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(54) Title: NOVEL SALT OF TEGASEROD

(57) Abstract: The present invention relates to a novel salt of tegaserod, namely tegaserod pimelate,and to processes for the preparation thereof. The invention also relates to crystalline forms of the novel salt and to pharmaceutical compositions comprising the novel salt. Further, the invention relates to uses of said compositions to provide methods of treating patients suffering from gastrointestinal disorders.

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NOVEL SALT OF TEGASEROD

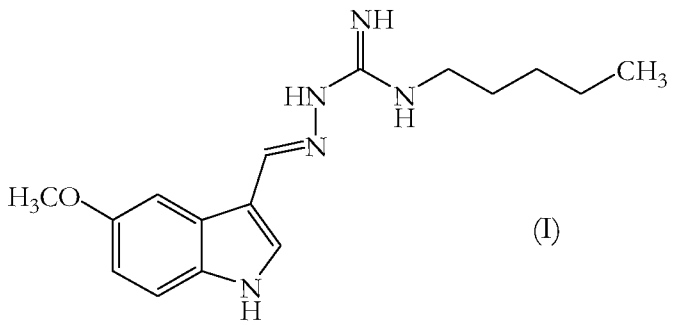
Field of the invention

The present invention relates to a novel salt of tegaserod, namely tegaserod pimelate, and to processes for the preparation thereof. The invention also relates to crystalline forms of the novel salt and to pharmaceutical compositions comprising the novel salt. Further, the invention relates to uses of said compositions to provide methods of treating patients suffering from gastrointestinal disorders.

Background of the invention

Tegaserod, chemically named 2-[(5-methoxy-1*H*-indol-3-yl)methylene]-*N*-pentylhydrazine-carboximidamide, is a selective serotonin 4 (5-HT_4) receptor agonist, which can be used to treat gastrointestinal disorders such as heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux. Tegaserod, as the maleate salt, is marketed for the short-term treatment of irritable bowel syndrome in women whose primary bowel symptom is constipation.

Tegaserod, represented by formula (I), was first described in US 5 510 353. Also described is the maleate salt, but interestingly a method of manufacturing tegaserod maleate is not disclosed. The only characterising data is the melting point which is disclosed as 190°C for the maleate salt and 124°C for the tegaserod base.



(I)

WO 2006/116953 describes crystalline forms of the hydrobromide, fumarate and oxalate salts of tegaserod. Also claimed is a process for preparing the hydrochloride, hydrobromide, fumarate, tartrate, citrate, lactate, mesylate, oxalate, succinate, glutarate, adipate, salicylate, sulphate, mandelate, camphor sulphonate and hydrogen sulphate salts of tegaserod from a specific crystalline form of tegaserod base. Another process described is a method of preparing the fumarate, maleate, tartrate, citrate, mesylate, lactate, succinate, oxalate, hydrochloride, salicylate, glutarate, adipate, hydrobromide, sulphate and hydrogen sulphate from a hydrogen halide salt of tegaserod.

There are often major hurdles to overcome before an active pharmaceutical ingredient (API) can be formulated into a composition that can be marketed. For example, the rate of dissolution of an API that has poor aqueous solubility is often problematic. The aqueous solubility is a major influence on the bioavailability of the API such that a poorly soluble API can mean the API is not available to have a pharmaceutical effect on the body. The API can also cause problems during manufacture of a pharmaceutical composition. For example, flowability, compactability and stickiness are all factors affected by the solid state properties of an API.

It has thus always been an aim of the pharmaceutical industry to provide many forms of an API in order to mitigate the problems described above. Different salts, crystalline forms also known as polymorphs, solvates, hydrates and amorphous forms are all forms of an API that can have different physiochemical and biological characteristics. Indeed, it has been discovered that the tegaserod maleate product on the market, Zelnorm®, has been linked to an increase in heart problems in a proportion of individuals. One possible reason is that the maleate moiety reacts with the tegaserod, resulting over time in the production of a toxic impurity. This impurity could be a contributor to the heart problems seen in some patients.

