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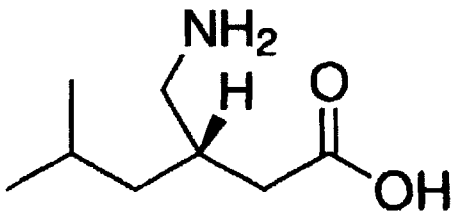
(54) Title: PHARMACEUTICAL FORMULATION OF PREGABALIN (PARTICLE SIZE 300-2500 MICROMETER)

(57) Abstract: The present invention relates pharmaceutical formulations comprising pregabalin that shall be used in the treatment of epilepsy, central nervous system disorders, Parkinson's disease; Huntington's disease; tardive dyskinesia; spasticity; cerebral ischemia; postherpetic neuralgia; social phobia; fibromyalgia and spinal cord injury induced chronic pains; neuropathic pains associated with diabetic peripheral neuropathy and common anxiety disorder and preparation methods of these formulations whereby the particle size of the prepared granules is from 300-2500 micrometer.

PHARMACEUTICAL FORMULATION OF PREGABALIN (PARTICLE SIZE 300-2500 MICROMETER)

The present invention relates to pharmaceutical formulations comprising pregabalin that shall be used in the treatment of epilepsy, central nervous system disorders, Parkinson's disease; Huntington's disease; tardive dyskinesia; spasticity; cerebral ischemia; postherpetic neuralgia; social phobia; fibromyalgia and spinal cord injury induced chronic pains; neuropathic pains associated with diabetic peripheral neuropathy and common anxiety disorder.

Pregabalin was first disclosed in the application numbered EP 0641330 Bl. In said document, it was disclosed that use of pregabalin is effective in the treatment of central nervous system disorders, epilepsy, Parkinson's disease; Huntington's disease; tardive dyskinesia; spasticity; cerebral ischemia.



Pregabalin is available in 25mg, 50mg, 75mg, lOOmg, 150mg, 200mg, 225mg and 300mg capsule, oral forms on the market.

It is seen that proper flow of the formulation mixture does not occur due to the reasons that the granules obtained cannot be provided free flow and/or possible friction between granule particles cannot be reduced, therefore homogeneity cannot be ensured in the pharmaceutical composition obtained and the mixture loses its homogeneity during processes in preparation of the formulations comprising pregabalin. Therefore, the abovementioned problems cause weight changes in the end product and increase in relative standard deviation values during forming the formulations into any solid dosage form. Weight and content uniformity cannot be provided in the end product due to these variations observed in weight of the end product obtained and due to the fact that formulation homogeneity cannot be provided. This situation poses problems to the manufacturer during production and quality control phases and also prevent the patient from taking equal amount of the drug during his/her treatment due to loss of weight and content uniformity observed in the dosage forms obtained and consequently, this reduces efficiency of the treatment.

As seen, there is still need to develop new approaches so as to obtain homogeneous pregabalin formulations that are produced in such a way that any change shall not be observed in unit dosage weight in order to perform an effective treatment and prevent the problems that may arise from loss of weight uniformity during quality and control phases by preventing the changes observed in weight and content of the end product obtained.

As a result of the studies they conducted in line with this requirement, the inventors have found that some physical characteristics of the formulations, which they have developed in order to prepare the dosage forms comprising pregabalin, have effect on relative standard deviation in dosage weight of the drug obtained, and said problems encountered during both quality control and using phases can be solved with the formulations developed by adjusting physical characteristics.

Description of the Invention

The present invention relates to pharmaceutical formulations comprising pregabalin and methods for preparation of these formulations. Surprisingly, it has been seen that in the case that the formulations wherein the average particle size of the granules comprising pregabalin, at least one excipient and optionally a second active agent is in the range of 300 - 2500 μm, preferably in the range of 350 - 2000 μπι, more preferably in the range of 500 - 1750 μm are formed into any solid dosage form, their relative standard deviation is low, a homogeneous pharmaceutical composition is obtained and weight and content uniformity are provided by preventing weight changes.

In this respect, the subject of the present invention is that average particle size of the granules comprising pregabalin, at least one excipient and optionally the second active agent is in the range of 300-2500 μm, preferably in the range of 350-2000 μιη, more preferably in the range of 500-1750 μπι in preparation of the formulations comprising pregabalin.

