

A&A Ref: 149717

PUBLICATION PARTICULARS AND ABSTRACT
(Section 32(3)(a) - Regulations 22(1)(g) and 31)

21	01	PATENT APPLICATION NO	22	LODGING DATE	43	ACCEPTANCE DATE
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• • 2004 / 1550

25 February 2004

17-11-2004

51	INTERNATIONAL CLASSIFICATION	NOT FOR PUBLICATION
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A61K, A61P

CLASSIFIED BY: ISA

71	FULL NAME(S) OF APPLICANT(S)
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AstraZeneca AB

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EARLIEST PRIORITY CLAIMED	COUNTRY	NUMBER	DATE
	33 SE	31 0102855-4	32 27 August 2001

NOTE: The country must be indicated by its International Abbreviation - see schedule 4 of the Regulations

54	TITLE OF INVENTION
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A combination of quetiapine and zolmitriptan

57	ABSTRACT (NOT MORE THAN 150 WORDS)
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NUMBER OF SHEETS 25

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.

~~The figure of the drawing to which the abstract refers is attached.~~

(54) Title: A COMBINATION OF QUETIAPINE AND ZOLMITRIPTAN

(57) Abstract: The present invention relates to a combination comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof, pharmaceutical compositions, processes for its preparation, the use thereof in the manufacture of a medicament and a method of treatment of disease and more particularly to a method of treatment of diseases typically treated with 5-HT_{1D} agonists and/or atypical antipsychotics, in particularly, migraine, related conditions and for reducing or eliminating of migraine recurrence.

A COMBINATION OF QUETIAPINE AND ZOLMITRIPTAN

The present invention relates to a combination comprising the antipsychotic dopamine D₂/5-HT_{2A} agent quetiapine or a pharmaceutically acceptable salt thereof and the 5-HT_{1B/1D} agonist zolmitriptan or a pharmaceutically acceptable salt thereof, pharmaceutical compositions, processes for its preparation, the use thereof in the manufacture of a medicament and a method of treatment of disease and more particularly to a method of treatment of diseases typically treated with 5-HT_{1B/1D} agonists and/or atypical antipsychotics. Such diseases include psychoses and related disorders, and migraine and related disorders. In particular, migraine or related conditions, and for reducing or eliminating of migraine recurrence.

The co-administration of quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof leads to benefits over existing therapies.

Quetiapine has the chemical name 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine and is an antipsychotic agent that has been sold as the fumarate salt under the trademark Seroquel™ for a number of years. Quetiapine fumarate is marketed for the treatment of schizophrenia and related disease conditions. A considerable body of literature describes how to use quetiapine fumarate. Specific references for the preparation and use of this agent are EP 240228 and 282236, US 4,879,288 and WO 97/45124.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl)-1H-indol-5-yl]methyl}-2-oxazolidinone. Specific references for the preparation and use of this agent are EP 486666 and WO 97/06162. Zolmitriptan is a selective 5-HT_{1B/1D}-receptor agonist. During migraine excessive cerebrovascular dilation and neurogenic inflammatory processes are considered to contribute to pain. The 5-HT_{1B/1D}-receptors mediate cerebrovascular vasoconstriction and inhibit neurogenic inflammation.

5-HT_{1B/1D} receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction and neurogenic inflammation in the cerebrovascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as migraine.

Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine and the treatment (direct and
5 prophylactic) of related conditions.

The co-administration of quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof is expected to provide benefit in the treatment of migraine and related conditions for example the symptomatic treatment of
10 pain relief, decreasing nausea, decreasing photophobia and phonophobia.

For example benefits may include greater efficacy where response to zolmitriptan alone is not as good as expected; greater efficacy (for example reduction in frequency and/or severity of episodes) against migraine attacks and their symptoms for example against persistent headache where recurrence is a problem and the rate of relapse needs to
15 be reduced or eliminated including for example as part of a withdrawal regimen; where a migraine patient also suffers from psychoses, depression or anxiety; and a further benefit could be that lower doses of zolmitriptan may be given leading to greater tolerability and/or safety. In summary, the benefits may include increased number of patients that exhibit efficacy to zolmitriptan, increased number of patients that achieve pain-free status
20 or near pain-free status, and decreased frequency of headache recurrence. Accordingly, the present invention provides a combination comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof.

