



(51) International Patent Classification:

A61K 9/00 (2006.01)

(21) International Application Number:

PCT/TR2019/050471

(22) International Filing Date:

19 June 2019 (19.06.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2018/08815 21 June 2018 (21.06.2018) TR

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: A COMBINATION COMPRISING FINGOLIMOD AND AT LEAST ONE ANTI-EPILEPTIC AGENT

(57) Abstract: The present invention relates to a pharmaceutical combination comprising fingolimod or a pharmaceutically acceptable salt thereof and at least one anti-epileptic agent.



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A COMBINATION COMPRISING FINGOLIMOD AND AT LEAST ONE ANTI-EPILEPTIC AGENT

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Field of the invention

The present invention relates to a pharmaceutical combination comprising fingolimod or a pharmaceutically acceptable salt thereof and at least one anti-epileptic agent.

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Background of the invention

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS) resulting in loss of muscle control, balance, and sensation. Autoimmunity, infectious agents, environmental triggers and hereditary factors influential in disease development.

15

Myelin provides a covering or insulation for nerves, improves the conduction of impulses along the nerves and also is important for maintaining the health of the nerves. In multiple sclerosis, inflammation causes the myelin to disappear. So, the electrical impulses become slower. In addition, the nerves themselves are damaged. Patient suffers from a range of symptoms which affect their health-related quality of life such as pain, muscle spasticity and spasm, bladder problems and sleep disturbance.

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Fingolimod is a sphingosine-1-phosphate receptor modulator, which sequesters lymphocytes in lymph nodes, preventing them from contributing to an autoimmune reaction. Fingolimod is used in the treatment of the relapsing form of multiple sclerosis. May also be used in chronic inflammatory demyelinating polyneuropathy.

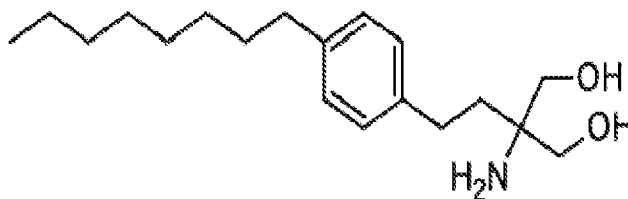
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Fingolimod is marketed by Novartis under the brand name Gilenya® for the treatment of multiple sclerosis. Gilenya® is presented as immediate-release hard gelatin capsules containing 0.56 mg of fingolimod hydrochloride as the active substance corresponding to 0.5 mg of fingolimod.

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The chemical name of fingolimod is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol. Fingolimod is shown as Formula I.

35



Formula I

In prior art, fingolimod derivatives are firstly disclosed in US5604229. The use of fingolimod derivatives as immune depressant and a preventive or remedy for autoimmune diseases is disclosed in EP0627406 (B1). The use of fingolimod derivatives in the prevention or treatment of chronic rejection in a recipient of organ or tissue allo- or xeno-transplant is disclosed in EP0941082 (B1).

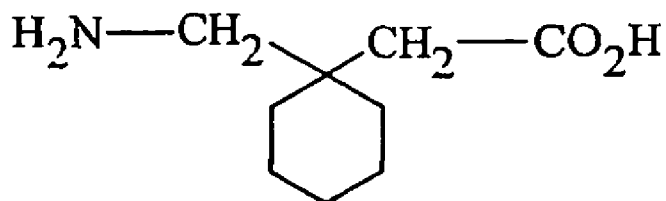
There is no known cure for MS until now. Current treatments typically focus on accelerating patient's recovery from attacks, slowing the progression of the disease and restraining MS symptoms. Fingolimod alone does not provide adequate treatment.

In the present invention, the strategy to improve the current state of MS treatment is to combine therapies. Thus, there is no combination of fingolimod with at least one anti-epileptic agent, in the prior art.

Anti-epileptic agents (AEDs) are the main type of treatment for most people with epilepsy. The treatment of epilepsy generally is directed toward reducing the frequency of seizures. An accurate diagnosis of the form of epilepsy is critical to selection of the drug most likely to be effective. The medicaments currently used for the prevention and/or treatment of epilepsy are fundamentally based on (voltage and neuronal receptor-associated) ion channel inhibitor compounds.

