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(54) Title: WATER DISPERSIBLE TABLETS OF LAMOTRIGINE

(57) Abstract: The present invention relates to water-dispersible tablets of lamotrigine and pharmaceutically acceptable acid addition salts thereof. The water-dispersible tablet includes granules or compacts. The granules or compacts include lamotrigine or a pharmaceutically acceptable salt thereof and one or more disintegrants. The one or more disintegrants are not swellable clay disintegrants. The tablet is capable of dispersing in water within a period of three minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710 µm in accordance with the test for dispersible tablets defined in British Pharmacopoeia 1988, volume II, page 895. The invention also relates to processes for the preparation of such tablets.



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WATER DISPERSIBLE TABLETS OF LAMOTRIGINE

Technical Field of the Invention

The present invention relates to water-dispersible tablets of lamotrigine and pharmaceutically acceptable acid addition salts thereof. The invention also relates to
5 processes for the preparation of such tablets.

Background of the Invention

Lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Lamotrigine is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

Conventional tablets are the most common delivery systems used for administering
10 therapeutically active compounds. However, in certain cases their use is limited by the problems associated with certain patients, such as the elderly and children, who have difficulty in swallowing. Also, this same difficulty arises in dosing critically ill patients in whom the ability to swallow anything is compromised. The solution to these problems is a dispersible tablet which when placed in water disperses to give a suspension which is
15 easily taken by the patient.

European Patent EP 685231 discloses a water-dispersible tablet that includes granules of 2% to 90% w/w lamotrigine and 0.25% to 40% w/w of a pharmaceutically acceptable swellable clay, such as smectite or attapulgit. The patent teaches the use of swellable clays as a disintegrant. Generally, the use of swellable clays in the manufacture
20 of tablets is avoided due to their off-white appearance, which causes discoloration in tablets, and because clays are prone to microbial contamination due to their origin from natural sources. Moreover, the viscosity also may vary due to their origin. Further, when the suspension produced by these tablets is consumed, it may give a feeling of chalkiness in the mouth. These factors may affect patient compliance.

25 The inventors have surprisingly found that dispersible tablets of lamotrigine can be prepared without using intragranular swellable clays and nonetheless the tablet is capable of dispersing in water within a period of 3 minutes to provide a suspension which passes through a sieve screen with a mesh aperture of 710 μ m in accordance with the test for dispersible tablets defined in the British Pharmacopoeia, 1988, volume II, page 895.

Summary of the Invention

In one general aspect there is provided a water-dispersible tablet that includes granules or compacts, the granules or compacts including lamotrigine or a pharmaceutically acceptable salt thereof and one or more disintegrants. The one or more
5 disintegrants are not swellable clay disintegrants. The tablet is capable of dispersing in water within a period of three minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710 μm in accordance with the test for dispersible tablets defined in British Pharmacopoeia 1988, volume II, page 895.

Embodiments of the tablet may include one or more of the following features. For
10 example, the tablet may be between about 2% w/w and about 90% w/w of lamotrigine or a pharmaceutically acceptable salt thereof.

The disintegrant may be one or more of cross-linked polyvinylpyrrolidone, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, alginic acid and alginates, pregelatinised starch, starch and starch derivatives,
15 low-substituted hydroxypropyl cellulose and combinations thereof. In particular, the disintegrant may be cross-linked polyvinylpyrrolidone and the tablet may include between about 3% w/w and about 10% w/w cross-linked polyvinylpyrrolidone. The disintegrant may be sodium starch glycolate and the tablet may include up to about 10% w/w sodium starch glycolate. The disintegrant may be between about 3% w/w and about 10% w/w
20 cross-linked polyvinylpyrrolidone and sodium starch glycolate. The disintegrant in particular may be cross-linked sodium carboxymethyl cellulose.