The term "average particle size" refers to average particle size by volume and it is also shown with d_{50} in short. In this sense, the term d_{50} signifies that half of the said substance by volume has a particle size over the value stated with d_{50} and the other half of the substance by volume has a particle size below the value stated with d_{50}

D_{50} value can be measured by one of the known measuring devices, for instance by a device which measures particle distribution by laser diffraction (for instance, Malvern Mastersizer etc.).

In another aspect, the present invention relates to a process that shall be used in production of the granules having an average particle size in the range of 300-2500 μm, preferably in the range of 350-2000 μm, more preferably in the range of 500-1750 μm and comprising pregabalin, at least one excipient and optionally the second active agent characterized in that said granules having an average particle size in the range of 300-2500 μm, preferably in the range of 350-2000 μm, more preferably in the range of 500-1 750 μm are obtained by

- being sieved by an appropriate sieve or
- being pulverized by the devices such as impact mill, jet mill, blade mill etc.

In the case that blade mill is used, pulverization is performed by the impact of rotating blades in the device.

In the case that impact mill is used, pulverization is performed by the impact of rotating hammers in the device.

In the case that jet mill is used, pulverization is performed by providing collision of the particles with each other with the help of high-pressured and high-speed airstream.

The pharmaceutical formulation according to the present invention can be obtained by a method comprising

- Mixing the granules obtained after granulating the active agent pregabalin and if available the second active agent with the granulation solution comprising at least one of the excipients homogeneously and drying the mixture obtained, bringing the granules to an average particle size in the range of 300-2500 μm by an appropriate method if required and optionally treating the mixture with at least one other excipient or
- Mixing the granules obtained after mixing the active pregabalin and if available the second active agent with at least one of the excipients homogeneously and optionally granulating them with the granulation solution comprising at least one excipient, and drying the mixture obtained, bringing the granules to an average particle size in the range of 300-2500 μm by an appropriate method if required and optionally treating them with at least one other excipient or
- Using any of the abovementioned methods separately for the active agent compositions and combining the formulations obtained in the case that two active agents are used.

The inventors have observed relative standard deviation of weight by changing the average particle size values of the granules in order to find the effect of the average particle size of the granules sieved after granulation and drying processes on weight changes and therefore on weight uniformity in the solid dosage form obtained. According to this, the average particle size values of the granules obtained after the sieving process and the relative standard deviation values (RSD %) observed according to these values are given in Table 1. As seen in the table, it is observed that when the average particle size of the granules obtained are in the range of 300-2500 μm, particularly in the range of 500-2000 μm, RSD% value is around 2% or less. According to this, it has been found that the solid dosage forms of the formulations prepared with the granules having an average particle size in the range of 300-2500 μm and more preferably in the range of 500-2000 μm have low relative standard deviation, and therefore weight uniformity is ensured.

Table 1: Average particle sizes of the granules and relative standard deviation values according to these particle sizes.

Average Particle Size of Granule (μm)	RSD%
50	7.4
100	6.2
200	3.8
300	2.2
400	1.5
500	1.4
750	1.3
1000	1.7
1250	1.9
1500	1.8
2000	2.1
2500	2.3
3000	3.4
3500	4.2

During the studies conducted, the inventors have seen that the parameters such as drying temperature and moisture ratio of the obtained granules are important in order to attain optimum values of hardness, fragility and stability characteristics of the granules obtained and the end product in solid form prepared by using said granules during preparation of the formulations comprising pregabalin and therefore important for preventing possible problems that may be encountered during quality control and use phases.

According to the studies conducted, the inventors have surprisingly seen that the granules obtained according to the process of the present invention by being dried at 10-120°C, preferably at 20-100°C and more preferably at 25-70°C show proper flow characteristics and the solid forms prepared with these granules have desired hardness and fragility.

According to this, in another aspect, the present invention relates to drying the granules comprising pregabalin, at least one excipient and optionally the second active agent at a temperature in the range of 10-120°C, preferably at a temperature in the range of 20-100°C and more preferably at a temperature in the range of 25-70°C in preparation of the formulations comprising pregabalin.

In line with this the studies conducted, the inventors have seen that moisture ratio of the granules obtained during preparation of the formulations comprising pregabalin has effect on the end product obtained in solid form for having desired physical properties and for providing weight preciseness and stability.

