Description

Preparation having improved therapeutic breadth, comprising nucleotide synthesis inhibitors

Strongly basic anion exchangers are employed in therapy as hypolipidemics in heterozygous familial hypercholesterolemia and other primary hyperlipoproteinemias having a principal proliferation of the LDL fraction or in chologenic diarrheas. Examples of suitable active substances which are employed as hypolipidemics are N-(2-aminoethyl)-N'-[2-[(2-aminoethyl)amino]ethyl]-1,2-ethanediamine polymers with (chloromethyl)oxirane, which is also called colestipol (Colestid®) or colestyramine (CAS-No. 11 041-12-6), which is a styrene/divinylbenzene copolymer. Isoxazole or crotonamide derivatives are described in the Patent Applications EP 484 223; EP 529 500; US 4 061 767; EP 538 783 or EP 551 230. Compounds which inhibit purine or pyrimidine synthesis are called nucleotide synthesis inhibitors (Burkhardt and Kalden; Rheumat. Int. (1997); 17: 85-90), these are, for example, compounds of the formula I and/or II, brequinar (6-fluoro-2-(2'-fluoro[1,1'biphenyl]-4-yl)-3-methyl-4-quinolinecarboxylic acid), mycophenolate mofetil (2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)-4-methyl-4-hexenoate), (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)-4-methyl-4-hexenoate, methotrexate (CAS No. 59-05-02) or mizoribine CAS No. 50924-49-7), are absorbed in the intestine of patients after oral administration and, after a brief increase in the blood levels after administration (absorption peak), lead to constant high blood levels. The abovementioned nucleotide synthesis inhibitors are excreted again in the intestine via the liver and the bile. The excreted compounds mentioned can partially be absorbed again from the intestine and secreted into the blood. The compounds mentioned are therefore subject to the enterohepatic circulation.

In the employment of nucleotide synthesis inhibitors for affecting the immune system, it was surprisingly found that only brief active effects of

these substances are needed for the desired action on the immune system. If blood levels of these substances which lead to active effects are maintained over a relatively long period, although the side effects increase, the desired action on the immune system is not increased. By limiting the active effects to a short period of time, the tolerability of a therapy can be improved while maintaining the desired pharmacodynamic effects on the immune system (=improved therapeutic breadth).

In the case of nucleotide synthesis inhibitors which are subject to the enterohepatic circulation, the duration of action can be reduced by administering substances which interrupt the enterohepatic circulation. Owing to interruption of the enterohepatic circulation, the desired action on the immune system is maintained, but the side effects are drastically reduced.

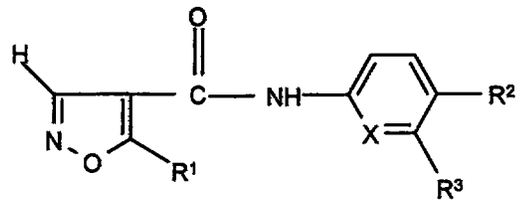
The abovementioned nucleotide synthesis inhibitors can also have an improved therapeutic breadth in their action if compounds which antagonize the action of the nucleotide synthesis inhibitors are administered with a displacement in time – i.e. later than the nucleotide synthesis inhibitors.

The term therapeutic breadth is understood here as meaning a measure of the tolerability of a pharmaceutical and is essentially the difference between the lowest dose which still leads to the desired therapeutic effects and the dose which leads to side effects. The yardstick for the improvements achieved is, for example, the amount of red blood corpuscles, hemoglobin content, hematocrit, amount of glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase, alkaline phosphatase (from bone marrow) or amylase and the weight in comparison with untreated patients.

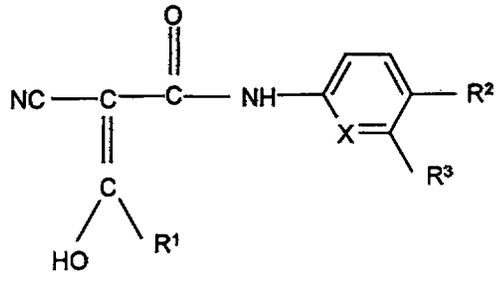
The invention therefore relates to a preparation comprising