The tablet may further include one or more extragranular disintegrants, fillers, binders, flavours, lubricants and glidants. The extragranular disintegrant may be one or more of sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked sodium
25 carboxymethyl cellulose, calcium carboxymethyl cellulose, alginic acid and alginates, pregelatinised starch, starch and starch derivatives, low-substituted hydroxypropyl cellulose, swellable clays, smectite, attapulgite, montmorillonite, bentonite, magnesium aluminium silicate and combinations thereof. The filler may be one or more of calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulphate, microcrystalline
30 cellulose, pregelatinized starch, lactose, sucrose, dextrose, mannitol, sorbitol, xylitol and combinations thereof. The binder may be one or more of polyvinylpyrrolidone, starch

mucilage, pregelatinised starch, sodium alginate, alginic acid, acacia mucilage, tragacanth, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, carboxymethylcellulose calcium, ethyl cellulose, polyethylene glycol, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polymethacrylates, carboxyvinyl polymers, carbopols, and combinations thereof. In particular, the binder may be polyvinylpyrrolidone and/or hydroxypropylmethylcellulose.

The lubricant may be one or more of magnesium stearate, calcium stearate, sodium lauryl sulphate, sodium stearyl fumarate, magnesium lauryl sulphate, stearic acid, zinc stearate and polyethylene glycol. In particular, the lubricant may be magnesium stearate.

10 The glidant may be colloidal silicon dioxide.

In another general aspect there is provided a process for the preparation of a water-dispersible tablet of lamotrigine or a pharmaceutically acceptable salt thereof. The process includes preparing a mixture of lamotrigine or a pharmaceutically acceptable salt thereof with one or more disintegrants and optionally one or more pharmaceutically acceptable excipients, the disintegrants not being a swellable clay disintegrant; granulating the mixture with a binder solution or solvent to form granules or compacting the mixture to form compacts; blending the granules or compacts with one or more pharmaceutically acceptable excipients to form a blend; and compressing the blend to form a tablet. The tablet is capable of dispersing within a period of three minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of $710\ \mu\text{m}$ in accordance with the test for dispersible tablets defined in British Pharmacopoeia, 1988, volume II, page 895.

Embodiments of the process may include one or more of the following features. For example, the tablet may include between about 2% w/w and about 90% w/w of lamotrigine or a pharmaceutically acceptable salt thereof.

The disintegrant may be selected from one or more of cross-linked polyvinylpyrrolidone, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, alginic acid and alginates, pregelatinised starch, starch and starch derivatives, low-substituted hydroxypropyl cellulose and combinations thereof. In particular, the disintegrant may be about 3% w/w to about 10% w/w of cross-linked polyvinylpyrrolidone. The disintegrant may be up to about 10% w/w

of sodium starch glycolate. The disintegrant may be cross-linked polyvinylpyrrolidone and sodium starch glycolate being present at from about 3% w/w to about 10% w/w of the tablet.

5 The pharmaceutically acceptable excipients may be one or more of extragranular disintegrant, fillers, binders, flavours, lubricants and glidants. The extragranular disintegrant may be one or more of cross-linked polyvinylpyrrolidone, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, alginic acid and alginates, pregelatinised starch, starch and starch derivatives, low-substituted hydroxypropyl cellulose, swellable clays, smectite, attapulgit, 10 montmorillonite, bentonite, magnesium aluminium silicate and combinations thereof.

The filler may be one or more of calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulphate, microcrystalline cellulose, pregelatinized starch, lactose, sucrose, dextrose, mannitol, sorbitol, xylitol and combinations thereof. The binder may be one or more of polyvinylpyrrolidone, starch mucilage, pregelatinised starch, 15 sodium alginate, alginic acid, acacia mucilage, tragacanth, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, carboxymethylcellulose calcium, ethyl cellulose, polyethylene glycol, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polymethacrylates, carboxyvinyl polymers like carbopols and combinations thereof. The lubricant may be one or more of magnesium stearate, calcium stearate, sodium lauryl 20 sulphate, sodium stearyl fumarate, magnesium lauryl sulphate, stearic acid, zinc stearate and polyethylene glycol. The glidant may be colloidal silicon dioxide.

The process may further include drying the granules prior to compressing into tablets. The process may further include sizing the compacts prior to compressing into tablets. The solvent used in forming the granules may be one or more of water, ethanol, 25 methanol, isopropyl alcohol, dichloromethane, and acetone.