Other objects of the present invention provides a pharmaceutical composition comprising said combination, processes for the preparation of said combinations, a kit
25 comprising said combination, optionally with instructions for use, and the use of said combination for the manufacture of a medicament for the treatment of migraine and related disorders, and for reduction or elimination of migraine recurrence.

A further object of the present invention provides a method of treating migraine or a related condition in a mammal which comprises administering to said mammal an amount
30 of quetiapine or a pharmaceutically acceptable salt thereof and an amount of zolmitriptan or a pharmaceutically acceptable salt thereof so that the combination is effective in treating migraine or the related condition.

Another further object of the present invention provides a method of treating reduction or elimination of migraine recurrence in a mammal which comprises administering to said mammal an amount of quetiapine or a pharmaceutically acceptable salt thereof and an amount of zolmitriptan or a pharmaceutically acceptable salt thereof so that the combination is effective in treating reduction or elimination of migraine recurrence.

Quetiapine has demonstrated efficacy against agitation and anxiety; agitation and anxiety may contribute to the onset and persistence of migraine headaches leading to a further benefit of using quetiapine and zolmitriptan in combination.

Treating includes the direct and prophylactic treatment of migraine or related condition. Direct treatment includes elimination, reduction and alleviation of the disease and/or symptoms; prophylactic treatment includes preventative measures.

Migraine and related conditions include conditions wherein vasoconstriction in the carotid vascular bed is indicated; for example, migraine, cluster headache, headache associated with vascular disorders and aura.

Quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof may be administered in the same formulation (co-formulation) or separately, conveniently using marketed dosage forms and strengths.

The dosage form, dosage strength and frequency of dosing of zolmitriptan administered depends on various factors known in the art including the weight, age and sex of the patient being treated and the particular migraine disease condition being treated. Typically, a unit dose of about 0.5 mg to 15 mg (for example, 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10 mg) of zolmitriptan is administered to the patient in need thereof. Zolmitriptan may be administered orally, intravenously, intranasally or by a fast-melt formulation that rapidly dissolves in the mouth. Typically, a daily dose for an adult human is in the range of about 0.5 mg to about 15 mg per day depending on the route of administration and the particular needs of the patient.

Formulations of zolmitriptan may be prepared according to EP 486666, WO 01/39772, US 5,178,878, US 6,024,981 and according to methods generally known in the art of formulation technology.

The dosage form, dosage strength and frequency of dosing of quetiapine administered also depends on the various factors known in the art including the weight, age and sex of the patient being treated. Typically, a unit dose of about 5 mg to 50 mg (for example, 5

mg, 10 mg, 25 mg and 40 mg) of quetiapine is administered to the patient in need thereof. Quetiapine may be administered parenterally or may be administered orally either in a conventional tablet or capsule or in a modified formulation such as a controlled, delayed or sustained release formulation.

5 Formulations of quetiapine may be prepared according to EP 240228 and according to methods generally known in the art of formulation technology. WO 01/21179 describes a formulation in the form of granules of quetiapine, which could be a further aspect of administration.

10 In a particular aspect, quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally or intranasally; preferably the drugs are administered orally, particularly the zolmitriptan is administered as a tablet or a fast melt formulation. Suitably zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a 2.5mg or 5mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is administered
15 in a 25mg unit dose.

20 In another particular aspect, quetiapine or a pharmaceutically acceptable salt thereof is administered in a controlled, delayed or sustained release dosage form. For example, dosage forms according to WO 97/45124 may be used. Such dosage forms provide a generally uniform and constant rate of release over an extended period of time to achieve a stable, desired blood (plasma) level of quetiapine without the need for frequent
20 administration. This is particularly beneficial if the patient suffers from recurring migraine attacks as a stable level of quetiapine can be maintained.

