



- (51) **International Patent Classification:**
A61K 9/20 (2006.01) *A61K 31/122* (2006.01)
- (21) **International Application Number:**
PCT/TR2013/000283
- (22) **International Filing Date:**
29 August 2013 (29.08.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
2012/09943 31 August 2012 (31.08.2012) TR
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AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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:

- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, — with international search report (Art. 21(3))

(54) **Title:** TABLET FORMULATIONS COMPRISING A QUINONE DERIVATIVE ACTIVE AGENT

(57) **Abstract:** The present invention is related to pharmaceutical formulations in tablet form comprising a quinone derivative active agent, production method of said formulations and their areas of use.



WO 2014/035356 A1

DESCRIPTION

TABLET FORMULATIONS COMPRISING A QUINONE DERIVATIVE ACTIVE AGENT

The present invention is related to pharmaceutical formulations in tablet form comprising a quinone derivative active agent, production method of said formulations and their areas of use.

The Prior Art

Idebenone is a quinone derivative drug which has the chemical formula of 2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl- cyclohexa-2,5-diene-1,4-dione and developed by the firm Takeda in order to be used in the treatment of Alzheimer's disease and other mental disorders.

The active agent is marketed in 45 mg oral tablet form (Mnesis®) in the treatment of central nervous system disorders in Europe and in 150 mg oral tablet form (Catena®) in the treatment of Friedreich's ataxia in Canada.

In addition to the indications given, effective use of the active agent in other indications (*such as neuromuscular diseases, MELAS syndrome, primary MS, Leber's Hereditary Optic Neuropathy and DMD-Duchenne muscular dystrophy*) is also being investigated.

Idebenone is a lipophilic molecule which has very low solubility in aqueous media. In line with this, it is seen that the active agent in the drugs in tablet form obtained in the case that the formulations comprising the active agent are compressed in tablet form cannot dissolve in bodily fluid entirely.

Water solubility of an active agent is one of the most critical factors influencing the bioavailability of the pharmaceutical formulation comprising the active agent. Lipophilic active agents such as idebenone have poor bioavailability as they cannot dissolve in water. Low absorption and bioavailability of a drug prevents enabling efficient treatment.

In the prior art, a method which is frequently used for active agents having low bioavailability could be formulating the active agent in parenteral form. The patent applications US2010130619 and US2010129431 disclose parenteral idebenone formulations. However, it requires pretty hard and laborious production steps to formulate an active agent having low

water-solubility for parenteral use. On the other hand, parental formulations are not generally preferred by patients due to their manner of application. Therefore, it is not preferable to produce this type of active agents in parenteral form.

In the prior art, there are other solutions in order to improve bioavailability of lipophilic drugs. The most known ones of these methods can be listed as changing the crystalline structure of the active agent by one of micronization, spraying or freezing methods or solubilize the active agent by using solubility enhancing agents, surfactants, complexing agents etc. in the formulations.

However, these methods are considerably laborious and costly as well as not certain to provide bioavailability in the obtained product.

For this reason, there is need to develop new formulations comprising idebenone which can provide high bioavailability, can be produced easily and are patient-friendly.

Detailed Description of the Invention

The present invention is related to pharmaceutical formulations in tablet form comprising idebenone, production method of these formulations and their areas of use.

The pharmaceutical formulations of the present invention are characterized in being in tablet form.

Another characteristic feature of the tablet formulations of the present invention is that the formulations are in film coated tablet form. The tablet formulations of the present invention are more advantageous in comparison to parenteral dosage forms as they are patient friendly, have long shelf life and can be produced easily.

The film coated tablet formulations of the present invention comprise idebenone as the active agent in the range of 1% and 50%, preferably in the range of 1% and 45%, more preferably in the range of 1% and 40% by weight.

Idebenone comprised in the film coated tablet formulations of the present invention can be in the form of idebenone or its pharmaceutically acceptable salt, racemate, solvate, hydrate, anhydrate, different polymorphic form and amorphous form or combinations thereof.

The film coated tablet formulations of the present invention comprise at least one pharmaceutically acceptable excipient in addition to the active agent selected from a group

comprising disintegrant, diluent, lubricant, glidant, binder, effervescent couple composed of at least one effervescent acid and at least one effervescent base, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent.