It would therefore be advantageous for the medicinal chemist to have a wide repertoire of alternative salts and crystalline forms of these and other known salts to aid in the preparation of products that are both efficacious and safe.

Summary of the invention

Accordingly, the present invention provides a novel salt of tegaserod, namely tegaserod pimelate, as well as a crystalline form of said salt.

As alluded to above, polymorphism influences every aspect of the solid state properties of an API and one of the important aspects of polymorphism in pharmaceuticals is the possibility of interconversion from one crystalline form to another. It is important that stable crystalline forms are used in pharmaceutical compositions as, for example, conversion from a form showing greater aqueous dissolution and potentially better bioavailability to a less soluble form can potentially have disastrous consequences.

Thus it is an object of the present invention to provide a novel tegaserod salt and a crystalline form according to the invention which may have an advantageous dissolution rate *in vivo*, leading to improved bioavailability, and further may provide advantageous characteristics during dosage form manufacture, for example, good conversion stability and formulation characteristics.

It is a further object of the present invention to provide a novel tegaserod salt and a crystalline form thereof which may have advantageous properties, for example, better solubility, bioavailability, stability including chemical and polymorphic stability, flowability, tractability, compressibility, compactability, toxicity, efficacy, or safety.

Accordingly, a first aspect according to the invention provides the compound tegaserod pimelate or tautomeric form thereof and/or a pharmaceutically acceptable solvate or hydrate thereof.

The tegaserod pimelate may exist in one or more polymorphic, tautomeric, hydrate and/or solvate forms. The present invention embraces all polymorphic forms and their mixtures, all tautomeric forms and their mixtures, all hydrate forms and their mixtures, and all solvate forms and their mixtures. Although tegaserod is defined for convenience by reference to one guanidino form only, the invention is not to be understood as being in any way limited by the particular nomenclature or graphic representation employed.

In a second aspect according to the invention a novel crystalline form of tegaserod pimelate is provided with a characteristic XRD spectrum having two or more peaks (preferably three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, fifteen or more, twenty or more, or twenty-two peaks) with 2θ values at 8.14, 11.23, 13.10, 13.60, 13.82, 15.24, 15.61, 15.89, 16.26, 17.82, 18.14, 18.52, 19.24, 19.77, 20.59, 21.17, 22.16, 22.50, 23.93, 24.78, 25.43, 28.85 ± 0.2 °2θ. In a particularly preferred embodiment tegaserod pimelate is provided with a characteristic XRD spectrum having peaks with 2θ values at 8.14, 11.23, 13.10, 13.60, 13.82, 15.24, 15.61, 15.89, 16.26, 17.82, 18.14, 18.52, 19.24, 19.77, 20.59, 21.17, 22.16, 22.50, 23.93, 24.78, 25.43, 28.85 ± 0.2 °2θ. Preferably the tegaserod pimelate has an XRPD trace substantially as shown in figure 1.

According to a third aspect of the present invention there is provided a crystalline form of tegaserod pimelate characterised by a DSC with an endothermic peak at about 229.8°C ± 0.5°C, preferably at about 229.78°C ± 0.5°C. Preferably the tegaserod pimelate has a DSC trace substantially as shown in figure 2.

The tegaserod pimelate may have a TGA trace substantially as shown in figure 3.

Preferably the tegaserod pimelate according to the above described aspects and embodiments has a chemical purity of greater than 95%, 96%, 97%, 98% or 99% (as measured by HPLC). Preferably the tegaserod pimelate according to the above described aspects and embodiments has a polymorphic purity of greater than 95%, 96%, 97%, 98% or 99% (as measured by XRPD or DSC).

A fourth aspect provides a process for the preparation of tegaserod pimelate according to the invention, preferably crystalline tegaserod pimelate, comprising the steps of:

(a) mixing tegaserod and pimelic acid in a solvent; and

(b) isolating the resultant salt.

In a preferred embodiment of the process the pimelic acid is added as a solution of the free acid, preferably the solvent of the pimelic acid solution is an aqueous solvent, most

preferably the aqueous solvent is water. In a further embodiment, in step (b), the salt is isolated by filtration, preferably by vacuum filtration.

