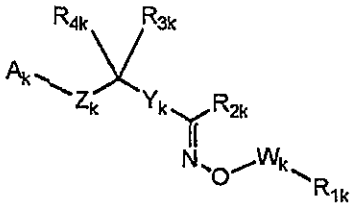
CLAIMS

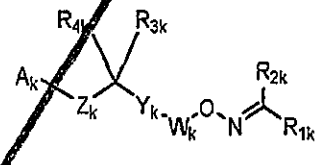
1. Use of a S1P receptor modulator or agonist in the manufacture of a medication, whereby said S1P receptor modulator or agonist is given at a dosage lower than the standard daily dosage of said S1P receptor modulator or agonist during the initial period of treatment and then the dosage is increased, up to the standard daily dosage of said S1P receptor agonist.

2. Use according to claim 1, wherein the medication is for the treatment of an autoimmune condition e.g. multiple sclerosis.

3. Use according to claim 1 or claim 2, wherein the S1P receptor modulator or agonist is a compound of formula Ia or Ib



Ia



Ib

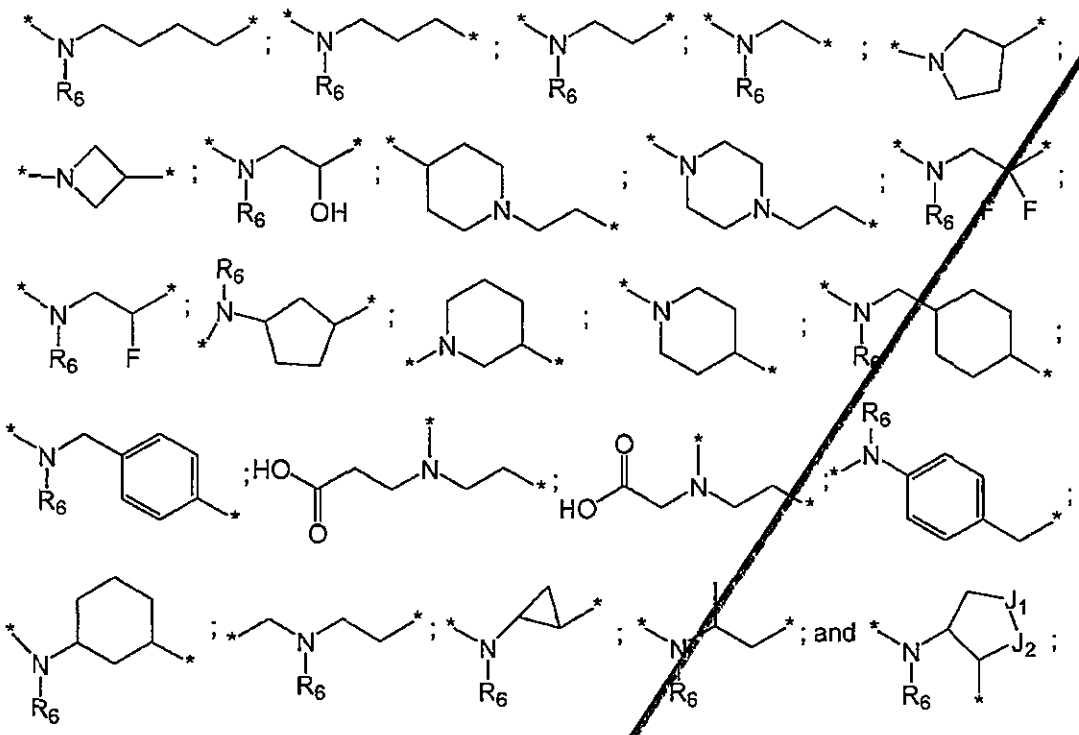
wherein

A_k is -$COOR_{5k}$, -$OPO(OR_{5k})_2$, -$PO(OR_{5k})_2$, -SO_2OR_{5k}, -$POR_{5k}OR_{5k}$ or 1*H*-tetrazol-5-yl, R_{5k} being H or C_{1-6}alkyl;

