CLAIMS

1. A combination comprising (a) methotrexate, and (b) a non-hepatotoxic DHODH inhibitor, wherein the non-hepatotoxic DHODH inhibitor is chosen from:

2-(3'-ethoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;

2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;

2-(3'-cyclopropoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;

2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)-5-methylnicotinic acid;

or a pharmaceutically acceptable salt or N-oxide thereof.

2. The combination according to claim 1, wherein the non-hepatotoxic DHODH inhibitor is 2-(3'-ethoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof.

3. The combination according to claim 1, wherein the non-hepatotoxic DHODH inhibitor is 2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof.

4. The combination according to claim 1, wherein the non-hepatotoxic DHODH inhibitor is 2-(3'-cyclopropoxy-3,5-difluorobiphenyl4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof.

5. The combination according to claim 1, wherein the non-hepatotoxic DHODH inhibitor is 2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)-5-methylnicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof.

6. The combination according to claim 1, wherein the active ingredients (a) methotrexate, and (b) non-hepatotoxic DHODH inhibitor form part of a single pharmaceutical composition.

7. The combination according to claim 1, further comprising at least one compound (c) chosen from:

(i) Anti-TNF-alpha monoclonal antibodies;

(ii) TNF-alpha Antagonists;

(iii) Calcineurin (PP-2B) Inhibitors/INS Expression Inhibitors;

(iv) IL-1 Receptor Antagonists;

(v) Anti-CD20 monoclonal antibodies;

(vi) p38 Inhibitors;

(vii) NF-kappaB (NFKB) Activation Inhibitors;

(viii) Another dihydrofolate reductase (DHFR) inhibitors;

(ix) Janus kinase (JAK) inhibitors;

(x) MEK inhibitors; and

(xi) Sphingosine-1 phosphate receptor agonists;

(xii) Interferons comprising Interferon beta 1a, and interferons comprising Interferon beta 1 b;

(xiii) Inmunomodulators; and

(xiv) Adenosine aminohydrolase inhibitors.

8. A product comprising (a) methotrexate, and (b) a non-hepatotoxic DHODH inhibitor according to claim 1, as a combined preparation for simultaneous, separate or sequential administration.

9. The product according to claim 8, further comprising at least one compound (c) chosen from:

(i) Anti-TNF-alpha monoclonal antibodies;

(ii) TNF-alpha Antagonists;

(iii) Calcineurin (PP-2B) Inhibitors/INS Expression Inhibitors;

(iv) IL-1 Receptor Antagonists;

(vi) p38 Inhibitors;

(vii) NF-kappaB (NFKB) Activation Inhibitors;

(viii) Another dihydrofolate reductase (DHFR) inhibitors;

(ix) Janus kinase (JAK) inhibitors;

(x) MEK inhibitors;

(xv) Interferons comprising Interferon beta 1a, and interferons comprising Interferon beta 1 b;

(xvi) Inmunomodulators; and

(xvii) Adenosine aminohydrolase inhibitors.

10. A kit of parts comprising (b) a non-hepatotoxic DHODH inhibitor according to

claim 1, together with instructions for simultaneous, separate or sequential administration in combination with (a) methotrexate.

11. The kit according to claim 10, further comprising at least one compound (c) chosen from:

(i) Anti-INF-alpha monoclonal antibodies;
(ii) TNF-alpha Antagonists;
(iii) Calcineurin (PP-2B) Inhibitors/INS Expression Inhibitors;
(iv) IL-1 Receptor Antagonists;
(vi) p38 Inhibitors;
(vii) NF-kappaB (NFKB) Activation Inhibitors;
(viii) Another dihydrofolate reductase (DHFR) inhibitors;
(ix) Janus kinase (JAK) inhibitors;
(x) MEK inhibitors;
(xviii) Interferons comprising Interferon beta 1a, and interferons comprising Interferon beta 1b;
(xix) Inmunomodulators; and
(xx) Adenosine aminohydrolase inhibitors.

12. A package comprising (b) a non-hepatotoxic DHODH inhibitor according to claim 1, and (a) methotrexate, for simultaneous, separate or sequential administration.