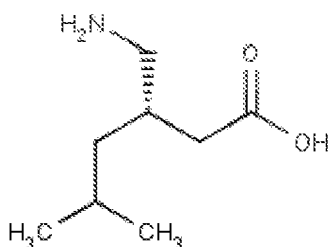
The anti-epileptic agents are selected from the group comprising gabapentin or pregabalin or phenytoin or phenobarbital or carbamazepine or oxcarbazepine or stiripentol or eslicarbazepine acetate or paramethadione or brivaracetam or etiracetam or levetiracetam or seletracetam or progabide or tiagabine or valproate or vigabatrin or combinations thereof .

One of the preferred antiepileptic is gabapentin (l-(aminomethyl)-cyclohexanecarboxylic acid) and its chemical structure is illustrated with Formula II given below.



Formula II

- 5 Gabapentin was designed as a GABA analog that would cross the blood-brain barrier. Gabapentin was found to have anticonvulsant and anti-spastic activity with extremely low toxicity in human. Gabapentin is presently marketed under the trademark Neurontin as adjunctive therapy in the treatment of partial seizures in patients with epilepsy.
- 10 Another preferred antiepileptic is pregabalin which is an analog of gamma-aminobutyric acid (GABA). Its chemical designation is (S)-3-(aminomethyl)-5-methyl hexanoic acid, with the chemical structure illustrated below with Formula III.



Formula III

- 15 It is known that pregabalin binds to the auxiliary sub-unit of voltage-sensitive calcium channels in the central nervous system, thereby replacing the [3H]-gabapentin. It also reduces the release of many neurotransmitters, including pregabalin glutamate, noradrenaline and the substance P. It is used for the treatment of epilepsy, simple or
- 20 complex partial convulsion, either accompanied or not by secondary generalized convulsions, and of neuropathic pain.

- In this invention, combining more than one molecule in one dosage form increases the patient's compliance. However, while this combination increases the patients' quality of life,
- 25 combining more than one molecule in one dosage form also reduces undesired multiple sclerosis symptoms which can be pain. Thus, there is a need to combine fingolimod with at

least one anti-epileptic agent, preferably the antiepileptic agents are gabapentin or pregabalin or mixtures thereof.

Detailed description of the Invention

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The main object of the present invention is to combine fingolimod with at least one anti-epileptic agent to eliminate multiple sclerosis symptoms, to provide rapid and effective treatment and to bring additional advantages over the relevant prior art.

10 Another object of the present invention is to obtain a stable combination formulation with synergistic effect for use in multiple sclerosis.

This invention also provides a pharmaceutical combination comprising an amount of fingolimod and an amount of an anti-epileptic agent, especially gabapentin or pregabalin, for
15 use in treating a human afflicted with multiple sclerosis, wherein fingolimod and an anti-epileptic agent are administered simultaneously, separately or sequentially.

The term "fingolimod" as used herein refers to fingolimod in the form of the free base or in the form of pharmaceutically acceptable salts, crystalline polymorph, solvates, hydrates,
20 esters or mixture thereof.

The term "gabapentin" as used herein refers to gabapentin in the form of the free base or in the form of pharmaceutically acceptable salts, crystalline polymorph, solvates, hydrates, esters or mixture thereof.

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The term "pregabalin" as used herein refers to pregabalin in the form of the free base or in the form of pharmaceutically acceptable salts, crystalline polymorph, solvates, hydrates, esters or mixture thereof.

30 According to one embodiment of the present invention, the pharmaceutical combination comprises fingolimod and at least one anti-epileptic agent.

According to one embodiment of the present invention, the anti-epileptic agent is selected from the group comprising gabapentin or pregabalin or phenytoin or phenobarbital or
35 carbamazepine or oxcarbazepine or stiripentol or eslicarbazepine acetate or paramethadione or brivaracetam or etiracetam or levetiracetam or seletracetam or progabide or tiagabine or valproate or vigabatrin or combinations thereof. Preferably, the anti-epileptic agent is

gabapentin or pregabalin or combinations thereof which is used as adjunctive therapy in pain control.

Thus, an embodiment of this present invention is to combine fingolimod with gabapentin or
5 pregabalin in a same and stable dosage form with desired dissolution profiles.

According to one embodiment of the present invention, the pharmaceutical combination comprises fingolimod and gabapentin.

10 This invention provides a method of treating a human afflicted with multiple sclerosis comprising periodical administration of an amount of fingolimod and an amount of anti-epileptic agent to the subject together, wherein these amounts described below are effective to treat a human.

15 According to this embodiment of the present invention, the pharmaceutical combination comprises fingolimod in an amount of between 0.05 and 20 mg and gabapentin in an amount of between 100 and 400 mg.