W_k is a bond, C_{1-3}alkylene or C_{2-3}alkenylene;

Y_k is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by 1 to 3 radicals selected from halogen, OH, NO_2, C_{1-6}alkyl, C_{1-6}alkoxy; halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

Z_k is chosen from



wherein the asterisks of Z_k indicate the point of attachment between -C(R_{3k})(R_{4k})- and A_k of Formula Ia or Ib, respectively; R_6 is chosen from hydrogen and C_{1-6}alkyl; and J_1 and J_2 are independently methylene or a heteroatom chosen from S, O and NR_{5k}; wherein R_{5k} is chosen from hydrogen and C_{1-6}alkyl; and any alkylene of Z_k can be further substituted by one to three radicals chosen from halo, hydroxy, C_{1-6}alkyl; or R_6 can be attached to a carbon atom of Y_k to form a 5-7 member ring;

R_{1k} is C_{6-10}aryl or C_{3-9}heteroaryl, optionally substituted by C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{3-9}heteroaryl, C_{3-9}heteroarylC_{1-4}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, C_{3-8}heterocycloalkyl or C_{3-8}heterocycloalkylC_{1-4}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{1k} may be substituted by 1 to 5 groups selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy and halo substituted-C_{1-6}alkyl or -C_{1-6}alkoxy;

R_{2k} is H, C_{1-6}alkyl, halo substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl: R_{2k} is in particular methyl; and

each of R_{3k} or R_{4k}, independently, is H, halogen, OH, C_{1-6}alkyl, C_{1-6}alkoxy or halo substituted C_{1-6}alkyl or C_{1-6}alkoxy.

and the N-oxide derivatives thereof or prodrugs thereof,

or a pharmacologically acceptable salt, solvate or hydrate thereof.

4. Use according to any one of claims 1, 2 or 3, wherein the S1P receptor modulator or agonist is Compound A or a pharmaceutically acceptable salt thereof.

5. Use according to any one of the preceding claims, comprising administering to the subject sub-therapeutic doses of the S1P receptor modulator or agonist during the initial period of treatment, e.g. 80 fold less, 40 fold less, 10-fold less or 4-fold less than the standard daily dosage.

6. Use according to any one of the preceding claims wherein, during the initial period of treatment, the administered dosage is increased stepwise.

7. Use according to claim 6, wherein the administered dosage is increased stepwise such that the dosage administered on a specific day during the initial period of treatment is the sum of the dosages administered on the previous two days within a range of ± 40%.

8. A method for treating a patient in need thereof (e.g. a patient suffering from an autoimmune condition e.g. multiple sclerosis), such a method comprising administering a S1P receptor modulator or agonist which induces a negative chronotropic effect in heart rate, to the subject at a daily dosage which is lower than the standard daily therapeutic dosage during an initial period of treatment and thereafter commencing the administration of said S1P receptor modulator or agonist at the required standard daily therapeutic dosage.

9. A method of ameliorating or preventing a negative chronotropic side effect associated with a treatment using an S1P modulator or agonist, e.g. compound A or a salt or prodrug thereof, of a subject suffering from an autoimmune disease, comprising administering to the subject in need thereof, said S1P receptor modulator or agonist at a

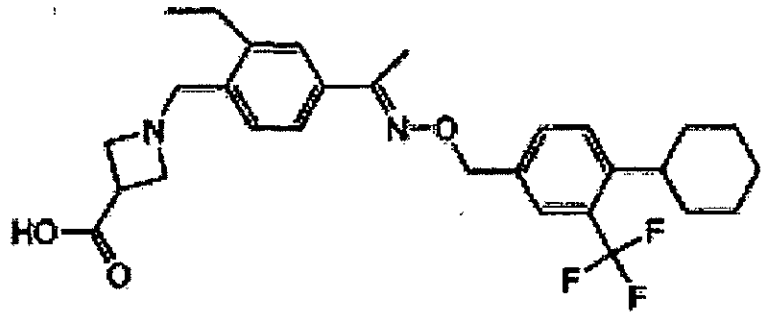
daily dosage which is lower than the standard daily dosage during an initial treatment period and raising the daily dosage stepwise up to the standard daily dosage.