25 In a particular aspect, the amount of zolmitriptan administered to a patient in need thereof can be lower than the amount of zolmitriptan that would be required if zolmitriptan were administered in the absence of quetiapine. Lower amounts of zolmitriptan may avoid side effects and/or improve tolerability in certain patients. In another particular aspect, the amount of quetiapine administered to a patient in need thereof can be lower than the amount of quetiapine that would be required if quetiapine were administered in the absence of zolmitriptan. Lower amounts of quetiapine may avoid side effects and/or improve
30 tolerability in certain patients.

 In another particular aspect, the administration of zolmitriptan and quetiapine can lead to greater and/or longer efficacy than would be the case in the absence of quetiapine.

In another aspect, quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof may be formulated in the same pharmaceutical composition with pharmaceutically acceptable carriers. Such a pharmaceutical composition may be administered orally (e.g. tablets, capsules) or by
5 injection (e.g. a solution). Such compositions may be prepared in a conventional manner with suitable pharmaceutically acceptable carriers such as binding agents, fillers, disintegrates and solubilizing agents.

There are currently no animal models of migraine that are considered to be completely predictive of efficacy in humans. However, animal models are available that are
10 considered to mimic important aspects of migraine pathophysiology. The injection of lipopolysaccharides (LPS) into the cerebral ventricles of rats causes cerebral inflammation, an inflammatory process that may occur in migraine. Directing an air puff to the head of the rat and measuring ultrasonic vocalizations can assess the pain resulting from this process. This method is described in detail below:

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i) Administration of LPS

Rats are allowed to habituate in the experimental laboratory for 15-20 minutes prior to treatment. Cerebral inflammation is induced by administration of LPS (endotoxin of gram-negative *E. coli* bacteria serotype 0111:B4, Sigma). LPS (2.4µg) is injected intracerebro-
20 ventricularly (i.c.v.), in a volume of 10µl, using standard stereotaxic surgical techniques under isoflurane anesthesia. The skin between the ears is pushed rostrally and a longitudinal incision of about 1cm is made to expose the skull surface. The puncture site is determined by the coordinates: 0.8 mm posterior to the bregma, 1.5 mm lateral (left) to the lambda (sagittal suture), and 5 mm below the surface of the skull (vertical) in the lateral
25 ventricle. LPS is injected via a sterile stainless steel needle (26-G 3/8) of 5 mm long attached to a 100-µl Hamilton syringe by polyethylene tubing (PE20; 10-15 cm). A 4 mm stopper made from a cut needle (20-G) is placed over and secured to the 26-G needle by silicone glue to create the desired 5mm depth.

Following the injection of LPS, the needle remains in place for an additional 10
30 seconds to allow diffusion of LPS, then is removed. The incision is closed, and the rat is returned to its original cage and is allowed to rest for a minimum of 3.5 hours prior to testing.

ii) Experimental setup for air-puff stimulation

The rats remain in the experimental laboratory following LPS injection and drug administration. At the time of testing all rats are removed and placed outside the laboratory. One rat at a time is brought into the testing laboratory and placed in a clear box (9 × 9 × 18 cm) which is then placed in a sound-attenuating ventilated cubicle measuring 62(w) × 35(d) × 46(h) cm (BRS/LVE, Div. Tech-Serv Inc). Air-puffs are delivered, through an air output nozzle of 0.32 cm, which is controlled by a system (AirStim, San Diego Instruments) capable of delivering puffs of air of fixed duration (0.2 s) and fixed intensity with a frequency of 1 puff per 10 seconds. A maximum of 10 puffs are administered, or until vocalization starts, whichever comes first. The first air puff marks the start of recording.