13. The package according to claim 12, further comprising at least one compound (c) chosen from:

(i) Anti-TNF-alpha monoclonal antibodies;
(ii) TNF-alpha Antagonists;
(iii) Calcineurin (PP-2B) Inhibitors/INS Expression Inhibitors;
(iv) 1L-1 Receptor Antagonists;
(vi) p38 Inhibitors;
(vii) NF-kappaB (NFKB) Activation Inhibitors;
(viii) Another dihydrofolate reductase (DHFR) inhibitors;
(ix) Janus kinase (JAK) inhibitors;
(x) MEK inhibitors;
(xxi) Interferons comprising Interferon beta 1a, and interferons comprising Interferon beta 1b;

(xxii) Inmunomodulators; and

(xxiii) Adenosine aminohydrolase inhibitors.

14. A method for preparing a medicament, comprising: combining (b) a non-hepatotoxic DHODH inhibitor according to claim 1, with (a) methotrexate.

15. Use of (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to the combination of claim 3 in the manufacture of a medicament for treating a human or animal patient suffering from a disease chosen from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, and Wegener's granulomatosis, wherein the disease is ameliorated by inhibition of dihydroorotate dehydrogenase.

16. Use of (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to the combination of claim 3 in the manufacture of a medicament for treating a human or animal patient suffering from a disease chosen from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, and Wegener's granulomatosis, wherein the medicament is effective for reducing hepatotoxicity resulting from liver fibrosis, hepatitis, cirrhosis, or liver cancer of the human or animal patient.

17. The use according to claim 15, wherein the medicament includes (a) methotrexate at a dose of 0.015 to 3 mg/kg/week, and the (b) non-hepatotoxic DHODH inhibitor at a dose of 0.03 to 30 mg/kg/day.

18. The combination of (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to claim 3 for use in treating a human or animal patient suffering from a disease chosen from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, and Wegener's granulomatosis, wherein the disease is ameliorated by inhibition of dihydroorotate dehydrogenase.

19. The combination of (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor according to claim 3 for use in treating a human or animal patient suffering from a disease chosen from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, and Wegener's granulomatosis,

wherein the combination of claim 3 is effective for reducing hepatotoxicity resulting from liver fibrosis, hepatitis, cirrhosis, or liver cancer of the human or animal patient.

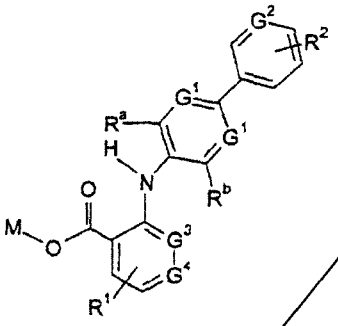
20. The combination according to claim 18, wherein the (a) methotrexate is at a dose of 0.015 to 3 mg/kg/week, and the (b) non-hepatotoxic DHODH inhibitor is at a dose of 0.03 to 30 mg/kg/day.

CLAIMS

1. A combination which comprises (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor.

2. A combination which comprises (a) methotrexate and (b) a DHODH inhibitor wherein the DHODH inhibitor is other than Leflunomide or any active metabolite thereof.

3. A combination according to claim 1 or 2, wherein the DHODH inhibitor (b) is a compound of formula (I):



wherein

- one of the groups G^1 represents a nitrogen atom or a group CR^c and the other represents a group CR^c;
- G^2 represents a nitrogen atom or a group CR^d;
- R^1 represents a group selected from hydrogen atoms, halogen atoms, C_{1-4} alkyl groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups, and C_{3-6} cycloalkyl groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups;
- R^2 represents a group selected from hydrogen atoms, halogen atoms, hydroxyl groups, C_{1-4} alkyl groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups, C_{1-4} alkoxy groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups, and C_{3-6} cycloalkyl groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups;