In another general aspect there is provided a method of treating epilepsy or bipolar disorder. The method includes administering a water-dispersible tablet that includes granules or compacts. The granules or compacts include lamotrigine or a pharmaceutically acceptable salt thereof and one or more disintegrants, the one or more 30 disintegrants not being swellable clay disintegrants. The tablet is capable of dispersing in water within a period of three minutes to provide a dispersion which is capable of passing

through a sieve screen with a mesh aperture of 710 μm in accordance with the test for dispersible tablets defined in British Pharmacopoeia 1988, volume II, page 895.

Embodiments of the method may include one or more of the following or any of the features described above. For example, the tablet may include between about 2% w/w
5 and about 90% w/w of lamotrigine or a pharmaceutically acceptable salt thereof.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

10 As used herein lamotrigine refers to its free base or acid addition salt, such as its methanesulphonate and isothionate salts. The concentration may vary from about 2%w/w to about 90%w/w lamotrigine or a lamotrigine salt.

The intragranular disintegrants as used herein include one or more of sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethyl
15 cellulose, calcium carboxymethyl cellulose, alginic acid and alginates, pregelatinised starch, starch and starch derivatives, low-substituted hydroxypropyl cellulose and combinations thereof. Additionally, the extragranular disintegrant may include swellable clays such as smectite, attapulgite, montmorillonite, bentonite, magnesium aluminium silicate and like. The disintegrant may be present in an amount of about 1%w/w to about
20 70%w/w, particularly about 1%w/w to about 50%w/w, and more particularly about 1% to about 40%w/w of the tablet.

Besides these ingredients, the tablet additionally may include one or more of fillers, binders, flavours, lubricants and glidants.

The fillers can be selected from one or more of the group consisting of calcium
25 carbonate, magnesium carbonate, calcium phosphate, calcium sulphate, microcrystalline cellulose, pregelatinized starch, lactose, sucrose, dextrose, mannitol, sorbitol, xylitol and combinations thereof. The amount of filler can vary from about 2%w/w to about 90%w/w, particularly from about 10%w/w to about 75%w/w of the tablet.

The binders can be selected from one or more of polyvinylpyrrolidone, starch mucilage, pregelatinised starch, sodium alginate, alginic acid, acacia mucilage, tragacanth, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, carboxymethylcellulose calcium, ethyl cellulose, polyethylene glycol, hydroxyethyl cellulose, hydroxypropyl
5 cellulose, methyl cellulose, polymethacrylates, carboxyvinyl polymers like carbopols and combinations thereof. The binder may be present in an amount of about 0.1%w/w to about 40%w/w, particularly about 0.1%w/w to about 30%w/w, and more particularly about 0.1%w/w to about 20%w/w of the tablet.

10 Flavours such as strawberry, raspberry, blackcurrant, orange, grape fruit and the like and sweeteners such as aspartame, saccharin sodium, lactose, dextrose, fructose, maltodextrin, maltose, mannitol and sorbitol can also be added.

The lubricants and glidants can be selected from one or more of magnesium stearate, calcium stearate, sodium lauryl sulphate, sodium stearyl fumarate, magnesium lauryl sulphate, stearic acid, zinc stearate, polyethylene glycol, colloidal silicon dioxide
15 and talc. The lubricant may be present from about 0.1%w/w to about 10%w/w of the tablet while the glidant may be present from about 0.1%w/w to about 3%w/w of the tablet.

In one of the embodiments, lamotrigine dispersible tablets are prepared by

- (i) preparing a mixture of lamotrigine or a pharmaceutically acceptable salt thereof with one or more of disintegrants, fillers, binders and
20 other excipients;
- (ii) granulating the mixture of step (i) with a granulating liquid such as a binder solution or solvent(s) such as water, ethanol, methanol, isopropyl alcohol, dichloromethane, acetone and mixtures thereof;
- (iii) drying the granules of step (ii) and blending the granules with one or
25 more extragranular excipients such as lubricant(s), glidant(s) and disintegrant(s); and
- (iv) compressing the mixture of step (iii) into a tablet using appropriate tooling.