According to this, in another aspect, the present invention relates to drying the granules comprising pregabalin, at least one excipient and optionally the second active agent to have a moisture ratio less than 1% by weight, preferably in the range of 0.1-0.9% by weight in preparation of the formulations comprising pregabalin.

Pregabalin comprised in the pharmaceutical formulations prepared according to the process of the present invention is in the form of its free base or pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations; in amorphous form or crystalline form or a combination thereof in terms of polymorphic structure.

The pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be prepared in any solid dosage form such as tablet,

effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enterically coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet.

The pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin are preferably in the form of effervescent tablet or tablet, more preferably in effervescent tablet form.

The pharmaceutical formulation obtained according to the present invention can be formed into any abovementioned dosage forms. In the case that the formulation is in tablet form, the obtained tablets can be treated with film coating agents for instance, sugar based coating agents, water soluble film coating agents, enterically coating agents, delayed release coating agents or coating compositions comprising a combination thereof.

Saccharose can be used singly or optionally with any of the agents such as talc, calcium carbonate, calcium phosphate, calcium sulphate, gelatine, gum arabic, polyvinylpyrrolidone and pullulan or a combination thereof as the sugar based coating agent.

The water soluble film coating agent can be selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose; synthetic polymers such as polyvinyl acetal diethyl aminoacetate, aminoalkyl methacrylate copolymers and polyvinylpyrrolidone and polysaccharides such as pullulan or combinations thereof.

The enterically coating agents can be selected from cellulose derivatives such as hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, cellulose acetate phthalate; acrylic acid derivatives such as methacrylic acid copolymer L, methacrylic acid copolymer LD and methacrylic acid copolymer S and natural substances such as shellac or the combinations thereof.

The delayed release coating agents can be selected from cellulose derivatives such as ethyl cellulose; acrylic acid derivatives such as aminoalkyl methacrylate copolymer RS, ethyl acrylate-methyl methacrylate copolymer emulsion or combinations thereof.

The pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can comprise various excipients in addition to the active agent pregabalin.

The pharmaceutical formulations prepared according to the process of the present invention and comprismg pregabalin comprise at least one excipient selected from a group comprising disintegrant, diluent, lubricant, glidant, binder, effervescent couple comprising at least one acidic agent and at least one basic agent, colouring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavouring agent in addition to the active agent pregabalin and lubricant.

The disintegrant that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from a group comprising carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, croscarmellose sodium, crospovidone, hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, chitosan, starch, sodium starch glycolate.

The diluent that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol.

The glidant that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from a group comprising tribasic calcium phosphate, colloidal silicone dioxide, magnesium silicate, magnesium trisilicate, talc.

The binder that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from a group comprising carboxymethyl cellulose sodium, ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminium silicate, maltodextrin, methyl cellulose, povidone, starch.

The acidic agent composing the effervescent couple comprising at least one acidic agent and at least one basic agent that can be used in the pharmaceutical compositions of the present invention comprising pregabalin selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid; and the basic agent can be selected from a

group comprising agents such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate.

The pH regulating agent that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from citrate, phosphate, carbonate, tartrate, fumarate, acetate and amino acid salts.

The surfactant that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from sodium lauryl sulphate, polysorbate, polyoxyethylene, polyoxypropylene glycol and similar agents.

The stabilizing agent that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from a group comprising tocopherol, tetrasodium edetate, nicotinamide, cyclodextrin.

The sweetener and/or taste regulating agent that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from a group comprising acesulfame, aspartame, dextrose, fructose, maltitol, maltose, mannitol, saccharine, saccharine sodium, sodium cyclamate, sorbitol, sucralose, sucrose, xylitol, sodium chloride.

The flavouring agent that can be used in the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can be selected from menthol, lemon, orange, vanilla, strawberry, raspberry, caramel and similar flavours.

The pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can comprise pregabalin in the range of 0.1 to 99.9 % by weight, preferably in the range of 1 to 99% by weight, more preferably in the range of 5 to 95% by weight.

The pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin can optionally comprise a second active agent in addition to pregabalin. The second active agent can be selected from antacid, anticholinergic, antispasmodic, antiemetic, antidiabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, 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 B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin B_{12}, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

Optionally, the pharmaceutical formulations prepared according to the process of the present invention and comprising pregabalin preferably comprise a vitamin; more preferably comprise vitamin B_{12} as the second active agent in addition to pregabalin.