- R^a, R^b and R^c independently represent groups selected from hydrogen atoms, halogen atoms, C_{1-4} alkyl groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups, and C_{1-4} alkoxy groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups;
- R^d represents a group selected from hydrogen atoms, halogen atoms, hydroxyl groups, C_{1-4} alkyl groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups, and C_{1-4} alkoxy groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups, and C_{3-6} cycloalkoxy groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups;
- one of the groups G^3 and G^4 is a nitrogen atom and the other is a CH group;
- M is a hydrogen atom or an pharmaceutically acceptable cation;

with the proviso that, when at least one of the groups R^a and R^b represent a hydrogen atom and G^2 is a group CR^d, then R^d represents a groups selected from C_{1-4} alkoxy groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups, C_{3-6} cycloalkoxy groups which may be optionally substituted by 1, 2 or 3 substituents selected from halogen atoms and hydroxy groups;

and the pharmaceutically acceptable salts and N-oxides thereof.

4. A combination according to claim 3 wherein each of the C_{1-4} alkyl groups, the C_{3-6} cycloalkyl groups, the C_{1-4} alkoxy groups and the C_{3-6} cycloalkoxy groups is optionally substituted by 1, 2 or 3 halogen atoms.

5. A combination according to claim 3 or 4 wherein R^1 is selected from the group consisting of hydrogen, bromine and fluorine atoms, methyl, ethyl, cyclopropyl and cyclobutyl.

6. A combination according to any one of claims 3 to 5 wherein G^3 represents a nitrogen atom and G^4 represents a group CH.

7. A combination according to any one of claims 3 to 5 wherein G^3 represents a group CH and G^4 represents a nitrogen atom.

8. A combination according to any one of claims 3 to 7 wherein both groups G^1 represent a group CR^c.

9. A combination according to any one of claims 3 to 8 wherein each R^c is independently selected from the groups consisting of hydrogen atoms, fluorine atoms, chlorine atoms and C_{1-3} alkyl groups.

10. A combination according to any one of claims 3 to 9 wherein the group G^2 represents a CR^d group.

11. A combination according to claim 10 wherein R^d is selected from the groups consisting of hydroxy groups, C_{1-3} alkoxy groups, 2,2,2-trifluoroethoxy and C_{3-4}cycloalkoxy groups.

12. A combination according to claim 11 wherein R^d is selected from the groups consisting of C_{1-3} alkoxy groups, 2,2,2-trifluoroethoxy and C_{3-4} cycloalkoxy groups

13. A combination according to any one of claims 3 to 12 wherein R^a is selected from the groups consisting of fluorine atoms, methyl groups and trifluoromethoxy groups.

14. A combination according to claim 13 wherein R^b is selected from the group consisting of hydrogen atoms, fluorine atoms and chlorine atoms.

15. A combination according to any one of claims 3 to 14 wherein R^2 is selected from the group consisting of hydrogen atoms and halogen atoms.

16. A combination according to claim 15 wherein R^2 is selected from the group consisting of hydrogen atoms and fluorine atoms.

17. A combination according to claim 3 or 4 wherein both groups G^1 represent $C(R^c)$ groups, G^2 represents a $C(R^d)$ group, R^a is a fluorine atom, R^b is selected from the group

consisting of hydrogen atoms and fluorine atoms and R^1 is selected from the group consisting of hydrogen, bromine and fluorine atoms, methyl, ethyl and cyclopropyl groups.

18. A combination according to claim 17 wherein G^2 is a group selected from C(OH), C(OMe) and C(OEt).

19. A combination according to claim 18 wherein both G^1 represent CH groups and G^2 is a group selected from C(OMe) and C(OEt).

20. A combination according to claim 17, wherein R^c is a hydrogen atom, R^d is selected from the group consisting of C_{1-3} alkoxy and C_{3-4} cycloalkoxy, and R^2 is a hydrogen atom.

21. A combination according to claim 20 wherein R^d is a hydroxy group or a C_{1-3} alkoxy group.

22. A combination according to claim 21 wherein R^d is a C_{1-3} alkoxy group.

23. A combination according to claim 20 or 21 wherein G^3 represents a nitrogen atom, G^4 represents a group CH and R^b is a fluorine atom.