In another embodiment, lamotrigine dispersible tablets are prepared by

- 5 (i) preparing a mixture of lamotrigine or a pharmaceutically acceptable salt thereof with one or more disintegrants, fillers, binders and other excipients;
- (ii) compacting the mixture of step (i) using compactor;
- (iii) sizing the compacts of step (ii) and blending them with extragranular excipients such as lubricant(s), glidant(s) and disintegrant(s); and
- (iv) compressing the mixture of step (iii) into a tablet using appropriate tooling.

10 The tablets prepared by these processes have sufficient hardness and less friability to withstand handling and storage. Typically, the tablet has a friability of 2% or less particularly 1% or less, and more particularly 0.5% or less. The tablet disperses quickly in water to give a fine suspension which is free from chalkiness and provides the intended dose uniformly. The tablets can also be swallowed as such like conventional tablets. The tablet disperses completely in water in about 2 minutes and particularly in about 1 minute.

15 The following examples are provided to enable one of ordinary skill in the art to prepare tablets of the invention and should not be construed as limiting the scope of the invention.

EXAMPLES 1-3

Ingredients	Quantity (mg)		
	Example 1	Example 2	Example 3
Lamotrigine	5	5	5
Calcium Carbonate	12	-	-
Microcrystalline Cellulose	20	32	12.5
Cross-linked polyvinylpyrrolidone	10	-	-
Sodium Starch Glycolate	-	10	5
Saccharin Sodium	1	1	1
Povidone K-30	3	3	1.5
Purified water	q. s.	q. s.	q. s.
Flavour	1	1	1
Low Substituted Hydroxypropyl cellulose	15	15	7.5
Microcrystalline Cellulose	20	20	10
Cross-linked polyvinylpyrrolidone	10	-	-
Sodium Starch Glycolate	-	10	5
Talc	1	1	0.5
Colloidal Silicon Dioxide	1	1	0.5
Magnesium Stearate	1	1	0.5
Total	100	100	50

Procedure:**Example 1**

Lamotrigine, microcrystalline cellulose, cross-linked polyvinylpyrrolidone, calcium carbonate, saccharin sodium and povidone K-30 were sifted through a 30# mesh and mixed for 10 minutes to form a blend. The blend was then granulated with a sufficient quantity of purified water to form granules. The granules were dried in a fluid bed dryer and sifted through a 25# sieve. Cross-linked polyvinylpyrrolidone, flavour, low-substituted hydroxypropylcellulose, microcrystalline cellulose, talc and colloidal silicon dioxide were sifted through a 40# sieve and mixed with the dried granules. This blend was then mixed with magnesium stearate and compressed using appropriate tooling.

Examples 2 and 3

The tablets of Examples 2 and 3 were prepared by following the procedure of Example 1 except that sodium starch glycolate was used in place of cross-linked polyvinylpyrrolidone.

15 EXAMPLES 4-6

Ingredients	Quantity (mg)		
	Example 4	Example 5	Example 6
Lamotrigine	200	5	2
Calcium Carbonate	25	6.25	2.5
Microcrystalline Cellulose	125	62	26.15
Cross-linked polyvinylpyrrolidone	16	4	1.6
Povidone K-30	15	3.75	1.5
Purified water	q.s.	q.s.	q.s.
Flavour	5	1.25	0.5
Aspartame	20	5	1.25
Low Substituted Hydroxypropyl cellulose	15	7.75	3.1
Microcrystalline Cellulose	55	24	9.6
Cross-linked polyvinylpyrrolidone	16	4	1
Talc	2	0.5	0.2
Colloidal Silicon Dioxide	2	0.5	0.2
Magnesium Stearate	4	1	0.4
Total	500	125	50

Procedure: Same as above

EXAMPLE 7

Ingredients	Quantity (mg)
	Example 7
Lamotrigine	200
Calcium Carbonate	25
Microcrystalline Cellulose	180
Cross-linked polyvinylpyrrolidone	16
Povidone K-30	15
Flavour	5
Aspartame	20
Low Substituted Hydroxypropyl cellulose	15
Cross-linked polyvinylpyrrolidone	16
Talc	2
Colloidal Silicon Dioxide	2
Magnesium Stearate	4
Total	500