In a further embodiment, the tegaserod pimelate is obtained on an industrial scale, preferably in batches of 0.5kg, 1kg, 5kg, 10kg, 50kg, 100kg, 500kg or more.

A fifth aspect according to the invention provides a pharmaceutical composition comprising tegaserod pimelate according to the invention or prepared according to the invention and one or more pharmaceutically acceptable excipients. Preferably the composition is a solid composition, most preferably a tablet or capsule composition.

A sixth aspect provides a composition according to the invention for use in the treatment or prevention of a gastrointestinal disorder, preferably selected from the list comprising heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux. Preferably the gastrointestinal disorder is irritable bowel syndrome.

In a seventh aspect there is provided tegaserod pimelate according to any of the aspects or embodiments described above for use as a medicament.

An eighth aspect provides tegaserod pimelate according to the invention for use in the treatment or prevention of a gastrointestinal disorder. In a preferred embodiment the gastrointestinal disorder is selected from the group comprising heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux, most preferably the disorder is irritable bowel syndrome.

In a ninth aspect according to the invention there is further provided a method of treating or preventing a gastrointestinal disorder, preferably selected from the group comprising heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux (preferably irritable bowel syndrome), comprising administering

to a patient in need thereof a composition comprising a pharmaceutically or prophylactically effective amount of tegaserod pimelate according to any of the aspects or embodiments described above. Preferably the patient is a mammal, preferably a human.

A tenth aspect provides the use of tegaserod pimelate according to any of the aspects or embodiments described above in the manufacture of a medicament for use in the treatment or prevention of a gastrointestinal disorder. In a preferred embodiment the gastrointestinal disorder is selected from the group comprising heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux, preferably irritable bowel syndrome.

Brief description of the accompanying figures

Figure 1 shows the XRPD of tegaserod pimelate.
Figure 2 shows the DSC of tegaserod pimelate.
Figure 3 shows the TGA of tegaserod pimelate.

Detailed description of the invention

As used herein the terms "crystalline form", "polymorph" and "polymorphic form" are used interchangeably.

The terms "XRD" and "XRPD" are used interchangeably herein and preferably refer to an X-ray powder diffraction trace, spectrum or pattern.

The present invention provides the novel pimelate salt of tegaserod and a process for its preparation. The process disclosed is simple and amenable to scale up and is capable of providing the salt in consistent crystalline and chemical purity of greater than 95% respectively, preferably greater than 96%, more preferably greater than 97%. Particularly preferred is a purity of greater than 98% and most preferred is a purity of greater than 99% irrespective of the scale of preparation.

A preferred process according to the invention for preparing tegaserod pimelate according to the invention comprises mixing tegaserod and pimelic acid. Preferably the pimelic acid is dissolved in a solvent. In a particularly preferred embodiment the solvent is an aqueous solvent, most preferably water. Preferably the tegaserod is in the form of the free base. Of course it will be understood that the tegaserod can be completely or only partially dissolved in one or a mixture of solvent(s) and the process still falls within the scope of the invention, and further that the tegaserod, pimelic acid and solvent can be combined in any order and the process remains within the scope of the invention. For example certain embodiments according to the invention comprise adding tegaserod to the solvent(s), to which is added the pimelic acid, preferably in solution. Whatever their nature the pimelic acid solution and the tegaserod solution should be miscible to create a single phase. Preferably when the pimelic acid is dissolved in an aqueous solvent, the solvent in which the tegaserod is dissolved should be miscible with the aqueous pimelic acid solution. The inventors have found that C_1-C_6 alcohols are advantageous, preferably selected from the group comprising methanol, ethanol, isopropyl alcohol (IPA), tert-butanol and isobutanol, more preferably methanol, but other polar organic solvents, especially polar protic organic solvents, capable of dissolving tegaserod can be utilised.

The resulting reaction mixture comprising the tegaserod and the pimelic acid, in certain embodiments can be stirred to increase the precipitation of the solid salt. It is preferred that the stirring occurs at between about 20-30°C or approximately room temperature, but it is envisaged that the stirring conditions may be varied and still remain within the scope of the invention. Preferably the reaction mixture comprising the tegaserod and the pimelic acid is stirred for between about 0.5-3 hours.