iii) Experimental setup for and ultrasound recording

The vocalizations are recorded for 10 minutes using microphones (G.R.A.S. sound and vibrations, Vedbaek, Denmark) placed inside each cubicle and controlled by LMS (LMS CADA-X 3.5B, Data Acquisition Monitor, Troy, Michigan) software. The frequencies between 0 and 32000Hz are recorded, saved and analyzed by the same software (LMS CADA-X 3.5B, Time Data Processing Monitor and UPA (User Programming and Analysis)). The number of ultrasonic vocalizations induced by air puffs is taken as a measure of pain experienced by the rats.

iv) Analysis

The recordings are run through a series of statistical and Fourier analyses to filter (between 20-24kHz) and to calculate the parameters of interest. The data are expressed as the mean ± SEM. Statistical significance are assessed using T-test for comparison between naive and LPS-treated rats, and one way ANOVA followed by Dunnett's multiple comparison test (post-hoc) for drug effectiveness. A difference between groups is considered significant with a minimum p value of ≤ 0.05 . Experiments are repeated a minimum of two times.

Examples

- 1) An adult patient experiencing the onset of migraine is treated with quetiapine fumarate (25 mg) and zolmitriptan (5 mg). Quetiapine fumarate is administered as a tablet ('Seroquel') and zolmitriptan is also administered as a tablet ('Zomig').

- 2) A tablet is prepared as follows:

	<u>mg</u>	
10	Quetiapine Fumarate	28
	Zolmitriptan	5
	Povidone	7.00
	Calcium Hydrogen Phosphate	8.72
	Microcrystalline cellulose	28.50
15	Lactose monohydrate	19.00
	Sodium starch glycollate	7.00
	Magnesium stearate	1.00

Coating

20	Methylhydroxypropylcellulose	1.56
	Macrogel 400	0.31
	Titanium dioxide	0.59
	Ferric oxide, red	0.02
	Ferric oxide, yellow	0.02

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The ingredients are mixed with purified water, blended and compressed into tablets, which are then coated.

CLAIMS

1. A combination comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof.
2. A combination according to claim 1 for use simultaneously, sequentially or separately as a medicament.
3. A combination according to claim 1 for use simultaneously, sequentially or separately for the treatment of migraine or related conditions.
4. A combination according to claim 1 for use simultaneously, sequentially or separately for reducing or eliminating of migraine recurrence.
5. A combination according to anyone of claims 1-4 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally or intranasally.
6. A combination according to claim 5 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally.
7. A combination according to claim 6 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered as a tablet and zolmitriptan or a pharmaceutically acceptable salt thereof is administered as a tablet.
8. A combination according to any one of claims 1-7 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered as a fast melt formulation.

9. A combination according to any one of claims 1-7 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered in a controlled delayed or sustained release dosage form.
10. A combination according to any one of claims 1-9 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a unit dose of about 0.5 to 15 mg and quetiapine or a pharmaceutically acceptable salt thereof is administered in a unit dose of about 5 to 50 mg.
11. A combination according to claim 10 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a 5 mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is administered in a 25 mg unit dose.
12. A combination according to any one of claims 1-11 wherein the quetiapine pharmaceutically acceptable salt is quetiapine fumarate.
13. A combination according to any one of claims 1-12 comprising zolmitriptan and quetiapine fumarate.
14. A pharmaceutical composition comprising the combination according to any one of claims 1-13 and optionally a pharmaceutical carrier or diluent.
15. A pharmaceutical composition according to claim 14 for use simultaneously, sequentially or separately as a medicament.
16. A pharmaceutical composition according to claim 15 for use simultaneously, sequentially or separately in the treatment of migraine or related conditions.
17. A first pharmaceutical composition comprising quetiapine or a pharmaceutically acceptable salt thereof and optionally a pharmaceutical carrier or diluent and a second pharmaceutical composition comprising zolmitriptan or a pharmaceutically acceptable salt thereof and optionally a pharmaceutical carrier or diluent.