10. A method according to any one of claims 8 or 9, comprising administering to the subject, a S1P receptor modulator or agonist at a daily dosage which is lower than the standard daily dosage during the first 10 days and raising the daily dosage stepwise up to the standard daily dosage.

11. A method according to any one of claims 8 to 10, wherein the S1P receptor modulator or agonist is Compound A or a pharmaceutically acceptable salt thereof.

CLAIMS

1. An S1P receptor modulator or agonist compound of formula Ia



1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid (Compound A),
a salt, a pharmaceutically acceptable salt thereof or prodrug thereof, wherein said prodrug is transformed to the compound of formula Ia by hydrolysis,
for use in the treatment of an autoimmune condition, whereby said S1P receptor modulator or agonist is given at a dosage lower than the standard daily dosage of said S1P receptor modulator or agonist during the initial period of treatment and then the dosage is increased, up to the standard daily dosage of said S1P receptor agonist.

2. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to claim 1, wherein Compound A is used as hemifumarate salt.

3. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to claim 1 or 2, wherein during the initial period the daily dosage is administered according to a Fibonacci series.

4. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to any of the preceding claims wherein the initial period of treatment is 5 days.

5. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to any one of the preceding claims wherein the same dose is

given during the first 2 days of treatment.

6. An S1P receptor modulator or agonist compound according to claim for use in the treatment of an autoimmune condition according to any of the preceding claims, wherein the first dosage increase occurs on day 3.

7. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to any of the preceding claims, wherein the second dosage increase occurs on day 4.

8. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to any one of the preceding claims, wherein the highest initial dose is 0.25 mg.

9. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to any of the preceding claims, wherein the standard daily dosage is 1 to 3 mg.

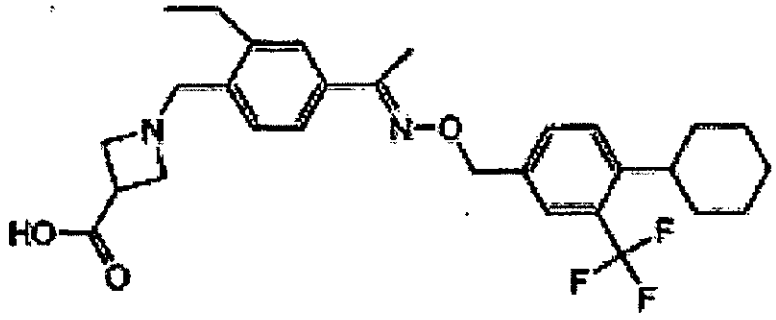
10. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to any of the preceding claims, wherein Compound A is used for treating patients at risk of cardiac side effects, patients at risk of heart failure, arrhythmias, patients with high grade atrio-ventricular blocks or sick sinus syndrome, patients with a history of syncopal episodes, patients requiring or under beta blockers, patients requiring or under anti-arrhythmic treatment or patients under treatment with Class Ia or Class III anti-arrhythmic drugs.

11. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to any of the prece-ding claims, wherein Compound A is used for treating patients having undergone an interruption or treatment holiday in the maintenance dosage regime of greater than 4 days.

12. An S1P receptor modulator or agonist compound according to claim 1 for use in the treatment of an autoimmune condition according to any of the prece-ding claims wherein the autoimmune

condition is multiple sclerosis.

13. A kit comprising a blister pack containing four different dosage forms of an S1P receptor modulator or agonist of formula Ia



1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid (Compound A),

or a salt or prodrug thereof, wherein said prodrug may be transformed to the compound of formula Ia by hydrolysis,

in which the blisters in the pack contain the daily dosages for administration to the patient during the initial treatment phase, for use as defined in claim 1.