1) at least one compound which essentially prevents the enterohepatic circulation of the nucleotide synthesis inhibitors or antagonizes the action of the nucleotide synthesis inhibitors with a displacement in time, and
2) at least one nucleotide synthesis inhibitor from the group consisting of brequinar, mycophenolate mofetil (2-morpholinoethyl (E)-6-(1,3-

dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)-4-methyl-4- hexenoate), methotrexate, mizoribine and compound of the formulae I or II



(I)



(II)

and/or an optionally stereoisomeric form of the compound of the formula I or II and/or a physiologically tolerable salt of the compound of the formula II, where

R^1 is a) $(C_1\text{-}C_4)$-alkyl,
b) $(C_3\text{-}C_5)$-cycloalkyl,
c) $(C_2\text{-}C_6)$-alkenyl or
d) $(C_2\text{-}C_6)$-alkynyl,

R^2 is a) $-CF_3$,
b) $-O\text{-}CF_3$,
c) $-S\text{-}CF_3$,
d) -OH,
e) $-NO_2$,
f) halogen,
g) benzyl,
h) phenyl,
i) -O-phenyl,
k) -CN or
l) -O-phenyl, mono- or polysubstituted by
1) $(C_1\text{-}C_4)$-alkyl,
2) halogen,
3) $-O\text{-}CF_3$ or
4) $-O\text{-}CH_3$,

R^3 is a) $(C_1\text{-}C_4)$-alkyl,

b) halogen, or

c) a hydrogen atom, and

X is a) a –CH group or

b) a nitrogen atom.

A mixture of the nucleotide synthesis inhibitors and compound of the formula I and II or salts of the compound of the formula II and a mixture of the compounds which essentially prevent the enterohepatic circulation of the compound of the formula I or II can also be employed.

The term "compound which essentially prevents the enterohepatic circulation of the compound of the formula I or II" is understood as meaning, for example, strongly basic anion exchangers such as colestipol and colestyramine or active carbon. The term "compound which antagonize the action of the nucleotide synthesis inhibitors with a displacement in time" are understood as meaning compounds such as uridine, purine, purine nucleotides or pyrimidine nucleotides.

The use of a compound of the formula I and/or II and/or an optionally stereoisomeric form of the compound of the formula I or II and/or a salt of the compound of the formula II is preferred, where,

R^1 is a) methyl,

b) cyclopropyl or

c) $(C_3$-$C_5)$-alkynyl,

R^2 is $-CF_3$ or -CN,

R^3 is a hydrogen atom or methyl, and

X is a –CH group,

in combination with at least one compound from the group consisting of colestipol, colestyramine and active carbon.

The use of N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide, N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide, 2-cyano-3-cyclopropyl-3-hydroxyacrylic acid (4-cyanophenyl)amide or N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxyhept-2-en-6-ynecarboxamide in combination with colestyramine is particularly preferred.

The compound of the formula I or II is prepared according to known processes such as are described in EP 484 223; EP 529 500; US 4 061 767; EP 538 783 or EP 551 230. The starting substances for the chemical reactions are known or can easily be prepared by methods which are known from the literautre.

The terms alkyl, alkenyl and alkynyl are understood as meaning radicals whose carbon chain can be straight chain or branched. The alkenyl or alkynyl radicals can furthermore also contain a number of double bonds or a number of triple bonds. Cyclic alkyl radicals are, for example, 3- to 5-membered monocyclic systems such as cyclopropyl, cyclobutyl or cyclopentyl. Salts of the compound of the formula II are, for example, sodium or lysinium salts which can be prepared as described in European Patent Application No. EP 0769296.

The preparation according to the invention is suitable, for example, for the treatment of

- immunological disorders
- inflammatory and cytotoxic processes in connection with gene therapy interventions
- cancers such as lung cancer, leukemia, ovarian cancer, sarcomas, Kaposi's sarcoma, meningioma, intestinal cancer, lymph node cancer, brain tumors, breast cancer, pancreatic cancer, prostate cancer or skin cancer
- autoimmune disorders such as systemic lupus erythematosus or multiple sclerosis
- rheumatic disorders
- transplantations or graft-versus-host reactions or host-versus-graft reactions
- disorders which are caused by strongly proliferating cells
- psoriasis or atypical dermatitis
- allergy, asthma, urticaria, rhinitis or uveitis
- type II diabetes
- cystic fibrosis, colitis, liver fibrosis or sepsis

- chronic inflammatory disorders such as arteriosclerosis, Crohn's disease, ulcerative colitis.