Procedure:

Lamotrigine, microcrystalline cellulose, cross-linked polyvinylpyrrolidone, calcium carbonate, and povidone K-30 were sifted through a 30# mesh and mixed for 10 minutes to form a blend. The blend was then compacted using a compactor. The compacts were passed through a 25# sieve. Cross-linked polyvinylpyrrolidone, flavour, low-substituted hydroxypropylcellulose, aspartame, microcrystalline cellulose, talc and colloidal silicon dioxide were sifted through a 36# sieve and mixed with the granules. This blend was then mixed with magnesium stearate and compressed using appropriate tooling.

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

We claim:

- 1 1. A water-dispersible tablet comprising granules or compacts, the granules or
2 compacts comprising lamotrigine or a pharmaceutically acceptable salt thereof and
3 one or more disintegrants, the one or more disintegrants not being swellable clay
4 disintegrants and the tablet being capable of dispersing in water within a period of
5 three minutes to provide a dispersion which is capable of passing through a sieve
6 screen with a mesh aperture of 710 μm in accordance with the test for dispersible
7 tablets defined in British Pharmacopoeia 1988, volume II, page 895.
- 1 2. The water-dispersible tablet according to claim 1, wherein the tablet comprises
2 between about 2% w/w and about 90% w/w of lamotrigine or a pharmaceutically
3 acceptable salt thereof.
- 1 3. The water-dispersible tablet according to claim 1 wherein the disintegrant
2 comprises one or more of cross-linked polyvinylpyrrolidone, sodium starch
3 glycolate, cross-linked sodium carboxymethyl cellulose, calcium carboxymethyl
4 cellulose, alginic acid and alginates, pregelatinised starch, starch and starch
5 derivatives, low-substituted hydroxypropyl cellulose and combinations thereof.
- 1 4. The water-dispersible tablet according to claim 3 wherein the disintegrant
2 comprises cross-linked polyvinylpyrrolidone.
- 1 5. The water-dispersible tablet according to claim 4 wherein the tablet comprises
2 between about 3% w/w and about 10% w/w cross-linked polyvinylpyrrolidone.
- 1 6. The water-dispersible tablet according to claim 3 wherein the disintegrant
2 comprises sodium starch glycolate.
- 1 7. The water-dispersible tablet according to claim 6 wherein the tablet comprises up
2 to about 10% w/w sodium starch glycolate.
- 1 8. The water-dispersible tablet according to claim 3, wherein the disintegrant
2 comprises between about 3% w/w and about 10% w/w cross-linked
3 polyvinylpyrrolidone and sodium starch glycolate.

- 1 9. The water-dispersible tablet according to claim 3 wherein the disintegrant
2 comprises cross-linked sodium carboxymethyl cellulose.
- 1 10. The water-dispersible tablet according to claim 1 wherein the tablet further
2 comprises one or more extragranular disintegrants, fillers, binders, flavours,
3 lubricants and glidants.
- 1 11. The water-dispersible tablet according to claim 10 wherein the extragranular
2 disintegrant comprises one or more of sodium starch glycolate, cross-linked
3 polyvinylpyrrolidone, cross-linked sodium carboxymethyl cellulose, calcium
4 carboxymethyl cellulose, alginic acid and alginates, pregelatinised starch, starch
5 and starch derivatives, low-substituted hydroxypropyl cellulose, swellable clays,
6 smectite, attapulgite, montmorillonite, bentonite, magnesium aluminium silicate
7 and combinations thereof.
- 1 12. The water-dispersible tablet according to claim 10 wherein the filler comprises one
2 or more of calcium carbonate, magnesium carbonate, calcium phosphate, calcium
3 sulphate, microcrystalline cellulose, pregelatinized starch, lactose, sucrose,
4 dextrose, mannitol, sorbitol, xylitol and combinations thereof.
- 1 13. The water-dispersible tablet according to claim 10 wherein the binder comprises
2 one or more of polyvinylpyrrolidone, starch mucilage, pregelatinised starch,
3 sodium alginate, alginic acid, acacia mucilage, tragacanth, hydroxypropylmethyl
4 cellulose, carboxymethylcellulose sodium, carboxymethylcellulose calcium, ethyl
5 cellulose, polyethylene glycol, hydroxyethyl cellulose, hydroxypropyl cellulose,
6 methyl cellulose, polymethacrylates, carboxyvinyl polymers, carbopols, and
7 combinations thereof.
- 1 14. The water-dispersible tablet according to claim 13 wherein the binder comprises
2 polyvinylpyrrolidone.
- 1 15. The water-dispersible tablet according to claim 13 wherein the binder comprises
2 hydroxypropylmethylcellulose.
- 1 16. The water-dispersible tablet according to claim 10 wherein the lubricant comprises
2 one or more of magnesium stearate, calcium stearate, sodium lauryl sulphate,

