CLAIMS

1. ~~A~~ Use of a C5aR1 inhibitor ~~for use~~ in manufacture of a medicament for the prevention or treatment of a hypersensitivity reaction (HSR) to a taxane in an individual.

2. ~~A C5aR1 inhibitor for~~The use as claimed in claim 1, wherein said taxane is selected from paclitaxel, N*ab*™-paclitaxel, docetaxel and cabazitaxel.

3. ~~A C5aR1 inhibitor for~~The use as claimed in claim 1 or 2, wherein said C5aR1 inhibitor is for use in the prevention of a hypersensitivity reaction to a taxane in said individual and the inhibitor is to be administered one or more times prior to each administration of said taxane.

4. ~~A C5aR1 inhibitor for~~The use as claimed in claim 3, wherein said C5aR1 inhibitor is to be administered one or more times between 30 minutes and 24 hours before administering the taxane to the individual.

5. ~~A C5aR1 inhibitor for~~The use as claimed in claim 3 or 4, wherein said individual is a cancer patient that has had a previous HSR episode to a taxane, has resulted positive in a skin prick test for sensitivity to said taxane and/or has a history of atopy.

6. ~~A C5aR1 inhibitor for~~The use as claimed in any one of claims 3 to 5, wherein said C5aR1 inhibitor~~it~~ is to be administered in combination with one or more corticosteroids and/or antihistamines.

7. ~~A C5aR1 inhibitor for~~The use as claimed in claim 1 or 2, wherein said C5aR1 inhibitor is for use in the acute treatment of a hypersensitivity reaction to a taxane in said individual and the inhibitor is to be administered at the onset of the symptoms of the hypersensitivity reaction.

8. ~~A C5aR1 inhibitor for~~The use as claimed in any one of claims 1 to 7, wherein said C5aR1 inhibitor is selected from C5aR1 competitive antagonists, anti-C5aR1 antibodies able to block the C5a binding sites on the receptor and C5aR1 non-competitive allosteric inhibitors.

9. ~~A C5aR1 inhibitor for~~The use as claimed in any one of claims 1 to 8, wherein said C5aR1 inhibitor~~which~~ is a C5aR1 antagonists selected from the group consisting of:

- (2R,3S)-2-[4-(Cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (Avacopan, Vynpenta®);
- N-Acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine-N-5.2-C-1.6-lactam (PMX-53);

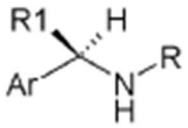
- Acetylated phenylalanine-[ornithyl-proline-(D)cyclohexylalanine-tryptophyl-arginine];
- L-Alanyl-L-seryl-glycyl-L-alanyl-L-prolyl-L-alanyl-L-prolyl-glycyl-L-prolyl-L-alanyl-glycyl-L-prolyl-L-leucyl-L-arginyl-L-prolyl-L-methionyl-L-phenylalanine;
- N,N-Bis(1,3-benzodioxol-5-ylmethyl)-N-(1-butyl-2,4-diphenyl-1H-imidazol-5-ylmethyl)amine;
- N-[2-(4-Chlorophenyl)ethyl]-N-(1,4-dioxaspiro[4.5]dec-8-yl)-2-isobutylbenzamide;
- N-[2-(4-Chlorophenyl)ethyl]-N-(4-hydroxycyclohexyl)-1-benzothiophene-3-carboxamide;
- N-[2-(4-Chlorophenyl)ethyl]-N-(4-hydroxycyclohexyl)naphthalene-1-carboxamide;
- 2-(2-Ethyl-6-methylphenyl)-4-methoxy-N-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydroquinolin-5-amine;
- 2-(2,6-Diethylphenyl)-N-ethyl-4-methoxy-N-(1-naphthyl)-5,6,7,8-tetrahydroquinolin-5-amine;
- N-[2,6-Dioxohexahydropyrimidin-4(S)-ylcarbonyl]-L-phenylalanyl-L-ornithyl-L-prolyl-5-methyl-L-norleucyl-4-fluoro-L-phenylalanyl-L-phenylalaninamide (JPE-1375; JSM-1375);
- N-(3-Phenylpropionyl)-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine N-5.1-C-1.5-lactam (PMX-205);
- N,N'-Bis(4-amino-2-methylquinolin-6-yl)urea (NSC12155);
- N-[4-(Dimethylamino)benzyl]-N-(4-isopropylphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide hydrochloride (W54011);
- L-Phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine N-5.2-C-1.6-cyclic peptide;
- (4aR,16aS)-6,18-Dihydroxy-23(S)-[2(S)-hydroxy-2-[2(R)-hydroxy-6(R)-methyl-5(R)-[2(S)-methylbutyl]tetrahydro-2H-pyran-2-yl]propionamido]-22(S)-isopropyl-7(S),19(R)-dimethyldocosahydro-13H,22H-dipyridazino[6,1-f:6',1'-o][1,4,7,10,13,16]oxapentaazacyclononadecine-5,7,11,17,20,24-hexanone (L-156602).