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18. Use of a combination comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of migraine or related conditions.
19. Use of a combination comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for reducing or eliminating migraine recurrence.
20. A method for lowering the unit dose of zolmitriptan or a pharmaceutically acceptable salt thereof by administration of a combination according to any one of claims 1-17.
21. Use of a combination according to any one of claims 1-17, in the manufacture of a medicament for reducing the frequency and/or severity of episodes of migraine attacks and their symptoms.
22. Use of quetiapine or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use with zolmitriptan or a pharmaceutically acceptable salt thereof for reducing or eliminating migraine recurrence.
23. A method for improving the efficacy of zolmitriptan or a pharmaceutically acceptable salt thereof by using quetiapine or a pharmaceutically acceptable salt thereof.
24. Use of quetiapine or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use with zolmitriptan or a pharmaceutically acceptable salt thereof for treating migraine or a related condition in a mammal.
25. Use according to claim 24 wherein the medicament and the zolmitriptan or a pharmaceutically acceptable salt thereof are administrable simultaneously, sequentially or separately.

26. Use of quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of a disease, disorder or condition.
27. Use of quetiapine or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use with zolmitriptan or a pharmaceutically acceptable salt thereof for treatment of a disease, disorder or condition, wherein said medicament and said zolmitriptan or a pharmaceutically acceptable salt thereof are administrable simultaneously, sequentially or separately.
28. Use of zolmitriptan or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use with quetiapine or a pharmaceutically acceptable salt thereof for treatment of a disease, disorder or condition, wherein said medicament and said quetiapine or a pharmaceutically acceptable salt thereof are administrable simultaneously, sequentially or separately.
29. Use according to any one of claims 22 or 24 or 26 to 28 wherein quetiapine or a pharmaceutically acceptable salt thereof is administrable orally and the zolmitriptan or a pharmaceutically acceptable salt thereof is administrable orally or intranasally.
30. Use according to claim 29 wherein quetiapine or a pharmaceutically acceptable salt thereof is administrable orally and the zolmitriptan or a pharmaceutically acceptable salt thereof is administrable orally.
31. Use according to claim 30 wherein quetiapine or a pharmaceutically acceptable salt thereof is administrable as a tablet and the zolmitriptan or a pharmaceutically acceptable salt thereof is administrable as a tablet.
32. Use according to any one of claims 18, or 19, or 22, or 24 to 31, wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administrable

as a fast melt formulation.

33. Use according to any one of claims 18, or 19, or 22, or 24 to 31, wherein quetiapine or a pharmaceutically acceptable salt thereof is administrable in a controlled, delayed or sustained release dosage form.
34. Use according to any one of claims 22, or 24 to 33, wherein zolmitriptan or a pharmaceutically acceptable salt thereof is effective in a unit dose of about 0.5 to 15 mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is effective in a unit dose of about 5 to 50 mg unit dose.
35. Use according to claim 34 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is effective in a 5 mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is effective in a 25 mg unit dose.
36. Use according to any one of claims 18, or 19, or 22, or 24 to 35, wherein the quetiapine pharmaceutically acceptable salt is quetiapine fumarate.
37. Use of zolmitriptan and quetiapine fumarate according to any one of claims 18, or 19, or 22, or 24 to 35.
38. A process for the preparation of a combination according to any one of claims 1- 16 wherein quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof are incorporated in the same pharmaceutical composition.
39. A process for the preparation of a combination according to any one of claims 1-17 wherein quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof are in different pharmaceutical composition.
40. A kit comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof, optionally with instructions and/or labeling for the use.

41. The kit according to claim 40 wherein quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof are for simultaneous or contemporaneous administration.
42. A substance or composition for use in a method treatment, said substance or composition comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition.
43. A substance or composition for use with zolmitriptan or a pharmaceutically acceptable salt thereof in a method of treatment, said substance or composition comprising quetiapine or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition and said zolmitriptan or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately.
44. A substance or composition for use with quetiapine or a pharmaceutically acceptable salt thereof in a method of treatment, said substance or composition comprising zolmitriptan or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition and said quetiapine or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately.
45. A substance or composition for use in a method for the treatment of migraine or related conditions, said substance or composition comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition.
46. A substance or composition for use with zolmitriptan or a pharmaceutically acceptable salt thereof in a method for the treatment of migraine or related conditions, said substance or composition comprising quetiapine or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition and said zolmitriptan simultaneously, sequentially or separately.