A significant factor affecting the dissolution rate of pharmaceutical formulations is type and amount of the excipients in the formulations in addition the active agent.

The film coated tablet formulations of the present invention comprise at least one filling agent selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose or pharmaceutically acceptable derivatives thereof, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol.

During their studies for new formulations comprising idebenone, the inventors have discovered that the highest dissolution and therefore the highest bioavailability in the formulations can be obtained in the case that the formulations are prepared in tablet form and said tablet formulation comprises lactose or a pharmaceutically acceptable derivative thereof as the filling agent at least at 50% by weight.

A characteristic feature of the film coated tablet formulations of the present invention is that said formulations comprise lactose or a pharmaceutically acceptable derivative thereof in the range of 50% and 85% by weight.

A characteristic feature of the film coated tablet formulations of the present invention is that said formulations comprise lactose or a pharmaceutically acceptable derivative thereof in the range of 50% and 80% by weight.

The ratio of lactose or a pharmaceutically acceptable derivative thereof and idebenone comprised in the formulations of the present invention to each other is in the range of 1.5 and 10, preferably in the range of 2 and 10, more preferably in the range of 2.5 and 10 by weight.

“Lactose or a pharmaceutically acceptable derivative thereof” used herein refers to lactose, lactose monohydrate or lactose anhydrate.

The lactose derivative preferred in the film coated tablet formulations of the present invention is lactose monohydrate.

As the diluent; alkali metal carbonates such as calcium carbonate; alkali metal phosphates such as calcium phosphate; alkali metal sulfates such as calcium sulfate; cellulose derivatives such as cellulose, microcrystalline cellulose, cellulose acetate; magnesium oxide, dextrin, fructose, dextrose, glyceryl palmitostearate, lactitol, kaolin, lactose, maltose, mannitol, simethicone, sorbitol, starch, pregelatinized starch, talc, xylitol and/or anhydrides, hydrates and/or pharmaceutically acceptable derivatives thereof or combinations thereof can be used in the film coated tablet formulations of the present invention.

As the binder; starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatine; cellulose derivatives such as microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol and water or a combination thereof can be used in the film coated tablet formulations of the present invention.

As the disintegrant; cellulose derivatives such as cross-linked carboxymethyl cellulose and/or its salts, microcrystalline cellulose, cellulose, hydroxy propyl cellulose, hydroxy ethyl cellulose, hydroxy propyl methyl cellulose, hydroxy propyl ethyl cellulose, methyl cellulose; sodium starch glycolate, alginic acid, sodium alginate, chitosan, colloidal silicon dioxide, starch, pregelatinized starch, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone or combinations thereof can be used in the film coated tablet formulations of the present invention.

As the lubricant; metallic stearates (such as magnesium stearate, calcium stearate, aluminum stearate), fatty acid esters (such as sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oil, leucine, polyethylene glycols, metallic lauryl sulfate (such as sodium lauryl sulfate, magnesium lauryl sulfate), sodium chloride, sodium benzoate, sodium acetate and talc or a combination thereof can be used in the film coated tablet formulations of the present invention.

The film coating agents that that can be used for film coating of the film coated tablet formulations of the present invention can be selected from a group comprising cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxymethyl cellulose, ethyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose;

synthetic polymers such as polyvinyl acetal diethyl amino acetate, aminoalkyl methacrylate copolymers and polyvinylpyrrolidone; polysaccharides such as pullulan; titanium dioxide, triacetin; black, yellow and/or red iron oxides or combinations thereof.

The formulations of the present invention can optionally comprise at least another active agent.

The other active agent that can be used in the formulations can be selected from antacid, anticholinergic, antispasmodic, antiemetic, antibiotic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, anti-dementia, antiviral, antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, thiazolidinedione, biguanide, immunostimulant, immunosuppressant, myorelaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogues, vitamin B₁, vitamin C, vitamin E, vitamin B₃, vitamin B₅, vitamin B₆, vitamin B₇, vitamin B₉, vitamin B₁₂, vitamin B₂, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium or binary, ternary etc. combinations thereof.

