A_4, which may be identical or different and mean hydrogen, an alkyl residue having 1 to 12 carbon atoms, which may be branched or unbranched, an aryl residue, aralkyl residue, cycloalkyl residue or a heterocyclic residue, wherein these residues may additionally be substituted by functional groups, a metal of main group 1, 2 or 3 of the periodic system, such as Na, K, Ca, Mg, Al, as well as substituted or unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

R_1, means H, OH,

X, which may also be absent or may mean $(CH_2)_{1-5}$, amidino,

R_2, may mean





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* C L M S *

4. Use of bisphosphonic acids and the derivatives thereof in combination with autoantigens or allergens for the production of pharmaceutical preparations for the prevention and treatment of autoimmune conditions and allergies according to claim 1, 2 or 3, characterised in that the following are used for the treatment of

multiple sclerosis	myelin basic protein (MBP), further extracts from nervous system tissue,
rheumatoid arthritis	type I, II or III collagen,
Hashimoto thyroiditis	thyroglobulin,
myasthenia gravis	acetylcholine receptor protein,
lupus erythematosus	DNA,
diabetes mellitus	islet cell extracts, human insulin,
primary biliary cirrhosis	liver extracts,
active chronic hepatitis	liver cell extracts,
adrenalitis/Addison's disease	adrenal cortex extracts,
polymyositis	skin extracts, muscle extracts,
dermatomyositis	muscle and/or skin extracts,
autoimmune haemolytic anaemia	haemopoetic cell line extracts,
myocarditis myopericarditis	heart extracts,
scleroderma	skin extracts, skin cell extracts,

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uveitis (phacouveitis, sympathetic ophthalmia)	eye lens proteins, S-antigens, S-antigen mixtures,	
pemphigus vulgaris	skin extracts,	
pemphigoid	skin extracts,	
pernicious anaemia	gastric cell extracts, parietal cell extracts, intrinsic factor,	
autoimmune atrophic gastritis	gastric cell extracts,	
Crohn's disease	intestinal extracts,	
colitis ulcerosa	intestinal extracts	may
allergies	allergy-specific allergens.	also be absent

5. Use of bisphosphonic acids and the derivatives thereof for the production of pharmaceutical preparations for the prevention and treatment of autoimmune conditions or allergies according to claim 1, 2 or 3, characterised in that the combination preparations are administered in solid form, as ointments, as solutions or as sprays.

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