The pharmaceutical formulations prepared according to the process of the present invention and comprising a second active agent in addition to pregabalin can be prepared in any solid dosage forms such as tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enterically coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet in the case that two active agents are comprised in the same formulation; in dosage forms such as layered tablet, capsule in the case that the two active agents are in different formulations but in the same dosage form; in treatment package form comprising a combination of the solid dosage forms such as tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enterically coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet or in the form of capsule comprising micro tablet and/or micropellet in the case that the two active agents are in different formulations and dosage forms.

The pharmaceutical formulation according to the present invention can be used in the prevention and treatment of epilepsy, central nervous system disorders, Parkinson's disease; Huntington's disease; tardive dyskinesia; spasticity; cerebral ischemia; postherpetic neuralgia; social phobia; fibromyalgia and spinal cord injury induced chronic pains; neuropathic pains associated with diabetic peripheral neuropathy and common anxiety disorder.

The examples of the formulations according to the present invention are given below. These examples are given in order to explain the invention, yet the present invention is not limited to these examples.

EXAMPLES

Example 1:

Film Coated Tablet Dosage Form Comprising Pregabalin

Content	Amount (%)
Active agent	
Pregabalin	40,5
Excipients	
Diluent	33,0
Binder	12,0
Disintegrant	4,0
Film coating agent	7,0
Other excipients	3,5
Total	**100,0**

Pregabalin and the diluent are mixed. The mixture is granulated with the granulation solution comprising the binder. The granules obtained are dried, mixed with the disintegrant and other excipients. The final mixture obtained is compressed in tablet compression machine and coated with the film coating agent.

Example 2:

Effervescent Tablet Dosage Form Comprising Pregabalin;

Content	Amount (%)
Active agent	
Pregabalin	5.5
Excipients	
Taste regulating agent	3.5
Acidic agent	44.5
Basic agent	39.0

Lubricant	**2.5**
Binder	**3.0**
Sweetener	**1.5**
Flavouring agent	**0.5**
Total	**100.0**

The formulation comprising pregabalin and excipients is granulated with the granulation solution comprising a pharmaceutically acceptable binder. The granulation solution used herein can comprise any solvent in addition to the binder. The granules are dried and sieved. The sweetener, the flavouring agent and the lubricant are added and the formulation is finalised. Optionally tablet compression is performed.

CLAIMS

1. A process that shall be used in preparation of pharmaceutical formulations comprising pregabalin, characterized in that
    - The granules comprising pregabalin, at least one excipient and optionally a second active agent
        - are sieved and pulverized such that they have an average particle size in the range of 300-2500 μm.
    - The granules are dried and
    - The granules mixed with at least one excipient.
2. The process according to claim 1, characterized in that the granules comprising pregabalin, at least one excipient and optionally a second active agent are sieved or pulverized such that they have an average particle size in the range of 350- 2000 μm.
3. The process according to claims 1-2, characterized in that the granules comprising pregabalin, at least one excipient and optionally a second active agent are sieved or pulverized such that they have an average particle size in the range of 500- 1750 μm.
4. The process according to claims 1-3, characterized in that
    - The granules comprising pregabalin, at least one excipient and optionally a second active agent
        - are sieved such that they have an average particle size in the range of 300-2500 μm,
    - The granules are dried and
    - The granules are mixed with at least one excipient.
5. The process according to claims 1-3, characterized in that
    - The granules comprising pregabalin, at least one excipient and optionally a second active agent
        - are pulverized such that they have an average particle size in the range of 300-2500 μm,
    - The granules are dried and
    - The granules are mixed with at least one excipient.
6. The process according to claims 1-3, 5, characterized in that pulverization process is performed by impact mill, jet mill or blade mill.

7. The process according to claims 1-6, characterized in that the granules comprising pregabalin, at least one excipient and optionally a second active agent are dried at a temperature between 10-120°C.

8. The process according to claims 1-7, characterized in that the granules comprising pregabalin, at least one excipient and optionally a second active agent are dried at a temperature between 20-I00°C.

9. The process according to claims 1-8, characterized in that the granules comprising pregabalin, at least one excipient and optionally a second active agent are dried at a temperature between 25-70°C.