The other active agent or active agent group preferred for the formulations of the present invention is at least one anti-dementia agent and said anti-dementia agents are selected from a group comprising donepezil, galantamine, memantine, rivastigmine, ginkgo biloba extract, tacrine and/or their pharmaceutically acceptable salts, enantiomers, hydrates, anhydrates etc. derivatives or binary or ternary combinations thereof.

In another aspect, the present invention presents a method for production of idebenone tablet formulations.

A characteristic feature of the formulations of the present invention is that said formulations are produced by wet granulation method.

Said production method comprises the steps of mixing the active agent or if available at least one other active agent with lactose monohydrate and at least another excipient; wet-granulating the mixture; drying and sieving the granules; adding at least another

pharmaceutically acceptable excipient into the dried granules; compressing the final mixture in tablet form and film-coating the obtained tablet.

The film coated idebenone tablet formulations of the present invention are used in the treatment of cerebral arteriosclerosis, symptoms following stroke and cerebral hemorrhage, age-associated cognitive decline, chronic cerebrovascular disease, multi-infarct dementia and mild and moderate Alzheimer's type dementia and frailty, speech disorders, memory loss, short attention span associated with these diseases, symptoms of vascular and degenerative cerebral pathologies such as psychomotor activity and depression.

There are examples given below for these formulations. The invention cannot be restricted to these examples.

Example. Film Coated Idebenone Formulation

Component	Amount (%)
Idebenone	20
Diluent	15
Lactose Monohydrate	55
Disintegrant	5
Lubricant	1
Binder	2.5
Film Coating	2.5

Production Method:

Idebenone, diluent and lactose monohydrate are mixed. The mixture is wet-granulated with a granulation solution comprising the binder and at least one solvent. The granules are dried and sieved. The disintegrant is added to the obtained dry granules and they are mixed. The mixture is treated with the lubricant. The final mixture is compressed in tablet form and the tablets are coated with film.

CLAIMS

1. Film coated tablet formulations comprising idebenone as the active agent.
2. The film coated tablet formulations according to claim 1, characterized in that said formulations comprise idebenone in the range of 1% and 50% by weight.
3. The film coated tablet formulations according to claims 1-2, characterized in that said formulations comprise idebenone in the range of 1% and 45% by weight.
4. The film coated tablet formulations according to claims 1-3, characterized in that said formulations comprise idebenone in the range of 1% and 40% by weight.
5. The film coated tablet formulations according to any preceding claims, characterized in that the active agent idebenone in said formulations is in form of idebenone or a pharmaceutically acceptable salt, racemate, solvate, hydrate, anhydrate, different polymorphic form and amorphous form of idebenone or combinations thereof.
6. The film coated tablet formulations according to any preceding claims, characterized in that said formulations comprise at least one pharmaceutically acceptable excipient in addition to the active agent selected from a group comprising disintegrant, diluent, lubricant, glidant, binder, effervescent couple composed of at least one effervescent acid and at least one effervescent base, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent.
7. The film coated tablet formulations according to claim 6, characterized in that said formulations comprise at least one filling agent selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose or pharmaceutically acceptable derivatives thereof, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol.
8. The film coated tablet formulation according to claim 7, characterized in that said formulations comprise lactose or a pharmaceutically acceptable derivative thereof as the filling agent at least at 50% by weight.
9. The film coated tablet formulation according to claim 8, characterized in that said formulations comprise lactose or a pharmaceutically acceptable derivative thereof as the filling agent in the range of 50% and 85% by weight.