The solid product obtained can then be isolated by any means common in the field or known to the skilled artisan. In one embodiment the solid salt is obtained by evaporation of the solvent. However, in a particularly preferred embodiment the solid product is filtered. Preferably the product is dried at a temperature that does not induce conversion of the crystalline form obtained or cause the salt or crystalline form to degrade. The inventors have found that drying the product at about 35-40°C is advantageous. Preferably, in certain embodiments the solid product is dried under vacuum until a constant weight is obtained.

The tegaserod pimelate according to the invention may also be further purified if required. The inventors have found that dissolving the tegaserod pimelate in an organic solvent and then causing the salt to precipitate from the solution results in particularly pure tegaserod pimelate. In preferred embodiments the organic solvent is a protic or aprotic solvent, preferably ethyl acetate. Preferably, the mixture is heated to facilitate dissolution of the tegaserod pimelate, in certain embodiments to between about 40-90°C, most preferably to between about 70-80°C, when the solvent is ethyl acetate. The mixture may then be cooled to precipitate the tegaserod pimelate or in alternative embodiments an anti-solvent may be added. In preferred embodiments the mixture is cooled to between about 20-30°C. The resultant precipitated solid can be isolated by any means, preferably by vacuum filtration. The solid obtained may then be washed, preferably with ethyl acetate, and is preferably dried, preferably at about 40°C, preferably until a constant weight is achieved.

The inventors have found that preparation of tegaserod pimelate as described above and further crystallisation from solvents such as ethyl acetate result in tegaserod pimelate having both chemical and crystalline purity of greater than 99%.

Illustrative of the invention is a pharmaceutical composition comprising tegaserod pimelate and one or more pharmaceutical excipients. In a further aspect a process for preparing the composition is provided comprising mixing tegaserod pimelate according to the invention and a pharmaceutically acceptable excipient. A yet further aspect of the invention provides treatment of a 5-HT_4 receptor mediated disorder in a subject in need thereof comprising administering to the subject a composition comprising a therapeutically effective amount of tegaserod pimelate. 5-HT_4 receptor mediated disorders comprise gastrointestinal disorders such as heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux.

In another aspect according to the invention there is provided tegaserod pimelate for treating a 5-HT_4 receptor mediated disorder in a subject in need thereof. Of course, it will be realised that the tegaserod pimelate may be in amorphous form or any of a number of crystalline forms.

In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition for a variety of purposes. Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulphate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. Carbopol®), carboxymethyl cellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminium silicate, maltodextrin, methyl cellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminium silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavouring agents and flavour enhancers make the dosage form more palatable to the patient. Common flavouring agents and flavour enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, the tegaserod salt and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerine.

Liquid pharmaceutical compositions may further contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel or organoleptic qualities of the product and/or

coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid, bentonite, carbomer, carboxymethyl cellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethyl cellulose, gelatin, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxytoluene, butylated hydroxyanisole and ethylenediaminetetraacetic acid may be added at levels safe for ingestion to improve storage stability.

According to the present invention, a liquid composition may also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate or sodium acetate.

Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts. Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and lozenges, as well as liquid syrups, suspensions and elixirs.

The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or a soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerine and sorbitol, and an opacifying agent or colourant. The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredient and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition may be prepared conventionally by dry granulation. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

In further embodiments the composition of the invention may further comprise one or more additional active ingredients. Further active ingredients may include other 5-HT_4

receptor agonists such as prucalopride, RS 67333 (1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-n-butyl-4-piperidinyl)-1-propanone), RS 67506 (1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-[2-[(methylsulphonyl)amino]ethyl]-4-piperidinyl]-1-propanone), cisapride, renzapride, norcisapride, mosapride, zacopride, SB 205149, SC 53116, BIMU 1, and BIMU 8; proton pump inhibitors such as omeprazole, rabeprazole, pantoprazole, and lansoprazole; 5-HT_3 receptor agonists such as cilansetron which is described in EP 297 651, alosetron which is described in WO 99/17755, ramosetron, azasetron, ondansetron, dolasetron, granisetron, and tropisetron; selective serotonin reuptake inhibitors such as citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine, zimeldine, norzimeldine, clomipramine, alaproclate, venlafaxine, ericlamine, duloxetine, milnacipran, nefazodone, OPC 14503, and cyanodothiepin; and dipeptidyl peptidase IV (DPP-IV) inhibitors. Of course it will be obvious that the above is not an exhaustive list.