10. The process according to claims 1-9, characterized in that the granules comprising pregabalin, at least one excipient and optionally a second active agent are dried such that they have a moisture ratio less than 1%.

11. The process according to claims 1-10, characterized in that the granules comprising pregabalin, at least one excipient and optionally a second active agent are dried such that they have a moisture ratio in the range of 0.1- 0.9%.

12. The pharmaceutical formulation comprising pregabalin, characterized in that

- Said formulation comprises granules which are composed of pregabalin, at least one excipient and optionally a second active agent and
- The average particle size of the granules comprising pregabalin, at least one excipient and optionally a second active agent is in the range of 300-2500 μm.

13. The pharmaceutical formulation comprising pregabalin according to claim 12, characterized in that

- Said formulation comprises granules which are composed of pregabalin, at least one excipient and optionally a second active agent and
- The average particle size of the granules comprising pregabalin, at least one excipient and optionally a second active agent is in the range of 350-2000 μm.

14. The pharmaceutical formulation comprising pregabalin according to claims 12 and 13, characterized in that

- Said formulation comprises granules which are composed of pregabalin, at least one excipient and optionally a second active agent and

- The average particle size of the granules comprising pregabalin, at least one excipient and optionally a second active agent is in the range of 500-1750 µm.

15. The pharmaceutical formulation according to any preceding claims, wherein said formulation is in any dosage forms of tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enterically coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet.
16. The pharmaceutical formulation according to any preceding claims, wherein said formulation is in effervescent tablet form.
17. The pharmaceutical formulation according to any preceding claims, wherein pregabalin is in the form of free base or its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers, hydrates, anhydrates or combinations thereof.
18. The pharmaceutical formulation according to any preceding claims, wherein pregabalin is in pharmaceutically acceptable free base form of pregabalin.
19. The pharmaceutical formulation according to any preceding claims, wherein at least one excipient comprised in said formulation in addition to pregabalin is selected from a group comprising disintegrant, diluent, lubricant, glidant, binder, effervescent couple comprising at least one acidic agent and at least one basic agent, colouring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavouring agent.
20. The pharmaceutical formulation according to any preceding claims, wherein said formulation comprises the active agent pregabalin in the range of 0.1 to 99.9 % by weight.
21. The pharmaceutical formulation according to any preceding claims, wherein said formulation comprises the active agent pregabalin in the range of 1 to 99% by weight.
22. The pharmaceutical formulation according to any preceding claims, wherein said formulation comprises the active agent pregabalin in the range of 5 to 95% by weight.
23. The pharmaceutical formulation according to any preceding claims, wherein the second active agent that can be optionally comprised along with pregabalin in said formulation is selected from antacid, anticholinergic, antispasmodic, antiemetic, antidiabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic,

antibiotic, antiseptic, antiacne, antibacterial, antimycotic, 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 B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin **B12**, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

24. The pharmaceutical formulation according to claim 25, wherein said formulation optionally comprises vitamin B12 as the second active agent in addition to pregabaline

25. The pharmaceutical composition according to any preceding claims, wherein said composition is used in the treatment of epilepsy, central nervous system disorders, Parkinson's disease; Huntington's disease; tardive dyskinesia; spasticity; cerebral ischemia; postherpetic neuralgia; social phobia; fibromyalgia and spinal cord injury induced chronic pains; neuropathic pains associated with diabetic peripheral neuropathy and common anxiety disorder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000221

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/197 A61K9/46 A61K9/16 A61K9/20 A61P25/00
A61P25/08
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 A61P

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 , BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/151745 Al (ELITE LAB INC [US] ; DICK CHRISTOPHER C [US] ; ERK0B0NI DAVID F [US] ; BE) 29 December 2010 (2010-12-29) paragraph [0033] - paragraph [0034] paragraph [0064] - paragraph [0065]	1-25
X	W0 2006/078811 A2 (PHARMAN0VA INC [US] ; QUAY PHARMACEUTICALS LTD [GB] ; BROWN RODNEY A [US) 27 July 2006 (2006-07-27) paragraph [0024] ; exampl e 1 cl aims 20-23	1-25
Y	EP 2 389 933 Al (SAN0VEL I LAC SANAYI VE TI CARET A S [TR]) 30 November 2011 (2011-11-30) cl aims 9-10	1-25

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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