(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2020 (11.06.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/117151 A2

(51) International Patent Classification:
A61K 31/00 (2006.01)

(21) International Application Number:
PCT/TR2019/050480

(22) International Filing Date:
20 June 2019 (20.06.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2018/08821 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))*

WO 2020/117151 A2

(54) Title: A COMBINATION COMPRISING FINGOLIMOD AND MODAFINIL

(57) Abstract: The present invention relates to a pharmaceutical combination comprising fingolimod or a pharmaceutically acceptable salt thereof and modafinil or a pharmaceutically acceptable salt thereof for use in the treatment of multiple sclerosis in human, preferably in the prevention or the treatment of fatigue symptom of multiple sclerosis disease.

A COMBINATION COMPRISING FINGOLIMOD AND MODAFINIL

Field of the invention

The present invention relates to a pharmaceutical combination comprising fingolimod or a pharmaceutically acceptable salt thereof and modafinil or a pharmaceutically acceptable salt thereof for use in the treatment of multiple sclerosis in human, preferably in the prevention or the treatment of fatigue symptom of multiple sclerosis disease.

Background of the invention

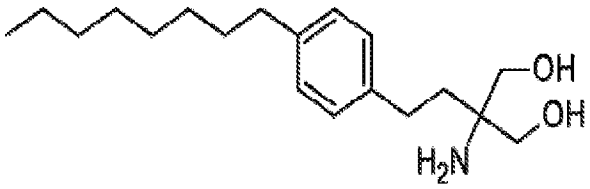
Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS) resulting in loss of muscle control, balance, and sensation. Autoimmunity, infectious agents, environmental triggers and hereditary factors influential in disease development.

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, fatigue, muscle spasticity and spasm, bladder problems and sleep disturbance.

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.

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.

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



Formula I

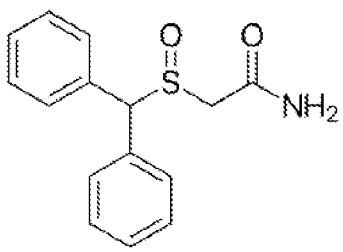
In the prior art, fingolimod derivatives are firstly disclosed in US5604229. The use of fingolimod derivatives as immune depressant and preventive for autoimmune diseases is disclosed in EP0627406 (B1). The use of fingolimod derivatives in the prevention or in the treatment of chronic rejection in a 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 is to improve the current state of MS treatment with combination therapy.

Fatigue is a common symptom of people with MS. This is called "MS fatigue" and this is different from fatigue experienced by persons without MS. This also can arise from associated conditions or accumulation of disease burden. Specific causes to consider include sleep disorders, depression, disability status.

Therefore, there is a need in the prior art to develop a formulation comprising fingolimod and an active agent for reducing undesired multiple sclerosis symptoms which can be fatigue as well as an improved side effect profile and increased patient compliance.

Modafinil is a wakefulness-promoting agent for oral administration. Modafinil is a racemic compound. The chemical name of modafinil is 2-[(diphenylmethyl)sulfinyl]acetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.35. It has the following structural formula as Formula II.



Formula II

Thus, there is no combination of fingolimod with modafinil in the prior art.

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, combining more than one molecule in one dosage form also reduces undesired multiple sclerosis symptoms and provide effective treatment.

Detailed description of the Invention

The main object of the present invention is to combine fingolimod with modafinil to eliminate multiple sclerosis symptoms and to provide effective treatment.

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

This invention also provides a pharmaceutical combination comprising an effective amount of fingolimod and effective amount of modafinil, for use in treating a human afflicted with multiple sclerosis. The combination is 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, esters or mixture thereof.

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

According to one embodiment of the present invention, the pharmaceutical combination comprises fingolimod and modafinil. The combination is used as adjunctive therapy in fatigue for multiple sclerosis treatment.

According to another embodiment of the present invention, the combination is for use in the treatment of multiple sclerosis in human.