10. ~~A C5aR1 inhibitor for~~The use as claimed in any one of claims 1 to 8, wherein said C5aR1 inhibitor~~which~~ is an anti-C5aR1 antibody selected from the group consisting of:

- Avdoralimab (IPH-5401)
- MOR-044254;
- NOX-D20;
- Anti-C5aR1ab-C5-SiRNA;
- m20/70 mIgG2a.1;
- 3C5;
- 7F3.

11. ~~A C5aR1 inhibitor for~~The use as claimed in any one of claims 1 to 8, wherein said C5aR1 inhibitor~~which~~ is a non-competitive allosteric inhibitor selected from

- (2*R*)-2-[3-(furan-2-carbonyl)phenyl]-*N*-[4-(trifluoromethyl)-1,3-thiazol-2-yl]propenamide (DF2427); and
- compounds having general formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

i) **R** is selected from:

- 2 -thiazolyl or 2-oxazolyl, unsubstituted or substituted by a group selected from methyl, tert -butyl or trifluoromethyl group;
- C(Ra)=N-W wherein W is linear or branched C_1-C_4 alkyl,
- CORa, SORa, SO_2Ra, PORa, PO_2Ra,

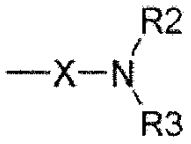
wherein

Ra is selected from

- C_1-C_5-alkyl, C_3-C_6-cycloalkyl, C_2-C_5-alkenyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino;
- a heteroaryl group selected from pyridine, pyrimidine, pyrrole, thiophene, furane, indole, thiazole, oxazole, such heteroaryl being unsubstituted or substituted with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkoxy, hydroxy, C_1-C_4- acyloxy, phenoxy, cyano, nitro, amino;
- a α or β carboxyalkyl residue consisting of straight or branched C_1- C_6-alkyl, C_3-C_6-

cycloalkyl, C_2-C_6-alkenyl, C_1-C_6-phenylalkyl, optionally substituted with a further carboxy (COOH) group;

- an ω-aminoalkylamino group of formula (II):



(II)

wherein in said formula (II)

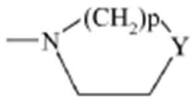
X is:

- linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene, optionally substituted by: a) a CO_2R4 group, wherein R4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group, or b) by a CONHR5 group wherein R5 represents hydrogen, linear or branched C_2- C_6 alkyl or an OR4 group, R4 being defined as above;

- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R4 or CONHR5 group, as defined above, wherein a) B is an oxygen, or sulfur atom, or nitrogen atom optionally substituted by a C_1-C_4 alkyl group, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3, or b) B is a CO, SO or CONH group, m is an integer from 1 to 3 and n is an integer from 2 to 3;

R2 and **R3** are independently hydrogen, linear or branched C_1-C_6 alkyl, optionally interrupted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group; or

R2 and **R3** together with the N atom to which they are bound, form a 3-7 membered nitrogen heterocyclic ring of formula (III)



(III)

wherein

Y represents:

- a single bond, CH_2, O, S, or a N-R6 group, where R6 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, unsubstituted or substituted phenyl with a group selected from

halogen, C_1-C_4-alkyl, C_1-C_4- alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino,

and p represents an integer from 0 to 3;

- a residue of formula SO_2R7 wherein R7 is C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, aryl and heteroaryl;

or

in said formula (II)

X together with the nitrogen atom to which it is bound and with the **R2** group, forms a nitrogen containing 3-7 membered heterocyclic, monocyclic or polycyclic ring, and **R3** represents hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4- acyloxy, phenoxy, cyano, nitro, amino;

ii) **R1** is linear or branched C_1-C_5 alkyl, C_3-C_5 cycloalkyl;

iii) **Ar** is

-a phenyl group unsubstituted or substituted by one or more groups independently selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino, C_1-C_4-acylamino, halo-C_1- C_3- alkyl, halo-C_1-C_3-alkoxy, benzoyl, heteroaryl carbonyl, heteroaryl, linear or branched C_1-C_8-alkanesulfonate, linear or branched C_1-C_8-alkanesulfonamides, linear or branched C_1-C_8 alkyl sulfonylmethyl; or

- a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan, indole~~.~~, and

~~Among~~ wherein among the above compounds, particularly preferred are compounds of said formula (I) or pharmaceutically acceptable salts thereof, wherein:

R is selected from:

