Treatment of depressed patients with anti-depressants, such as selective serotonin re-uptake inhibitors (SSRI) or serotonin and noradrenaline re-uptake inhibitors (SNRI) are generally associated with adverse events, such as nausea, sleep disturbances, sexual dysfunction, weight gain, headache and dry mouth [*Int.J.Psych.Clin.Pract.*, 10, 31-37, 2006]. Lowering the amount or severity of adverse events associated with treatment with anti-depressants is an obvious desire as it will increase patient comfort, increase compliance and thus ultimately improve treatment outcome.

Treatment of depression with the SSRI paroxetine administered as an immediate release (IR) tablet and as an enteric coated, sustained release tablet has been compared [*J.Clin Psych.*, 63, 577-584, 2002]. Treatment with enteric coated tablets was associated with less nausea. Other types of gastro intestinal (GI) related adverse events, such as diarrhea, however, appeared to increase as did the number of reported abnormal ejaculation, female genital disorders and dizziness.

Summary of the invention

The present inventors have found that administering 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof (Compound I) in a way so that Compound I is not released in the stomach lowers the amount of adverse events, and in particular the amount of GI tract related adverse events. Accordingly, in one aspect~~embodiment~~, there is provided ~~invention relates to~~ a pharmaceutical composition for oral administration comprising 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof as active compound wherein said composition is adapted so that release of said active compound does not take place in the stomach.

In one embodiment, the disclosure~~invention~~ relates to a method of treating a disease, said method comprising the administration of a pharmaceutical composition of the present invention to a patient in need thereof.

In one embodiment, the disclosure~~invention~~ relates to the use of the compound 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof in the manufacture of a medicament for oral administration for the treatment of a disease, wherein said medicament is adapted so that the release of said compound does not take place in the stomach.

In another aspect, there is provided the use of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof in the manufacture of a pharmaceutical composition for oral administration for the treatment of a disease selected from mood disorders; major depressive disorder; general anxiety disorder; panic disorder; post traumatic stress disorder; depression associated with cognitive impairments, Alzheimer's disease or anxiety; depression with residual symptoms; chronic pain; eating disorder or abuse, wherein said medicament is adapted so that 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof is not released in the stomach.

In one embodiment, the disclosure~~invention~~ relates to the compound 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof for use in the treatment of a disease, wherein said compound is in a pharmaceutical composition for oral administration adapted so that release of said compound does not take place in the stomach.

In yet another aspect, there is provided the compound 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof for use in the treatment of a disease selected from mood disorders; major depressive disorder; general anxiety disorder; panic disorder; post traumatic stress disorder; depression associated with cognitive deficits, Alzheimer's disease or anxiety; depression with residual symptoms; chronic pain; eating disorder or abuse, wherein said compound is in a pharmaceutical composition for oral administration adapted so that said compound is not released in the stomach.

Figures

Figure 1: Plasma concentration-time profiles obtained upon administration of compound I HBr. B: 20 mg compound I HBr IR; C: 9 mg Compound I HBr iv; D: 20 mg Compound I HBr released in the proximal bowl; E: 20 mg Compound I HBr released in the distal bowl.

Detailed description of the invention

In one embodiment, the invention relates to a pharmaceutical composition for oral administration comprising 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof as active compound wherein said composition is adapted so that said active compound is not released in the stomach. In particular, Compound I is released in the intestine and in particular in the small intestine.

In the present context, "not released in the stomach" is intended to indicate that Compound I upon administration to a subject is substantially not present in the stomach in dissolved form.

The presence of Compound I in the stomach in dissolved form may in principle be determined *in vivo* using techniques such as X-ray evaluation, NMR imaging, gamma scintigraphy, or indeed, direct sampling from the stomach. These tests are, however, difficult to carry out in humans. A more convenient test to determine the presence of Compound I in the stomach is a two-stage *in vitro* dissolution test, which incorporates a first phase in which the pharmaceutical composition is exposed to low pH mimicking the environment in the stomach, followed by a second stage with exposure to higher pH mimicking the environment in the small intestine. The assay criteria are guided by the pH in various parts of the GI tract and the time it takes e.g. a tablet or a capsule to pass through the stomach and into the intestine, as discussed below.

Claims

1. A pharmaceutical composition for oral administration comprising the compound 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof (Compound I), wherein said composition is adapted so that said compound is not released in the stomach.

2. The composition according to claim 1, wherein said composition is a sustained release composition.

3. The composition according to claim 1, wherein said composition is a delayed release composition.

4. The composition of claim 3, wherein said composition comprises a pH-sensitive coating.

5. The composition of claim 4, which composition is an enteric coated tablet.

6. The composition according to claim 4, which composition is a multiparticulate composition in which substantially each particle is enteric coated.

7. The composition according to claim 1, which composition is a tablet comprising Compound I, mannitol, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl cellulose and magnesium stearate, which tablet is coated with methacrylic acid ethyl acrylate (1:1) copolymer.

8. The composition according to any of claims 1-7, wherein Compound I is 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine HBr in an amount of 1-50 mg.

~~9. A method of treating a disease selected from mood disorders; major depressive disorder; general anxiety disorder; panic disorder; post traumatic stress disorder; depression associated with cognitive impairments, Alzheimer's disease or anxiety; depression with residual symptoms; chronic pain; eating disorder or abuse said~~

~~method comprising the administration of a therapeutically effective amount of a pharmaceutical composition according to any of claim 1-8 to a patient in need thereof.~~

9~~10~~. Use of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof (Compound I) in the manufacture of a pharmaceutical composition for oral administration for the treatment of a disease selected from mood disorders; major depressive disorder; general anxiety disorder; panic disorder; post traumatic stress disorder; depression associated with cognitive impairments, Alzheimer's disease or anxiety; depression with residual symptoms; chronic pain; eating disorder or abuse, wherein said medicament is adapted so that 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof is not released in the stomach.

10~~14~~. The use according to claim 9~~13~~, wherein said composition is a tablet or a multiparticulate composition coated with a pH sensitive coating

11~~15~~. The use according to claim 10~~14~~, wherein said pH sensitive coating is an enteric coating.

12~~16~~. The use according to claim 9~~13~~, wherein said composition is adapted so that the release of Compound I takes place in the small intestine.

13~~17~~. The use according to any of claims 9~~13~~-12~~16~~, wherein said composition comprises 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine HBr I an amount of 1-50 mg.

14~~18~~. The compound 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable acid addition salts thereof for use in the treatment of a disease selected from mood disorders; major depressive disorder; general anxiety disorder; panic disorder; post traumatic stress disorder; depression associated with cognitive deficits, Alzheimer's disease or anxiety; depression with residual symptoms; chronic pain; eating disorder or abuse, wherein said compound is in a

pharmaceutical composition for oral administration adapted so that said compound is not released in the stomach.

1519. The compound according to claim 1418, wherein said composition is a tablet or a multiparticulate composition coated with a pH sensitive coating

1620. The compounduse according to claim 1915, wherein said pH sensitive coating is an enteric coating.

1721. The compounduse according to claim 1814, wherein said composition is adapted so that
release of the cCompound 1takes place in the small intestine.

1822. The compound according to any of claims 1418-1721, which compound is 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine HBr I an amount of 1-50 mg.