24. A combination according to claim 20 or 21 wherein G^3 represents a group CH, G^4 represents a nitrogen atom.

25. A combination according to claim 3 or 4 wherein the DHODH inhibitor is one of:

2-(3-Fluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(3'-Ethoxy-3-fluorobiphenyl-4-ylamino)nicotinic acid;
2-(3-Fluoro-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(3'-Ethoxy-3-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(3'-Methoxy-3-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(2,5-Difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(3'-Ethoxy-2,5-difluorobiphenyl-4-ylamino)nicotinic acid;
2-(2',3-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;

2-(2-Methyl-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(3-Chloro-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(3-Chloro-3'-ethoxybiphenyl-4-ylamino)nicotinic acid;
2-(3-Methyl-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(3-Chloro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(3'-(Difluoromethoxy)-3-fluorobiphenyl-4-ylamino)nicotinic acid;
2-(3'-Cyclobutoxy-3-fluorobiphenyl-4-ylamino)nicotinic acid;
2-(3-Fluoro-3'-(2,2,2-trifluoroethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(3'-Cyclobutoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;
2-(3,5-Difluoro-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(3'-Ethoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;
2-(3,5-Difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
Lithium 3-(3'-ethoxy-3-fluorobiphenyl-4-ylamino) isonicotinate;
Lithium 3-(3-fluoro-3'-methoxybiphenyl-4-ylamino)isonicotinate;
Lithium 3-(3'-methoxy-3-(trifluoromethoxy)biphenyl-4-ylamino)isonicotinate;
Lithium 3-(3-fluoro-3'-(trifluoromethoxy)biphenyl-4-ylamino)isonicotinate;
2-(3'-Ethoxybiphenyl-4-ylamino)nicotinic acid;
2-(5-Fluoro-2-methyl-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(2',3-Difluoro-5'-isopropoxybiphenyl-4-ylamino)nicotinic acid;
2-(3-Fluoro-3'-methoxybiphenyl-4-ylamino)-5-methylnicotinic acid;
2-(3,5-Difluoro-3'-hydroxybiphenyl-4-ylamino)nicotinic acid;
5-Bromo-2-(3-fluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
5-Bromo-2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
5-Bromo-2-(3-fluoro-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(3-Fluoro-3'-(trifluoromethoxy)biphenyl-4-ylamino)-5-methylnicotinic acid;
5-Cyclopropyl-2-(3-fluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(3,5-Difluoro-3'-methoxybiphenyl-4-ylamino)-5-methylnicotinic acid;
2-(3'-Ethoxy-5-fluoro-2-methylbiphenyl-4-ylamino)nicotinic acid;
2-(5-Fluoro-3'-methoxy-2-methylbiphenyl-4-ylamino)nicotinic acid;
2-(3'-ethoxy-3,5-difluorobiphenyl-4-ylamino)-5-methylnicotinic acid;
5-cyclopropyl-2-(3'-ethoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;
2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)-5-ethylnicotinic acid;
5-bromo-2-(3'-ethoxy-2,5-difluorobiphenyl-4-ylamino)nicotinic acid;
5-cyclopropyl-2-(3'-ethoxy-2,5-difluorobiphenyl-4-ylamino)nicotinic acid;

2-(5-fluoro-3'-methoxy-2-methylbiphenyl-4-ylamino)-5-methylnicotinic acid;
5-cyclopropyl-2-(5-fluoro-3'-methoxy-2-methylbiphenyl-4-ylamino)nicotinic acid;
2-(2',3,5-trifluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(2'-chloro-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;
2-(3'-cyclopropoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;
2-(3,5-difluoro-2-methylbiphenyl-4-ylamino)nicotinic acid;
5-cyclopropyl-2-(2,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(3'-cyclopropoxy-3,5-difluorobiphenyl-4-ylamino)-5-cyclopropylnicotinic acid;
5-chloro-2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
5-cyclopropyl-2-(3,5-difluoro-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(2,3,5-trifluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(2'-chloro-3,5-difluorobiphenyl-4-ylamino)-5-cyclopropylnicotinic acid;
2-(3,5-difluoro-3'-methoxy-2-methylbiphenyl-4-ylamino)nicotinic acid;
2-(3,5-difluoro-2-methyl-3'-(trifluoromethoxy)biphenyl-4-ylamino)nicotinic acid;
2-(2'-chloro-3,5-difluoro-2-methylbiphenyl-4-ylamino)nicotinic acid;
5-chloro-2-(3,5-difluorobiphenyl-4-ylamino)nicotinic acid;
5-chloro-2-(2'-chloro-3,5-difluorobiphenyl-4-ylamino)nicotinic acid;
2-(2,3,5,6-tetrafluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(3,5-difluoro-2'-methylbiphenyl-4-ylamino)nicotinic acid;
3-(3'-cyclopropoxy-3-fluorobiphenyl-4-ylamino)isonicotinic acid;