The details of the invention, its objects and advantages are explained hereunder in greater detail in relation to non-limiting exemplary illustrations.

Examples

Example 1: Preparation of tegaserod pimelate

Tegaserod (1eq) was taken in 3.3 volumes of methanol at 25-30°C. To this slurry was added a solution of pimelic acid (2eq) in 5 volumes of water and the mixture was stirred for about 30 minutes at 25-30°C. The precipitated salt was filtered and washed with 5 volumes of water and dried at 35°C under vacuum for about 2 hours.

^{1}H-NMR indicated formation of tegaserod pimelate.

Yield = 74%

Chemical purity > 99% (as measured by HPLC)

Polymorphic purity > 99% (as measured by DSC)

Example 2: Purification of crude tegaserod pimelate

1g of tegaserod pimelate was added to 25 volumes of ethyl acetate and heated to about 77°C for about 10 minutes. The reaction mixture was then cooled to between about 25-30°C for about 30 minutes. The slurry was filtered and the resultant solid washed with 5 volumes of ethyl acetate. The solid product was dried at 40°C under vacuum until a constant weight was obtained.

^{1}H-NMR indicated formation of tegaserod pimelate. XRPD data confirmed that the tegaserod pimelate product obtained had a crystalline structure.

Yield = 99%

Chemical purity > 99% (as measured by HPLC)

Polymorphic purity > 99% (as measured by DSC)

Claims

1. Tegaserod pimelate or tautomeric form thereof and/or a pharmaceutically acceptable solvate or hydrate thereof.

2. A crystalline form of tegaserod pimelate with a characteristic XRD spectrum having two or more peaks with 2θ values at 8.14, 11.23, 13.10, 13.60, 13.82, 15.24, 15.61, 15.89, 16.26, 17.82, 18.14, 18.52, 19.24, 19.77, 20.59, 21.17, 22.16, 22.50, 23.93, 24.78, 25.43, 28.85 ± 0.2 °2θ.

3. A crystalline form of tegaserod pimelate having an XRPD trace substantially as shown in figure 1.

4. A crystalline form of tegaserod pimelate characterised by a DSC with an endothermic peak at about 229.8°C ± 0.5°C.

5. A crystalline form of tegaserod pimelate having a DSC trace substantially as shown in figure 2.

6. A crystalline form of tegaserod pimelate having a TGA trace substantially as shown in figure 3.

7. Tegaserod pimelate according to any one of claims 1-6, having a chemical purity of greater than 95% (as measured by HPLC).

8. Tegaserod pimelate according to any one of claims 1-7, having a polymorphic purity of greater than 95% (as measured by XRPD or DSC).

9. A process for the preparation of tegaserod pimelate according to any one of claims 1-8, comprising the steps of:

(a) mixing tegaserod and pimelic acid in a solvent; and

(b) isolating the resultant salt.

10. A process according to claim 9, wherein the pimelic acid is added as a solution of the free acid.

11. A process according to claim 10, wherein the solution comprises an aqueous solvent and pimelic acid.

12. A process according to claim 11, wherein the aqueous solvent is water.

13. A pharmaceutical composition comprising tegaserod pimelate according to any one of claims 1-8 or prepared by a process according to any one of claims 9-12, and one or more pharmaceutically acceptable excipients.

14. A composition according to claim 13, wherein the composition is a solid composition.

15. A composition according to claim 14, wherein the composition is a tablet or capsule composition.

16. A composition according to any one of claims 13-15, for use in the treatment or prevention of a gastrointestinal disorder.