47. A substance or composition for use with quetiapine or a pharmaceutically acceptable salt thereof in a method for the treatment of migraine or related conditions, said substance or composition comprising zolmitriptan or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition and said quetiapine or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately.
48. A substance or composition for use in a method for reducing or eliminating migraine recurrence, said substance or composition comprising quetiapine or a pharmaceutically acceptable salt thereof and zolmitriptan or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition.
49. A substance or composition for use with zolmitriptan or a pharmaceutically acceptable salt thereof in a method for reducing or eliminating migraine recurrence, said substance or composition comprising quetiapine or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition and said zolmitriptan or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately.
50. A substance or composition for use with quetiapine or a pharmaceutically acceptable salt thereof in a method for reducing or eliminating migraine recurrence, said substance or composition comprising zolmitriptan or a pharmaceutically acceptable salt thereof, and said method comprising administering said substance or composition and said quetiapine simultaneously, sequentially or separately.
51. A substance or composition for use in a method of treatment according to any one of claims 43, or 44, or 46, or 47, or 49, or 50 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally or intranasally.

52. A substance or composition for use in a method of treatment according to claim 51 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered orally and zolmitriptan or a pharmaceutically acceptable salt thereof is administered orally.
53. A substance or composition for use in a method of treatment according to claim 52 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered as a tablet and zolmitriptan or a pharmaceutically acceptable salt thereof is administered as a tablet.
54. A substance or composition for use in a method of treatment according to any one of claims 41 to 53 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered as a fast melt formulation.
55. A substance or composition for use in a method of treatment according to any one of claims 41 to 53 wherein quetiapine or a pharmaceutically acceptable salt thereof is administered in a controlled delayed or sustained release dosage form.
56. A substance or composition for use in a method of treatment according to any one of claims 42 to 55 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a unit dose of about 0.5 to 15 mg and quetiapine or a pharmaceutically acceptable salt thereof is administered in a unit dose of about 5 to 50 mg.
57. A substance or composition for use in a method of treatment according to claim 56 wherein zolmitriptan or a pharmaceutically acceptable salt thereof is administered in a 5 mg unit dose and quetiapine or a pharmaceutically acceptable salt thereof is administered in a 25 mg unit dose.
58. A substance or composition for use in a method of treatment according to any one of claims 41 to 57 wherein the quetiapine pharmaceutically acceptable salt is quetiapine fumarate.
59. A substance or composition for use in a method of treatment according to

any one of claims 41 to 58 wherein zolmitriptan and quetiapine fumarate are used.

60. A substance or composition for use in a method for reducing the frequency and/or severity of episodes of migraine attacks and their symptoms, said substance or composition comprising a combination according to any one of claims 1 – 17, and said method comprising administering said substance or composition.
61. A combination according to any one of claims 1 to 13, substantially as herein described and illustrated.
62. A composition according to any one of claims 14 to 17, substantially as herein described and illustrated.
63. A substance or composition for use in a method of treatment according to any one of claims 2 to 17, or 42 to 60, substantially as herein described and illustrated.
64. Use according to any one of claims 18, or 19, or 21, or 22, or 24 to 37, substantially as herein described and illustrated.
65. A method according to claim 20, or claim 23, substantially as herein described and illustrated.
66. A process according to claim 38, or claim 39, substantially as herein described and illustrated.
67. A kit according to claim 40, substantially as herein described and illustrated.
68. A new combination, a substance or composition for a new use in a method of treatment; a new composition; a new use of quetiapine or a pharmaceutically acceptable salt thereof and/or zolmitriptan or a pharmaceutically acceptable salt thereof; a new method of administration; a

new method of improving the efficacy of zolmitriptan or a pharmaceutically acceptable salt thereof; a new process for preparing a combination; or a new kit, substantially as herein described.