or a pharmaceutically acceptable salt or N-oxide thereof;

26. A combination according to claim 3 or 4 wherein the DHODH inhibitor is 2-(3'-ethoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof

27. A combination according to claim 3 or 4 wherein the DHODH inhibitor is 2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof

28. A combination according to claim 3 or 4 wherein the DHODH inhibitor is 2-(3'-cyclopropoxy-3,5-difluorobiphenyl-4-ylamino)nicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof

29. A combination according to claim 3 or 4 wherein the DHODH inhibitor is 2-(3,5-difluoro-3'-methoxybiphenyl-4-ylamino)-5-methylnicotinic acid or a pharmaceutically acceptable salt or N-oxide thereof

30. A combination according to any one of the preceding claims characterised in that the active ingredients (a) and (b) form part of a single pharmaceutical composition.

31. A combination according to any one of the preceding claims, which further comprises (c) another compound selected from:

(i) Anti-TNF-alpha monoclonal antibodies such as Infliximab, Certolizumab pegol, Golimumab, Adalimumab and AME-527 from Applied Molecular Evolution;
(ii) TNF-alpha Antagonists such as Etanercept, Lenercept, Onercept and Pegsunercept;
(iii) Calcineurin (PP-2B) Inhibitors / INS Expression Inhibitors such as cyclosporine A, Tacrolimus and ISA-247 from Isotechnika;
(iv) IL-1 Receptor Antagonists such as Anakinra and AMG-719 from Amgen
(v) Anti-CD20 monoclonal antibodies such as Rituximab, Ofatumumab; Ocrelizumab and TRU-015 from Trubion Pharmaceuticals;
(vi) p38 Inhibitors such as AMG-548 (from Amgen), ARRY-797 (from Array Biopharma), Chlormethiazole edisylate, Doramapimod, PS-540446 (from BMS), SB-203580, SB-242235, SB-235699, SB-281832, SB-681323, SB-856553 (all from GlaxoSmithKline), KC-706 (from Kemia), LEO-1606, LEO-15520 (all from Leo), SC-80036, SD-06 (all from Pfizer), RWJ-67657 (from R.W. Johnson), RO-3201195, RO-4402257 (all from Roche), AVE-9940 (from Aventis), SCIO-323, SCIO-469 (all from Scios), TA-5493 (from Tanabe Seiyaku), and VX-745 and VX-702 (all from Vertex);
(vii) NF-kappaB (NFKB) Activation Inhibitors such as Sulfasalazine and Iguratimod;
(viii) Another dihydrofolate reductase (DHFR) inhibitor such as Aminopterin and CH-1504 from Chelsea;
(ix) Janus kinase (JAK) inhibitors, such as CP-690, 550 from Pfizer and INCB-18424, from Incyte;

(x) MEK inhibitor, such as ARRY-162 from Array; and

(xi) Sphingosine-1 phosphate receptor agonists, such as fingolimod (Novartis);

(xv) Interferons comprising Interferon beta 1a such as Avonex from Biogen Idec, CinnoVex from CinnaGen and Rebif from Merck Serono, and Interferon beta 1b such as Betaferon from Schering and Betaseron from Berlex;

(xvi) Inmunomodulators suchs as BG-12 (fumaric acid derivative) from Biogen Idec/Fumapharm AG;

(xvii) Adenosine aminohydrolase inhibitors such as cladribine from Merck Serono.