17. A composition according to claim 16, wherein the gastrointestinal disorder is selected from the list comprising heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux.

18. A composition according to claim 17, wherein the gastrointestinal disorder is irritable bowel syndrome.

19. Tegaserod pimelate according to any one of claims 1-8 or prepared by a process according to any one of claims 9-12, for use as a medicament.

20. Tegaserod pimelate according to claim 19, for use in the treatment or prevention of a gastrointestinal disorder.

21. Tegaserod pimelate according to claim 20, wherein the gastrointestinal disorder is selected from the group comprising heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux.

22. Tegaserod pimelate according to claim 21, wherein the gastrointestinal disorder is irritable bowel syndrome.

23. A method of treating or preventing a gastrointestinal disorder, comprising administering to a patient in need thereof a therapeutically of prophylactically effective amount of tegaserod pimelate according to any one of claims 1-8 or 19-22, or of tegaserod pimelate prepared by a process according to any one of claims 9-12, or of a pharmaceutical composition according to any one of claims 13-18.

24. A method according to claim 23, wherein the gastrointestinal disorder is selected from the group comprising heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome and gastro-oesophageal reflux.

25. A method according to claim 24, wherein the gastrointestinal disorder is irritable bowel syndrome.

26. A method according to any one of claims 23-25, wherein the patient is a mammal.

27. A method according to claim 26, wherein the mammal is a human.

28. Use of tegaserod pimelate according to any one of claims 1-8 or 19-22, or prepared by a process according to any one of claims 9-12, in the manufacture of a medicament for use in the treatment or prevention of a gastrointestinal disorder.

29. Use according to claim 28, wherein the gastrointestinal disorder is heartburn, bloating, postoperative ileus, abdominal pain or discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, irritable bowel syndrome or gastro-oesophageal reflux.