10. The film coated tablet formulation according to claim 9, characterized in that said formulations comprise lactose or a pharmaceutically acceptable derivative thereof as the filling agent in the range of 50% and 80% by weight.
11. The film coated tablet formulation according to claims 8-10, characterized in that the ratio of lactose or a pharmaceutically acceptable derivative thereof and idebenone to each other is in the range of 1.5 and 10 by weight.
12. The film coated tablet formulation according to claims 11, characterized in that the ratio of lactose or a pharmaceutically acceptable derivative thereof and idebenone to each other is in the range of 2 and 10 by weight.
13. The film coated tablet formulation according to claims 12, characterized in that the ratio of lactose or a pharmaceutically acceptable derivative thereof and idebenone to each other is in the range of 2.5 and 10 by weight.
14. The film coated tablet formulation according to claims 7-13, characterized in that lactose or a pharmaceutically acceptable derivative thereof used in said formulations as the filling agent is lactose, lactose monohydrate or lactose anhydrate.
15. The film coated tablet formulation according to claims 14, characterized in that lactose or a pharmaceutically acceptable derivative thereof used in said formulations as the filling agent is lactose monohydrate.
16. The film coated tablet formulation according to any preceding claims, characterized in that said formulations optionally comprise at least another active agent.
17. The film coated tablet formulation according to claim 16, characterized in that at least another active agent that can be used in said formulations is at least one anti-dementia agent.
18. The film coated tablet formulation according to claim 17, characterized in that at least one anti-dementia agent that can be used in said formulations is selected from a group comprising donepezil, galantamine, rivastigmine, ginkgo biloba extract, tacrine and/or their pharmaceutically acceptable salts, enantiomers, hydrates, anhydrides etc. derivatives or binary or ternary combinations thereof.
19. A production method of film coated tablet formulations according to claim 1, characterized in that said method is wet-granulation method.
20. The production method according to claim 19, characterized in that said method comprises the steps of mixing the active agent and if available at least one other active agent with lactose monohydrate and at least another excipient; wet-granulating the mixture; drying and sieving the granules; adding at least another pharmaceutically

acceptable excipient into the dried granules; compressing the final mixture in tablet form and film-coating the obtained tablet.

INTERNATIONAL SEARCH REPORT

International application No

PCT/TR2013/000283

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/20 A61K31/122
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 108 366 A1 (SANTHERA PHARMACEUTICALS CH [CH]) 14 October 2009 (2009-10-14) paragraph [0030] -----	1-20
X	EP 0 788 793 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 13 August 1997 (1997-08-13) page 4, lines 41,42; examples 1,2 -----	1-20
X	EP 0 629 400 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 21 December 1994 (1994-12-21) page 2, line 42; example 1 -----	1-20
X	US 5 962 535 A (MIYAMOTO MASAOMI [JP] ET AL) 5 October 1999 (1999-10-05) column 11, lines 5-8 column 15, line 40 - column 16, line 27 ----- -/-	1-20

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 December 2013

Date of mailing of the international search report

18/12/2013

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INTERNATIONAL SEARCH REPORT

International application No

PCT/TR2013/000283

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/02149 A2 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]; MIYAMOTO MASAOMI [JP]; HIRAI KEIS) 22 January 1998 (1998-01-22) page 11, lines 8,9; examples 1,2 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/TR2013/000283

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2108366	A1	14-10-2009	AT 529104 T 15-11-2011
		AU 2009235681 A1 15-10-2009	
		CA 2719440 A1 15-10-2009	
		DK 2108366 T3 30-01-2012	
		EP 2108366 A1 14-10-2009	
		ES 2370607 T3 20-12-2011	
		HR P20110813 T1 30-11-2011	
		JP 2011516513 A 26-05-2011	
		NZ 588181 A 25-11-2011	
		PT 2108366 E 10-11-2011	
		SI 2108366 T1 31-01-2012	
		US 2011092469 A1 21-04-2011	
		WO 2009124693 A1 15-10-2009	
EP 0788793	A1	13-08-1997	CA 2196488 A1 02-08-1997
		CN 1164388 A 12-11-1997	
		EP 0788793 A1 13-08-1997	
		US 5916925 A 29-06-1999	
EP 0629400	A1	21-12-1994	AT 184788 T 15-10-1999
		CA 2125822 A1 19-12-1994	
		DE 69420776 D1 28-10-1999	
		DE 69420776 T2 18-05-2000	
		DK 0629400 T3 14-02-2000	
		EP 0629400 A1 21-12-1994	
		ES 2136167 T3 16-11-1999	
		GR 3032041 T3 31-03-2000	
		JP H0761923 A 07-03-1995	
US 5962535	A	05-10-1999	NONE
WO 9802149	A2	22-01-1998	AT 218060 T 15-06-2002
		AU 3458997 A 09-02-1998	
		CA 2252519 A1 22-01-1998	
		DE 69712888 D1 04-07-2002	
		EP 0915696 A2 19-05-1999	
		US 6271266 B1 07-08-2001	
		WO 9802149 A2 22-01-1998	