32. Use of (a) methotrexate and (b) a DHODH inhibitor as defined in any one claims 1 to 29 for the preparation of a medicament for simultaneous, separate or sequential use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of dehydroorotate dehydrogenase.

33. Use according to claim 32 wherein the pathological condition or disease is selected from rheumatoid arthritis, psoriatic arthritis, ankylosing spondilytis, multiple sclerosis, Wegener's granulomatosis, systemic lupus erythematosus, psoriasis and sarcoidosis.

34. A product comprising (a) methotrexate and (b) a DHODH inhibitor as defined in any one of claims 1 to 29, as a combined preparation for simultaneous, separate or sequential use in the treatment of a human or animal patient suffering from or susceptible to a pathological condition or disease as defined in claim 32 or 33.

35. A product according to claim 34, which further comprises an active compound (c), as defined in claim 31.

36. A kit of parts comprising (b) a DHODH inhibitor as defined in any one of claims 1 to 29 together with instructions for simultaneous, separate or sequential use in combination with (a) methotrexate for the treatment of a human or animal patient

suffering from or susceptible to a pathological condition or disease as defined in claim 32 or 33.

37. A kit according to claim 36, which further comprises an active compound (c), as defined in claim 31.

38. A package comprising (b) a DHODH inhibitor as defined in any one of claims 1 to 29 and (a) methotrexate, for simultaneous, separate or sequential use in the treatment of a pathological condition or disease as defined in claim 32 or 33.

39. A package according to claim 38, which further comprises an active compound (c), as defined in claim 31.

40. Use of (b) a DHODH inhibitor as defined in any one of claims 1 to 29 for the preparation of a medicament, for use in combination with (a) methotrexate, for the treatment of a pathological condition or disease as defined in claim 32 or 33.

41. Use of (a) methotrexate, for use in combination with (b) a DHODH inhibitor as defined in any one of claims 1 to 29 for the treatment of a pathological condition or disease as defined in claim 32 or 33.

42. Use according to claim 40 or 41, wherein the methotrexate (a) is for administration at a dosage regime which involves administration of 0.015 to 3 mg/kg/week of methotrexate and the DHODH inhibitor (b) is for administration at a dosage regime which involves administration of 0.03 to 30 mg/kg/day of DHODH inhibitor.

43. Use according to any one of claims 32, 33 and 40 to 42, wherein the medicament is for use in treating a human or animal patient suffering from or susceptible to hepatic impairment or a condition that would be aggravated by hepatotoxicity.

44. Use according to claim 43, wherein said condition that would be aggravated by hepatotoxicity is liver fibrosis, hepatitis, cirrhosis or liver cancer.

45. Use of a DHODH inhibitor as defined in any one of claims 1 to 29 in the manufacture of a medicament for use in treating a human or animal patient suffering from or susceptible to a pathological condition or disease as defined in claim 32 or 33, wherein the human or animal patient is suffering from or susceptible to hepatic impairment or a condition that would be aggravated by hepatotoxicity, as defined in claim 43 or 44.

46. A method of treating a human or animal patient suffering from or susceptible to a pathological condition or disease as defined in claim 32 or 33, which method comprises simultaneously, separately or sequentially administering to said human or animal patient a therapeutically effective amount of (a) methotrexate and (b) a DHODH inhibitor as defined in any one of claims 1 to 29.

47. A method of treating a human or animal patient suffering from or susceptible to a pathological condition or disease as defined in claim 32 or 33, wherein the human or animal patient is suffering from or susceptible to hepatic impairment or a condition that would be aggravated by hepatotoxicity as defined in claim 43 or 44, which method comprises administering to said human or animal patient a therapeutically effective amount of a DHODH inhibitor as defined in any one of claims 1 to 29

48. A combination according to any of claims 1 to 31 for use in treating a pathological condition or disease as defined in claim 32 or 33.

49. A DHODH inhibitor as defined in any one of claims 1 to 29 for use in treating a human or animal patient suffering from or susceptible to a pathological condition or disease as defined in claim 32 or 33, wherein the human or animal patient is suffering from or susceptible to hepatic impairment or a condition that would be aggravated by hepatotoxicity as defined in claim 43 or 44.