30. Use according to claim 29, wherein the gastrointestinal disorder is irritable bowel syndrome.

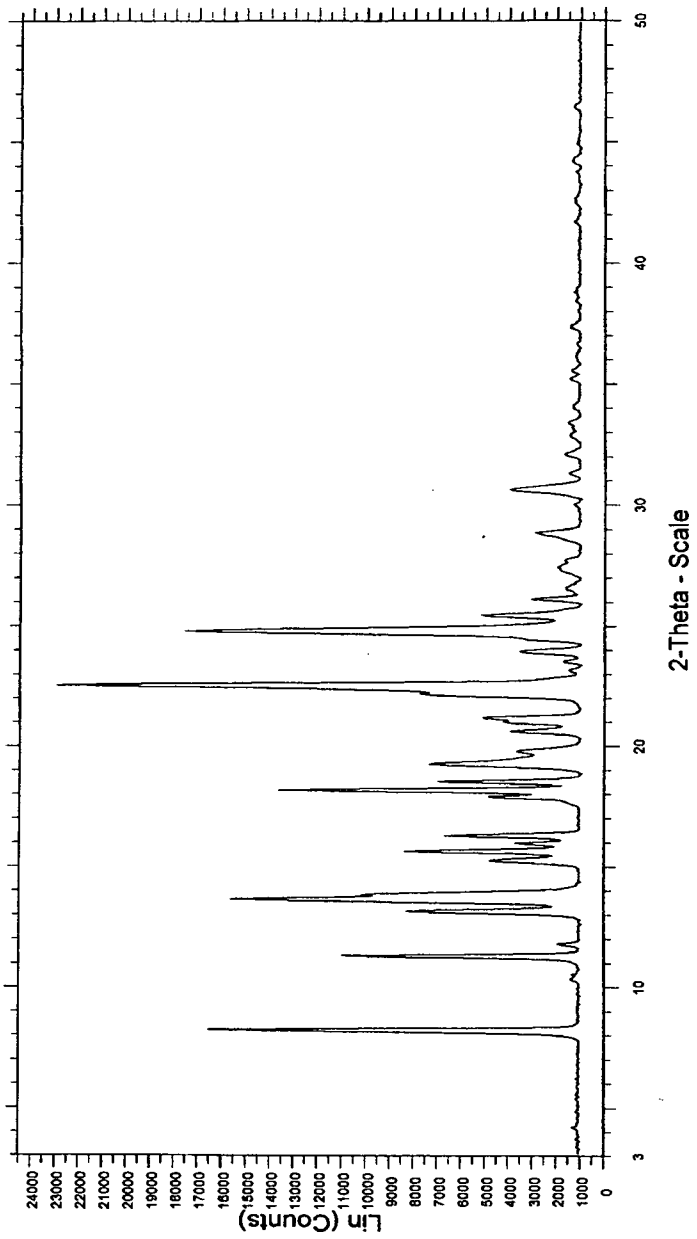


Figure 1

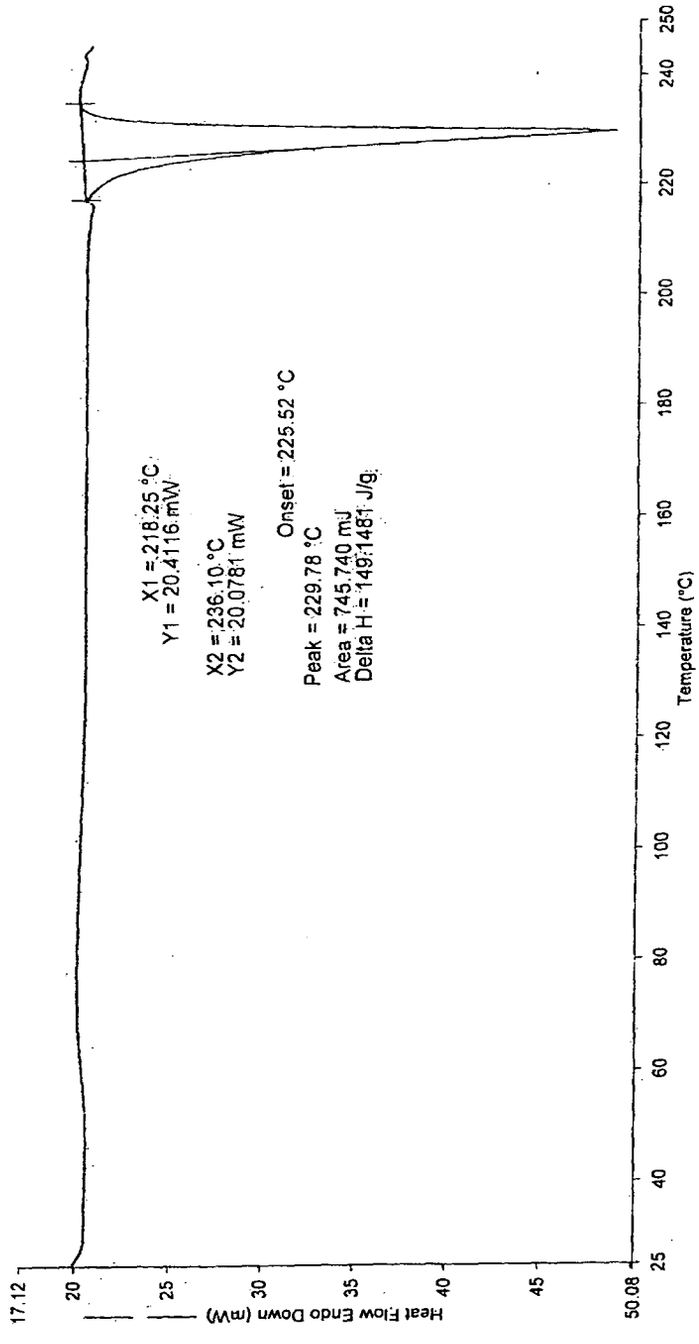

X1 = 218.25 °C
Y1 = 20.4116 mW
X2 = 236.10 °C
Y2 = 20.0781 mW
Onset = 225.52 °C
Peak = 229.78 °C
Area = 745.740 mJ
Delta H = 148.1481 J/g
Heat Flow Endo Down (mW)
Temperature (°C)
17.12
50.08
20
25
30
35
40
45
25
40
60
80
100
120
140
160
180
200
220
240
250