According to a further embodiment of the present invention, the combination is for use to prevent or treatment fatigue symptom of MS disease.

An embodiment of this present invention is to combine fingolimod with modafinil in a same and stable dosage form with desired dissolution profiles.

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

According to one embodiment of the present invention, the pharmaceutical combination comprises fingolimod is present in an amount of between 0.05 and 20 mg and modafinil is present in an amount of between 100 and 300 mg.

According to one embodiment of the present invention, the weight ratio of fingolimod to modafinil is between 0.0001 - 2.0, preferably 0.001 -1.0 or more preferably 0.001 - 0.2.

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 compression agent, surfactants, lubricants, glidants, sweeteners, stabilizers, coating agents, coloring agents or 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, dextrates, 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, laponite, bentonite, 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 dodecyl 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, hydroxyethyl cellulose, hydroxymethyl cellulose, gelatin, polyethylene oxide, acacia, dextrin, starch, polyhydroxyethylmethacrylate, sodium carboxymethylcellulose, carboxymethyl cellulose, sodium alginate, alginic acid, pectin, polyglucoronic acid, polygalacturonic acid, chondroitic sulfate, carrageenan, lambda carregeenan, iota carregeenan, furcellaran, xanthan gum, a polymer of acrylic acid, carbopol, agar, guar gum, psyllium seed gum, gellan gum, locust bean 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 mixtures thereof.

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, poloxamer 407, sodium benzoate, docusate sodium, alpha

tocopherol, ascorbyl palmitate, citric acid, polyethoxylated fatty acid esters, polyoxyethylene hydrogenated castor oil or mixtures thereof.

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, glyseryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

Suitable glidants are selected from the group comprising colloidal silicon dioxide, corn starch, talc or mixtures thereof.

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.

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 agent 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; low-substituted 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 this 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, trilayer 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 a film-coated tablet or bilayer tablet or trilayer tablet.

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

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 manufacturing process are in favor of industrial production.

CLAIMS

1. A pharmaceutical combination comprising fingolimod and modafinil.

2. The pharmaceutical combination according to claim 1, wherein fingolimod is present in an amount of between 0.05 and 20 mg and modafinil is present in an amount of between 100 and 300 mg.

3. The pharmaceutical combination according to claim 2, wherein the weight ratio of fingolimod to modafinil is between 0.0001 - 2.0, preferably 0.001 -1.0.

4. The pharmaceutical combination according to claim 3, wherein the weight ratio of fingolimod to modafinil is between 0.001 – 0.2.

5. The pharmaceutical combination according to any one of the preceding claims, wherein comprising at least one pharmaceutically acceptable excipient which is selected from fillers, binders, disintegrants, solvents and co-solvents, rate controlling polymers, direct compression agent, surfactants, lubricants, glidants, sweeteners, stabilizers, coating agents, coloring agents or mixtures thereof.

6. The pharmaceutical combination according to any one of the preceding claims, wherein the combination is administered orally.

7. The pharmaceutical combination according to claim 6, 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.

8. The pharmaceutical combination according to claim 7, wherein the pharmaceutical combination is in the form of a tablet.

9. The pharmaceutical combination according to claim 8, wherein the pharmaceutical combination is formulated as tablets comprising film-coated tablets, bilayer tablets, trilayer 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.

10. The pharmaceutical combination according to claim 9, wherein the pharmaceutical combination is in the form of a film-coated tablet or bilayer tablet or trilayer tablet.

11. The pharmaceutical combination according to claim 7, wherein the pharmaceutical combination is in the form of a capsule.

12. A method for preparing the pharmaceutical combination according to any 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.

13. The pharmaceutical combination according to any preceding claims, for use in the treatment of multiple sclerosis in human.

14. The pharmaceutical combination according to claim 13, for use in the prevention or the treatment of fatigue symptom of multiple sclerosis disease.