The invention also relates to a process for the production of the preparation, which comprises bringing the nucleotide synthesis inhibitors and a compound which essentially prevents the enterohepatic circulation of the nucleotide synthesis inhibitors, or antagonizes the action of the nucleotide synthesis inhibitors with a displacement in time, into a suitable administration form with a pharmaceutically suitable and physiologically acceptable vehicle and, if appropriate, further suitable active compounds, additives or excipients.

The preparation according to the invention can also include compositions or combination packs in which the constituents are placed next to one another and can therefore be used simultaneously, separately or sequentially on one and the same human or animal body. The sequential administration of the compound of the formula I and/or II before the administration of the compound which essentially prevents the enterohepatic circulation of the compound of the formula I or II is preferred. To this end, for example, N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide (called compound 1 in the following) is administered first. Colestyramine, which essentially prevents the enterohepatic circulation of the compound I, is administered with a displacement in time, i.e., for example, 2 hours or 4 hours after the administration of compound 1. Owing to this time-displaced administration of the compound 1 and colestyramine, the compound 1 is initially absorbed unhindered from the digestive tract. After the administration of colestyramine, which is not absorbed systemically, the compound 1 excreted via the bowel is bound to colestyramine and can therefore not be reabsorbed again; as a result an interruption to the enterohepatic circulation is brought about. Owing to this measure, the duration of action and the blood level of the compound 1 is drastically reduced. Despite this drastically reduced blood level, the activity in the pathological animal model, such as adjuvant arthritis, is not reduced by the administration of colestyramine at a low, still just active doses of approximately 2.5 mg/kg/day of the compound 1. If high doses of

25 mg/kg/day of the compound 1, which already lead to various side effects, are employed in the same animal model, a clear reduction in the side effects with retention of the desired actions on the immune system is observed by means of administration of colestyramine.

The preparation according to the invention can be present as a dose unit in the form of pharmaceutical forms such as capsules (including microcapsules), which in general contain no pharmaceutical vehicles), tablets including coated tablets and pills, or suppositories, it being possible when using capsules for the capsule material to assume the function of the vehicle and for the contents to be present, for example, as a powder, gel, solution, emulsion or dispersion. It is particularly advantageous and simple, however, to prepare oral or peroral formulations which contain the calculated amounts of the active compounds together with any desired pharmaceutical vehicles using the two active compound components 1) (e.g. colestyramine) and 2) (compound of the formula I and/or II). An appropriate formulation (suppositories) for rectal therapy can also be used. Transdermal administration in the form of ointments or creams, parenteral (intraperitoneal, subcutaneous, intramuscular) injection or oral administration of solutions which contain the combinations according to the invention is likewise possible. In addition to the active compound, ointments, pastes, creams and powders can contain the customary vehicles, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, silicic acid, aluminum hydroxide, talc, zinc oxide, lactose, bentites, calcium silicate and polyamide powder or mixtures of these substances. The tablets, pills or granule bodies can be produced by processes such as pressing, dipping or fluidized-bed processes or pan coating and contain vehicles and other customary excipients such as gelatin, agarose, starch (e.g. potato, corn or wheat starch), celluloses such as ethylcellulose, silica, magnesium carbonate, various sugars such as lactose and/or calcium phosphates. The coating solution usually consists of sugar and/or starch syrup and mostly additionally contains gelatin, synthetic cellulose esters, gum arabic, polyvinylpyrrolidone, pigments, surface-active substances, plasticizers and similar additives according to the prior art. For the production of the preparation forms, any customary flow-regulating agent,

lubricant or glidant such as magnesium stearate and release agents can be used. The preparations preferably have the form of coating/core tablets or multilayer tablets, the active component 2 being in the coating or in the core or in one layer, while the active component 1 is in the core, in the coating or in another layer. The active compound components can also be present in delayed-release form or adsorbed on release-delaying material or included in the release-delaying material (e.g. those based on cellulose or polystyrene resins, e.g. hydroxyethylcellulose). Delayed release of the active compounds can also be achieved by providing the layer or the compartment concerned with customary enteric coatings.

A delayed release of the compound which essentially prevents the enterohepatic circulation of the compound of the formula I or II is preferred.