- 2-thiazolyl or 2-oxazolyl, unsubstituted or substituted by a group selected from methyl, tert-butyl or trifluoromethyl group;

- C(Ra)=N-W wherein W is linear or branched C_1-C_4 alkyl,

- CORa, SORa or SO_2Ra,

wherein Ra is as defined above; and

Ar is selected from:

3 ‘-benzoylphenyl, 3 '-(4-chloro-benzoyl)-phenyl, 3 '-(4-methyl-benzoyl)-phenyl, 3 '-acetyl-phenyl, 3'-propionyl-phenyl, 3'-isobutanoyl-phenyl, 4'-isobutyl-phenyl, 4' -trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 4'-

trifluoromethanesulfonylamino-phenyl, 4'-benzenesulfonylamino-phenyl, 4'-benzenesulfonylmethyl-phenyl, 4'-acetoxyphenyl, 4'-propionyloxy-phenyl, 4'-benzoyloxy-phenyl, 4'-acetylamino-phenyl, 4'-propionylamino-phenyl, 4'-benzoylamino-phenyl, 3 '-(furan-2-carbonyl)-phenyl, 3 '-(benzofuran-2-carbonyl)-phenyl, 3 '-(thiophen-2-carbonyl)-phenyl, 3 '-(pyridine-2-carbonyl)-phenyl, 3 '-(thiazole-2-carbonyl)-phenyl, 3'-(oxazole-2-carbonyl)-phenyl, 3'-(2-furyl)-phenyl, 3'-(2-oxazolyl)-phenyl, 3'-(3-isoxazolyl)-phenyl, 3'-(2-benzoxazolyl)-phenyl, 3'-(3- benzoisoxazolyl)-phenyl, 3'-(2-thiazolyl)-phenyl, 3'-(2-pyridyl)-phenyl, 3'-(2- thiophenyl)-phenyl;
or Ar is a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan or indole.

12. ~~A C5aR1 inhibitor for~~The use as claimed in any one of claims 1 to 8 and 11, wherein said C5aR1 inhibitor is a compound ~~is~~ selected from the group consisting of:

- (2R)-2-[3-(furan-2-carbonyl)phenyl]-N-[4-(trifluoromethyl)-1,3-thiazol-2-yl]propenamide (DF2427);
- 4-{(1R)-1-[(phenylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]benzenesulfonamide;
- 4-{(1R)-1-[(pyridine-3-ylsulfonyl)amino]ethyl}phenyltrifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]methanesulfonamide;
- N-{(1R)-1-[3-(2-furoyl)phenyl]ethyl}thiophene-2-sulfonamide;
- N-{(1R)-1-[3-(2-furoyl)phenyl]ethyl}methanesulfonamide;
- 4-{(1R)-1-[(thien-2-ylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]thiophene-2-sulfonamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]-3-pyrrolidin-1-ylpropane-1-sulfonamide;
- methyl 5-({[(1R)-1-(3-benzoylphenyl)ethyl]amino}sulfonyl)-2-furoate;
- 5-({[(1R)-1-(3-benzoylphenyl)ethyl]amino}sulfonyl)-2-furoic acid;
- 4-{(1R)-2-methyl-1-[(methylsulfonyl)amino]propyl}phenyltrifluoromethanesulfonate;
- N-((1R)-1-{4-[1-methyl-1-(phenylsulfonyl)ethyl]phenyl}ethyl)methanesulfonamide;
- 4-[(1R)-1-(isobutyrylamino)ethyl]phenyltrifluoromethanesulfonate;
- 4-{[(1R)-1-(pyridine-3-ylcarbonyl)amino]ethyl]}phenyltrifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]benzamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]-2-furamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]cyclobutanecarboxamide;
- N-[(1R)-1-(4-trifluoromethanesulfonyloxy)phenylethyl]-4-piperidin-1-yl butanamide (DF2593Y) ;

- 4-{(1R)-1-[(4-pyrrolidin-1-ylbutanoyl)amino]ethyl]}phenyl trifluoromethanesulfonate;
- 3-{(1R)-1-[4-(4-trifluoromethyl-1,3-thiazol-2-yl)amino]ethyl}phenyl) (phenyl)methanone;
- R(-)-2-[(4'-trifluoromethanesulfonyloxy)phenyl]-N-[3-(N'-pirrolidinyl)propyl] propionamide (DF2297X) or its chloride salt (DF2297A) ; and
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]tetrazol-2-ide (DF3966Y) or its sodium salt (DF3966A).

13. ~~A~~ Use of a pharmaceutical composition comprising a C5aR1 inhibitor as described in any one of claims 1 to 12 and at least one inert pharmaceutically acceptable excipient, in the manufacture of a medicament for ~~use in~~ the prevention or treatment of a hypersensitivity reaction (HSR) to a taxane in an individual.