3 sodium stearyl fumarate, magnesium lauryl sulphate, stearic acid, zinc stearate and
4 polyethylene glycol.

1 17. The water-dispersible tablet according to claim 15 wherein the lubricant comprises
2 magnesium stearate.

1 18. The water-dispersible tablet according to claim 10 wherein the glidant comprises
2 colloidal silicon dioxide.

1 19. A process for the preparation of a water-dispersible tablet of lamotrigine or a
2 pharmaceutically acceptable salt thereof, the process comprising:
3 preparing a mixture of lamotrigine or a pharmaceutically acceptable salt
4 thereof with one or more disintegrants and optionally one or more pharmaceutically
5 acceptable excipients, the disintegrants not being a swellable clay disintegrant;
6 granulating the mixture with a binder solution or solvent to form granules
7 or compacting the mixture to form compacts;
8 blending the granules or compacts with one or more pharmaceutically
9 acceptable excipients to form a blend; and
10 compressing the blend to form a tablet,
11 wherein the tablet is capable of dispersing within a period of three minutes
12 to provide a dispersion which is capable of passing through a sieve screen with a
13 mesh aperture of 710 μm in accordance with the test for dispersible tablets defined
14 in British Pharmacopoeia, 1988, volume II, page 895.

1 20. The process according to claim 19, wherein the tablet comprises between about 2%
2 w/w and about 90% w/w of lamotrigine or a pharmaceutically acceptable salt
3 thereof.

1 21. The process according to claim 19 wherein the disintegrant is selected from one or
2 more of cross-linked polyvinylpyrrolidone, sodium starch glycolate, cross-linked
3 sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, alginic acid
4 and alginates, pregelatinised starch, starch and starch derivatives, low-substituted
5 hydroxypropyl cellulose and combinations thereof.

1 22. The process according to claim 21 wherein the disintegrant comprises about 3%
2 w/w to about 10% w/w of cross-linked polyvinylpyrrolidone.

- 1 23. The process according to claim 21 wherein the disintegrant comprises up to about
2 10% w/w of sodium starch glycolate.
- 1 24. The process according to claim 21 wherein the disintegrant comprises cross-linked
2 polyvinylpyrrolidone and sodium starch glycolate being present at from about 3%
3 w/w to about 10% w/w of the tablet.
- 1 25. The process according to claim 19 wherein the pharmaceutically acceptable
2 excipients comprise one or more of extragranular disintegrant, fillers, binders,
3 flavours, lubricants and glidants.
- 1 26. The process according to claim 25 wherein the extragranular disintegrant
2 comprises one or more of cross-linked polyvinylpyrrolidone, sodium starch
3 glycolate, cross-linked sodium carboxymethyl cellulose, calcium carboxymethyl
4 cellulose, alginic acid and alginates, pregelatinised starch, starch and starch
5 derivatives, low-substituted hydroxypropyl cellulose, swellable clays, smectite,
6 attapulgite, montmorillonite, bentonite, magnesium aluminium silicate and
7 combinations thereof.
- 1 27. The process according to claim 25 wherein the filler comprises one or more of
2 calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulphate,
3 microcrystalline cellulose, pregelatinized starch, lactose, sucrose, dextrose,
4 mannitol, sorbitol, xylitol and combinations thereof.
- 1 28. The process according to in claim 25 wherein the binder comprises one or more of
2 polyvinylpyrrolidone, starch mucilage, pregelatinised starch, sodium alginate,
3 alginic acid, acacia mucilage, tragacanth, hydroxypropylmethyl cellulose,
4 carboxymethylcellulose sodium, carboxymethylcellulose calcium, ethyl cellulose,
5 polyethylene glycol, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl
6 cellulose, polymethacrylates, carboxyvinyl polymers like carbopols and
7 combinations thereof.
- 1 29. The process according to claim 25 wherein the lubricant comprises one or more of
2 magnesium stearate, calcium stearate, sodium lauryl sulphate, sodium stearyl
3 fumarate, magnesium lauryl sulphate, stearic acid, zinc stearate and polyethylene
4 glycol.