The dose to be used is, of course, dependent on various factors such as the living being to be treated (i.e. human or animal), age, weight, general state of health, the degree of severity of the symptoms, the disorder to be treated, possible concomitant disorders (if present), the nature of the concomitant treatment with other pharmaceuticals, or the frequency of the treatment. The doses are in general administered several times per day and preferably one to three times per day. The amounts of individual active compound used are based here on the recommended daily dose of the respective individual active compound and, in the combination preparation, should in general be from 10% to 300% of the recommended daily dose, preferably from 50% to 150%, in particular 80%. Suitable therapy with the combinations according to the invention thus consists, for example, in the administration of 1, 2 or 3 individual doses of the preparation consisting of N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide) or N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide in an amount of from 2 mg to 250 mg, preferably 5 mg to 150 mg, in particular 10 mg to 50 mg, particularly preferably 10 mg to 20 mg, and colestyramine in an amount of from 250 mg to 6000 mg, in particular from 1500 mg to 3000 mg.

The preparations according to the invention can furthermore also be employed together with other suitable active compounds, for example antiuricopathics, analgesics, steroidal or nonsteroidal antiinflammatories, platelet aggregation inhibitors, cytokines, cytokine agonists, cytokine

antagonists or immunosuppressant compounds such as cyclosporin A, FK 506 or rapamycin.

Example 1

Adjuvant-induced arthritis, modification according to Perper (Proc. Soc. exp. Biol. Med. 137, 506 (1971)

The experimental animals used were male rats of a Lewis strain (Moellegard, Denmark) having a body weight of from 160 to 210 g. On the 1st day, the animals were injected subcutaneously, into the tail root, with complete Freund's adjuvant containing a mycobacterium butyricum suspension in heavy paraffin oil (Difco; 6 mg/kg in paraffin oil; Merck). The compounds N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide and colestyramine were suspended in carboxymethylcellulose (1% in water) and administered orally. The compounds were administered once daily from the 1st to the 17th day of the experiment; the paw volume and arthritis index were then determined on the 18th day.

The severity of the disorder was determined by measuring the paw volume of both hind paws. The measurement was carried out by means of the water displacement method using a 2060 Plethys monitor (Rhema-Labortechnik, Hofheim, Germany). The arthritis index was furthermore determined in the 18th day after injection.

Determination of the arthritis index:

1. ears	0.5 points for each ear on which reddening occurs and nodules are formed
2. nose	1 point for connective tissue swelling
3. tail	1 point for the emergence of nodules
4. fore paws	0.5 points for each paw on which at least one inflammation occurs on a joint
5. hind paws	1 point for slight inflammation (swelling)
	2 points for a medium-strength inflammation
	3 points for a masive inflammatory reaction

On the 1st day, animals of an "arthritis contro" control group were given a subcutaneous injection, into the tail root, with complete Freund's adjuvant and were given, however, only the solvent (1% carboxymethylcellulose in water). 6 animals in each case were used per dose and in the control

group. Untreated animals were employed as a further "healthy control" control group. The activity criteria used were the reduction of the increase in the paw volume and the decrease in the arthritis index, compared with the untreated control group, and the weight of the animals, in each case in percent and based on the arthritis control. In the following table, N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide is described as compound 1. Colestyramine was administered 4 hours later than compound 1. Table 1 shows the results obtained.

Table 1

	Active substance (mg/kg of live weight	Paw volume (%)	Arthritis index (%)	Weight (%)
Healthy control				30
Arthritis control				18
Colestyramine	1000	35	44	8
Compound 1	2.5	-63	-77	20
Compound 1 + Colestyramine	2.5 + 1000	-70	-92	20
Compound 1	7.5	-83	-92	18
Compound 1 + Colestyramine	7.5 + 1000	-73	-95	27
Compound 1	25	-92	-100	-2
Compound 1 + Colestyramine	25 + 1000	-72	-100	3

The values shown in the table by a "-" indicate a decrease; all other values indicate an increase in comparison with the start of the experiment

The animals treated with the preparation according to the invention showed a weight increase which, in the case of the amounts 2.5 and 7.5 of compound 1, came very close to the healthy control and was significantly

better than with compound 1 alone, while the activity of compound 1 was completely retained.

Example 2

The experimental conditions are analogous to Example 1. The actions of the compound 1 and colestyramine on the amount of red blood corpuscles (RBC), hemoglobin content (HGB), hematocrit (HCT), amount of glutamate-oxalacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) were determined. Colestyramin was administered 4 hours later than compound 1. Table 2 shows the results obtained.