According to one embodiment of the present invention, the weight ratio of fingolimod to
20 gabapentin is between 0.000125 - 2.0, preferably 0.001 -1.0, preferably 0.001 - 0.2.

According to another embodiment of the present invention, the pharmaceutical combination comprises fingolimod and pregabalin.

25 According to this embodiment of the present invention, the pharmaceutical combination comprises fingolimod in an amount of between 0.05 to 20 mg and pregabalin in an amount of between 80 to 200 mg.

According to one embodiment of the present invention, the weight ratio of fingolimod to
30 pregabalin is between 0.0001 - 2.0, preferably 0.001 -1.0, more preferably 0.001 - 0.25.

In a preferred embodiment according to the present invention, said combination further comprises at least one pharmaceutically acceptable excipient which is selected from fillers, binders, disintegrants, solvents and co-solvents, rate controlling polymers, direct
35 compression agent, surfactants, lubricants, glidants, sweeteners, stabilizers, coating agents, coloring agents, inert agents or mixtures thereof.

Suitable fillers are selected from the group comprising microcrystalline cellulose, mannitol, spray-dried mannitol, lactose, lactose monohydrate, starch, dextrose, sucrose, fructose, maltose, sorbitol, xylitol, inositol, kaolin, inorganic salts, calcium salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrans, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate, calcium carbonate or mixtures thereof.

Suitable binders are selected from the group comprising polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, starch, pregelatinized starch, glucose, glucose syrup, natural gums, sucrose, sodium alginate, cellulose derivatives such as hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxy methyl cellulose, methyl cellulose, gelatin, carrageenan, guar gum, carbomer, polymethacrylates, methacrylate polymers, collagens, proteins like gelatin, agar, alginate, alginic acid, xanthan gum, hyaluronic acid, pectin, polysaccharides, carbomer, poloxamer, polyacrylamide, aluminium hydroxide, laponit, bentonit, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

Suitable disintegrants are selected from the group comprising polyvinyl pyrrolidone (crospovidone), povidone, cross-linked carboxymethyl cellulose (croscarmellose sodium), low-substituted hydroxypropyl cellulose, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, low substituted hydroxypropyl cellulose, polyacryline potassium, sodium alginate, corn starch, sodium starch glycolate, alginic acid, alginates, ion-exchange resins, magnesium aluminium silica, sodium dodesyl sulphate, poloxamer, sodium glycine carbonate, sodium lauryl sulphate or mixtures thereof.

Suitable solvents or co-solvents are selected from the group comprising water, propylene glycol, glycerin, ethanol, polyethylene glycol or mixtures thereof.

Suitable rate controlling polymers are selected from the group comprising ethyl acrylate, ethyl methacrylate copolymer, ethylcellulose, methylcellulose, hypromellose phthalate, polydextrose, polyvinylacetate phthalate, zein, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose E4M, hydroxypropyl methylcellulose K100MCR, hydroxyethyl cellulose, hydroxymethyl cellulose, gelatin, polyethylene oxide, acacia, dextrin, starch, polyhydroxyethylmethacrylate, sodium carboxymethylcellulose, carboxymethyl cellulose, sodium alginate, alginic acid, pectin, polyglucuronic acid, polygalacturonic acid, chondroitin sulfate, carrageenan, lambda carrageenan, iota carrageenan, furcellaran, xanthan gum, a