- 1 30. The process according to claim 25 wherein the glidant comprises colloidal silicon
2 dioxide.
- 1 31. The process according to claim 19, further comprising drying the granules prior to
2 compressing into tablets.
- 1 32. The process according to claim 19, further comprising sizing the compacts prior to
2 compressing into tablets.
- 1 33. The process according to claim 19 wherein the solvent comprises one or more of
2 water, ethanol, methanol, isopropyl alcohol, dichloromethane, and acetone.
- 1 34. A method of treating epilepsy or bipolar disorder, the method comprising
2 administering a water-dispersible tablet comprising granules or compacts, the
3 granules or compacts comprising lamotrigine or a pharmaceutically acceptable salt
4 thereof and one or more disintegrants, the one or more disintegrants not being
5 swellable clay disintegrants and the tablet being capable of dispersing in water
6 within a period of three minutes to provide a dispersion which is capable of
7 passing through a sieve screen with a mesh aperture of 710 μm in accordance with
8 the test for dispersible tablets defined in British Pharmacopoeia 1988, volume II,
9 page 895.
- 1 35. The method according to claim 34, wherein the tablet comprises between about 2%
2 w/w and about 90% w/w of lamotrigine or a pharmaceutically acceptable salt
3 thereof.

INTERNATIONAL SEARCH REPORT

International Application No

IB2004/001640

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/00 A61K31/53 A61K9/20

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)

IPC 7 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 practical, search terms used)

WPI Data, EPO-Internal, PAJ, 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	ANONYMOUS: "Lamictal dispersible - lamotrigine" INTERNET ARTICLE, 'Online! April 2003 (2003-04), XP002297185 Retrieved from the Internet: <URL:http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=3954> 'retrieved on 2004-09-21!	1-18, 34, 35
Y	Patient information leaflet last revised April 2003 the whole document	19-33
Y	EP 0 685 231 A (WELLCOME FOUND) 6 December 1995 (1995-12-06) cited in the application page 7, line 34-44 page 5, line 51 -page 6, line 2 -/--	19-33

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in 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 document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *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

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *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

23 September 2004

Date of mailing of the international search report

21/10/2004

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INTERNATIONAL SEARCH REPORT

International Application No

IB2004/001640

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96/17611 A (WELLCOME FOUND ; HISKETT SIMON PHILIP (GB); TAYLOR SUSAN ANN (GB)) 13 June 1996 (1996-06-13) page 3, line 5-8; claim 1 page 4, line 22 -page 5, line 1 -----	19-33
A	WO 95/05179 A (WELLCOME FOUND ; PURIFOY DOROTHY JANE MARTIN (GB); FIDDIAN ANTHONY PAU) 23 February 1995 (1995-02-23) page 5, line 9,10 page 5, line 15-20; examples 1-4 -----	1-33
A	US 4 486 354 A (MILLER ALISTAIR A ET AL) 4 December 1984 (1984-12-04) column 2, line 57 page 3, line 58-63 column 10 -----	1-35
P,A	WO 03/104192 A (TORRENT PHARMACEUTICALS LTD) 18 December 2003 (2003-12-18) claims 1,5,9,15 -----	1-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/001640

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 34-35
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 34 and 35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 34-35

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

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IB2004/001640

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