Table 2

	Active substance (mg/kg of live weight)	Paw volume (%)	Arthritis index (%)	GOT (U/l)	GPT (U/l)	RBC (*10^6/ mm^3)	HGB (g/dl)	HCT (%)	Number of animals
Healthy control				50.4	23.6	7.4	13.1	38.9	4
Arthritis control				50.8	20.3	7.3	13.0	38.0	6
Colestyramine	1000	10	22	43.5	25.2	7.6	10.2	31.4	6
Compound 1	25	-92	-100	85.3	25.1	3.8	6.1	18.7	6
Compound 1 + Colestyramine	25 + 1000	-72	-100	52.5	21.5	6.08	10.2	31.4	5

The values shown in the table by a "-" indicate a decrease; all other values indicate an increase in comparison with the start of the experiment

The animals treated with the preparation according to the invention showed a normalization of the amount of red blood corpuscles (RBC), hemoglobin content (HGB), hematocrit (HCT), amount of glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) which came very close to the healthy control and was significantly better than with compound 1 alone, while the activity of compound 1 was completely retained.

Example 3

The experimental conditions are analogous to Example 1. The actions of compound 1 and colestyramine on the amount of alkaline phosphatase (AP) and amylase were determined. Colestyramine was administered 4 hours later than compound 1. Table 2 shows the results obtained.

Table 3:

	Active substance (mg/kg of live weight)	Paw volume (%)	Arthritis index (%)	AP (U/l)	Amylase (U/l)	Number of tested animals
Healthy control				312.6	3058.3	6
Arthritis control				231.5	2251.6	6
Colestyramine	1000	-60	-46	271.8	2756.6	6
Compound 1	25	-110	-100	114.8	1306.5	6
Compound 1 + Colestyramine	25 + 1000	-86	-94	206.6	2783.3	3

The values shown in the table by a "-" indicate a decrease; all other values indicate an increase in comparison with the start of the experiment

The animals treated with the preparation according to the invention showed a normalization of the amount of alkaline phosphatase and, which came very close to the healthy control and was significantly better than with compound 1 alone, while the activity of compound 1 was completely retained.

Example 4

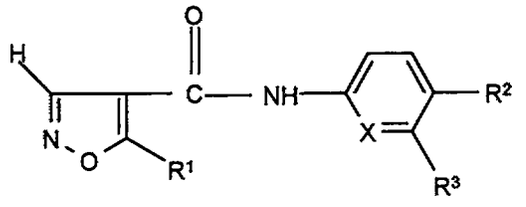
A preparation according to the invention consists of a small hard gelatin capsule which contains 400 mg of colestyramine and a larger hard gelatin capsule which contains 20 mg of N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide. The smaller hard gelatin capsule is completely enclosed by the larger capsule. The filling material employed between the two capsules is glucose.

Patent claims HMR 1998/L 080

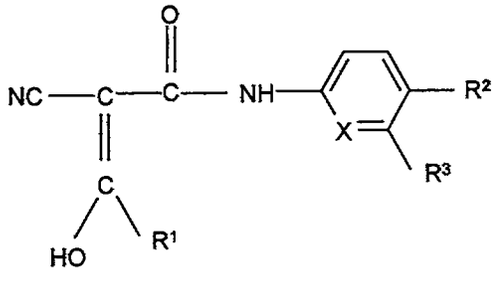
1. A preparation comprising

1) at least one compound which essentially prevents the enterohepatic circulation of the nucleotide synthesis inhibitors or antagonizes the action of the nucleotide synthesis inhibitors with a displacement in time, and

2) at least one nucleotide synthesis inhibitor from the group consisting of brequinar, mycophenolate mofetil [lacuna] (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)-4-methyl-4- hexenoate), methotrexate, mizoribine and compound of the formulae I or II



(I)



(II)

and/or an optionally stereoisomeric form of the compound of the formula I or II and/or a physiologically tolerable salt of the compound of the formula II, where

R^1 is a) $(C_1\text{-}C_4)$-alkyl,
b) $(C_3\text{-}C_5)$-cycloalkyl,
c) $(C_2\text{-}C_6)$-alkenyl or
d) $(C_2\text{-}C_6)$-alkynyl,