- polymer of acrylic acid, carbopol, agar, gua gum, psyllium seed gum, gellan gum, locust bean gum, tara gum, tamarind gum, gum arabic, curdlan, galactomannan, glucomannan, nitrocellulose, methylcellulose, proteoglycan, glycoprotein, actin, tubulin, hemoglobin, insulin, fibrin, albumin, myosin, collagen, casein, pullulan, chitosan, glycerol, propylene glycol, macrogols, phfchalate esters, dibutyl sebacetate, citrate esters, triacetin, castor oil, acetylated monoglycerides, fractionated coconut oil, hydrogenated vegetable oil, hydrogenated castor oil, carnauba wax, candellia wax, beeswax, paraffin wax, stearic acid, glyceryl behenate, cetyl alcohol, cetostearyl alcohol, or a mixtures thereof.
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- 10 Suitable direct compression agents are selected from the group comprising calcium hydrogen phosphate sodium alginate, pregelatinized starch, calcium citrate or mixtures thereof.
- Suitable surfactants are selected from the group comprising sodium docusate, glyceryl monooleate, polyethylene alkyl ether, polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, sorbic acid, sorbitan fatty acid ester, nonoxynol, polyoxyethylene stearates, polyethylene glycol, leucine, polaxomer 407, sodium benzoate, docusate sodium, alpha tocopherol, ascorbyl palmitate, citric acid, polyethoxylated fatty acid esters, polyoxyethylene hydrogenated castor oil or mixtures thereof.
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- 20 Suitable lubricants are selected from the group comprising from magnesium stearate, colloidal silicon dioxide, calcium stearate, zinc stearate, talc, waxes, boric acid, hydrogenated vegetable oil, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, polyethylene glycol, stearic acid, fatty acid, fumaric acid, glyceryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.
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- Suitable glidants are selected from the group comprising colloidal silicon dioxide, corn starch, talc or mixtures thereof.
- 30 Suitable sweeteners are selected from the group comprising aspartame, potassium acesulfame, sodium saccharinate, neohesperidine dihydrochalcone, sucralose, saccharin, sugars such as sucrose, glucose, lactose, fructose or sugar alcohols such as mannitol, sorbitol, xylitol, erythritol or mixtures thereof.
- 35 Suitable stabilizers are selected from the group comprising citric acid, fumaric acid, tartaric acid, sodium citrate, sodium benzoate, sodium dihydrogen phosphate, calcium carbonate,

magnesium carbonate, arginine, lysine, meglamine, ascorbic acid, gallic acid esters or the mixtures thereof, and preferably, citric acid, fumaric acid, arginine or mixtures thereof.

Suitable coating agents are selected from the group comprising polymethacrylates, polyalkylacrylates copolymers, hydroxyl propyl methyl cellulose, lactose monohydrate, hydroxypropyl cellulose, polyvinyl alcohol, polyethylene glycol, talc, polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat® IR), ethylcellulose dispersions (Surelease®), polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate copolymer (PVP-VA), all kinds of Opadry®, pigments, dyes, titanium dioxide, iron oxide or mixtures thereof.

Suitable coloring agents are selected from the group comprising ferric oxide, titanium dioxide, Food, Drug & Cosmetic (FD&C) dyes (such as; FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lakes), poncau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (such as; iron oxide red, yellow, black), quinoline yellow, flaming red, carmine, carmoisine, sunset yellow or mixtures thereof.

Suitable inert agents between the two molecules are selected from starch, lactose, sugar alcohol like D-mannitol, erythritol; lowsubstituted hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose, hydroxyethyl methylcellulose or mixtures thereof.

According to one embodiment of the present invention, the pharmaceutical combination is administered orally. The pharmaceutical combination is in the form of tablets, capsules, strips, syrups, powders, pastilles, sachets, effervescent compositions, pills, coated bead systems, granules, microspheres, dragees, films, orally administrable films, solutions, solids, suspensions or emulsions. Preferably, the pharmaceutical combination is in the form of tablets or capsules.

According to another embodiment of the present invention, the pharmaceutical combination is in the form of a tablet. The pharmaceutical combination is formulated as tablets comprising film-coated tablets, bilayer tablets, inlay tablets, orally disintegrating tablets, compressed tablets, coated or uncoated tablets, multilayer tablets, mini tablets, buccal tablets, sublingual tablets, effervescent tablets, gastric disintegrating tablets, chewable tablets, dispersing tablets or lozenges. Preferably, the pharmaceutical combination is in the form of tablets or capsules.

According to another embodiment of the present invention, the pharmaceutical combination is in the form of a capsule.

In one embodiment, the pharmaceutical combination further comprises a vitamin. The said vitamin is selected from the group comprising vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B4, vitamin B5, vitamin B6, vitamin B7, vitamin B9, vitamin B12, vitamin C, vitamin D, vitamin E, vitamin K.

In another embodiment, the vitamin is cobalamin (vitamin B12).

According to one embodiment of the present invention, the pharmaceutical combination comprises vitamin B12 in an amount of between 0.05 to 10 mg.

According to an embodiment of this present invention, the pharmaceutical combination comprises fingolimod and gabapentin wherein the dosage form of this combination provides immediate release.

According to an embodiment of this present invention, modified release dosage form is selected from the group comprising controlled release, sustained release, delayed release, extended release, repeat action system or mixtures thereof. In one embodiment, modified release dosage form is prepared using rate controlling polymers.

According to an embodiment of this present invention, the pharmaceutical combination comprises fingolimod and pregabalin wherein the combination provides both immediate release and modified release. Also, the combination may comprise vitamin B12.

In one embodiment, the pharmaceutical combination subjected to the invention is composed of at least two parts wherein at least one part provides modified and at least one part provides immediate release in an oral administration.

The combination is prepared using direct compression, wet or dry granulation, hot melt granulation, hot melt extrusion, fluidized bed granulation, extrusion, spheronization, slugging, spray drying or solvent evaporation.

In this present invention, a desired dissolution of the combination is obtained and a desired content uniformity and a simple preparation process are in favor of industrial production.

In this present invention, the combination is for use in the treatment of multiple sclerosis in human.

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CLAIMS

1. A pharmaceutical combination comprising fingolimod and at least one anti-epileptic agent.
- 5 2. The pharmaceutical combination according to claim 1, wherein the at least one anti-epileptic agents are selected from the group comprising gabapentin or pregabalin or phenytoin or phenobarbital or carbamazepine or oxcarbazepine or stiripentol or eslicarbazepine acetate or paramethadione or brivaracetam or etiracetam or levetiracetam or seletracetam or progabide or tiagabine or valproate or vigabatrin or
10 combinations thereof.
3. The pharmaceutical combination according to claim 2, wherein the anti-epileptic agent is gabapentin or pregabalin or combinations thereof.
4. The pharmaceutical combination according to claim 3, wherein the combination comprising fingolimod and gabapentin.
- 15 5. The pharmaceutical combination according to claim 4, wherein the fingolimod is present in an amount of between 0.05 mg and 20 mg and the gabapentin is present in an amount of between 100 mg and 400 mg.
6. The pharmaceutical combination according to claim 5, wherein the weight ratio of fingolimod to gabapentin is between 0.000125 - 2.0, preferably 0.001 - 1.0.
- 20 7. The pharmaceutical combination according to claim 6, wherein the weight ratio of fingolimod to gabapentin is between 0.001 - 0.2.
8. The pharmaceutical combination according to claim 3, wherein the combination comprising fingolimod and pregabalin.
9. The pharmaceutical combination according to claim 8, wherein the fingolimod is present
25 in an amount of between 0.05 mg and 20 mg and the pregabalin is present in an amount of between 80 mg and 200 mg.
10. The pharmaceutical combination according to claim 9, wherein the weight ratio of fingolimod to pregabalin is between 0.0001 - 2.0, preferably 0.001 - 1.0.
11. The pharmaceutical combination according to claim 10, wherein the weight ratio of
30 fingolimod to pregabalin is between 0.001 - 0.25.

12. The pharmaceutical combination according to any one of the preceding claims, further comprising at least one pharmaceutically acceptable excipient which is selected from fillers, binders, disintegrants, solvents and co-solvents, rate controlling polymers, direct compression agents, surfactants, lubricants, glidants, sweeteners, stabilizers, coating agents, coloring agents, inert agents or mixtures thereof.
13. The pharmaceutical combination according to any one of the preceding claims, wherein the combination is administered orally.
14. The pharmaceutical combination according to claim 13, wherein the pharmaceutical combination is in the form of tablets, capsules, strips, syrups, powders, pastilles, sachets, effervescent compositions, pills, coated bead systems, granules, microspheres, dragees, films, orally administrable films, solutions, solids, suspensions or emulsions.
15. The pharmaceutical combination according to claim 14, wherein the pharmaceutical combination is in the form of a tablet.
16. The pharmaceutical combination according to claim 15, wherein the pharmaceutical combination is formulated as tablets comprising film-coated tablets, bilayer tablets, inlay tablets, orally disintegrating tablets, compressed tablets, coated or uncoated tablets, multilayer tablets, mini tablets, buccal tablets, sublingual tablets, effervescent tablets, gastric disintegrating tablets, chewable tablets, dispersing tablets or lozenges.
17. The pharmaceutical combination according to claim 16, wherein the pharmaceutical combination is in the form of a capsule.
18. The pharmaceutical combination according to any one of the preceding claims, further comprising a vitamin.
19. The pharmaceutical combination according to claim 18, wherein the vitamin is B12.
20. A method for preparing the pharmaceutical combination according to any one of the preceding claims, comprising direct compression, wet or dry granulation, hot melt granulation, hot melt extrusion, fluidized bed granulation, extrusion, spheronization, slugging, spray drying or solvent evaporation.
21. The pharmaceutical combination according to any one of the preceding claims, for use in the treatment of multiple sclerosis in human.