R^2 is a) $-CF_3$,
b) $-O\text{-}CF_3$,
c) $-S\text{-}CF_3$,
d) -OH,
e) $-NO_2$,
f) halogen,
g) benzyl,
h) phenyl,

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i) -O-phenyl,

k) -CN or

l) -O-phenyl, mono- or polysubstituted by

1) (C_1-C_4)-alkyl,

2) halogen,

3) $-O-CF_3$ or

4) $-O-CH_3$,

R^3 is a) (C_1-C_4)-alkyl,

b) halogen, or

c) a hydrogen atom, and

X is a) a –CH group or

c) a nitrogen atom.

2. A preparation as claimed in claim 1, where a compound of the formula I and/or II and/or an optionally stereoisomeric form of the compound of the formula I or II and/or a salt of the compound of the formula II is employed, where

R^1 is a) methyl,

b) cyclopropyl or

c) (C_3-C_5)-alkynyl,

R^2 is $-CF_3$ or -CN,

R^3 is a hydrogen atom or methyl, and

X is a –CH group.

3. A preparation as claimed in claim 1 or 2, where N-(4-trifluoromethyl-phenyl)-5-methylisoxazole-4-carboxamide is employed as a compound of the formula I or N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide, 2-cyano-3-cyclopropyl-3-hydroxyacrylic acid (4-cyanophenyl)amide or N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxyhept-2-en-6-ynecarboxamide is employed as compound of the formula II.

4. A preparation as claimed in one or more of claims 1 to 3, wherein the compound employed which essentially prevents the enterohepatic circulation of the compound of the formula I or II is a

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compound from the group consisting of colestipol, colestyramine and active carbon.

5. A preparation according to one or more of claims 1 to 3, wherein the compound employed which antagonizes the action of the nucleotide synthesis inhibitors with a displacement in time is a compound from the group consisting of uridine, purine, purine nucleotides or pyrimidine nucleotides.

6. A preparation as claimed in one or more of claims 1 to 5, wherein additional active compounds from the group consisting of antiuricopathics, analgesics, steroidal or nonsteroidal antiinflammatories, cytokines, cytokine agonists, platelet aggregation inhibitors, cytokine antagonists or immunosuppressant compounds such as cyclosporin A, FK 506 or rapamycin are contained.

7. A preparation as claimed in one or more of claims 1 to 6, which consists of compositions or combination packs in which the constituents are placed next to one another and are therefore used simultaneously, separately or sequentially on one and the same human or animal body.

8. A preparation as claimed in claim 7, wherein the administration of the compound of the formula I and/or II is carried out timewise before the administration of the compound which essentially prevents the enterohepatic circulation of the compound of the formula I or II.

9. The use of the preparation as claimed in one or more of claims 1 to 8 for the production of a pharmaceutical for treating immunological disorders, inflammatory and cytotoxic processes in connection with gene therapy interventions, cancers such as lung cancer, leukemia, ovarian cancer, sarcomas, Kaposi's sarcoma, meningioma, intestinal cancer, lymph node cancer, brain tumors, breast cancer, pancreatic cancer, prostate cancer or skin cancer,

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autoimmune disorders such as systemic lupus erythematosus or multiple sclerosis,
rheumatic disorders,
transplantations or graft-versus-host reactions or host-versus-graft reactions,
disorders which are caused by strongly proliferating cells,
psoriasis or atypical dermatitis,
allergy, asthma, urticaria, rhinitis or uveitis,
type II diabetes,
cystic fibrosis, colitis, liver fibrosis or sepsis,
chronic inflammatory disorders such as arteriosclerosis, Crohn's disease or ulcerative colitis.

10. A process for the production of the preparation as claimed in claims 1 to 9, which comprises bringing at least one nucleotide synthesis inhibitor from the group consisting of brequinar, mycophenolate mofetil [lacuna] (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxoisobenzofuran-5-yl)-4-methyl-4-hexenoate), methotrexate, mizoribine and compound of the formulae I or II and a compound which essentially prevents the enterohepatic circulation of the compound of the formula I or II, or a compound which antagonizes the action of at least one of the nucleotide synthesis inhibitors with a displacement in time into a suitable administration form with a pharmaceutically suitable and physiologically acceptable vehicle, and, if appropriate, further suitable active compounds, additives or excipients.

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