Figure 2

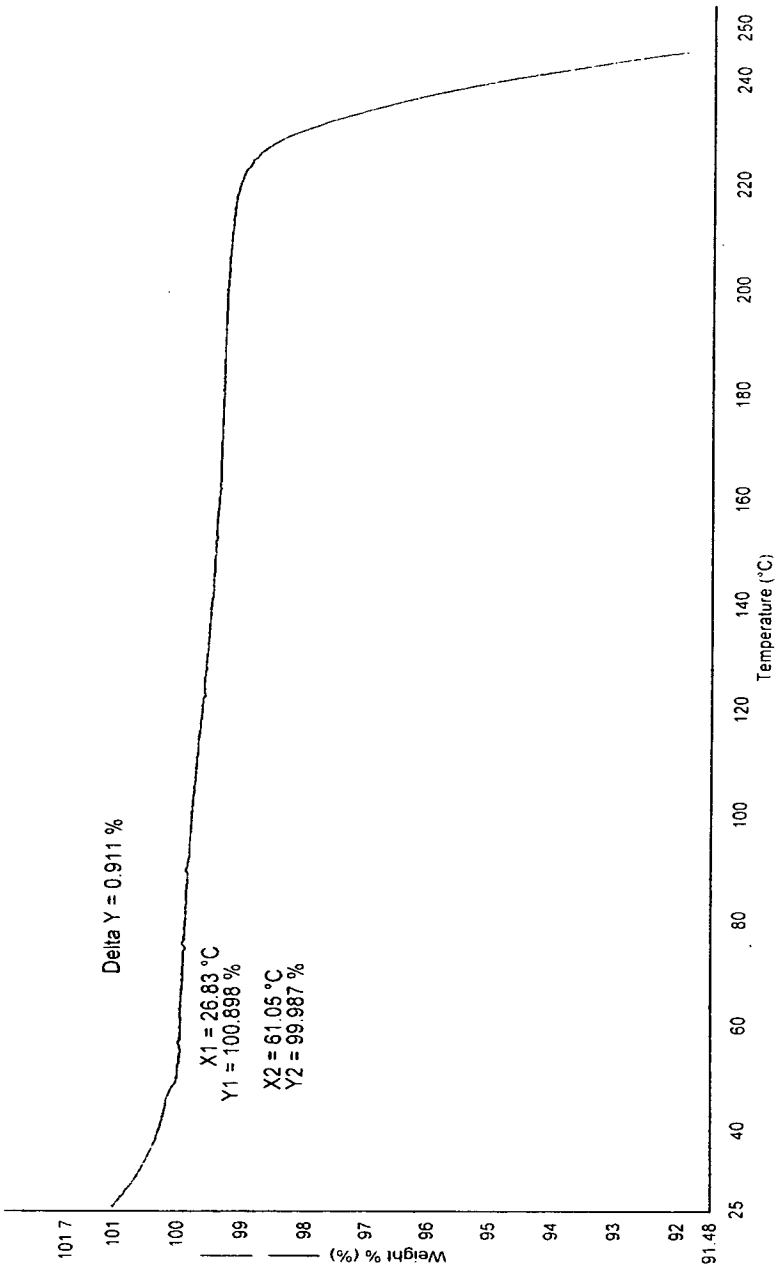

Delta Y = 0.911 %
X1 = 26.83 °C
Y1 = 100.898 %
X2 = 61.05 °C
Y2 = 99.987 %
Weight % (%)
Temperature (°C)
101.7
101
100
99
98
97
96
95
94
93
92
91.48
25
40
60
80
100
120
140
160
180
200
220
240
250

Figure 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/051123

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/14 A61K31/404 A61P1/00

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)
C07D

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)
EPO-Internal, WPI Data, CHEM ABS 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 2006/116953 A (ZENTIVA AS [CZ]; HAJICEK JOSEF [CZ]; PILARCIK TOMAS [CZ]) 9 November 2006 (2006-11-09) cited in the application page 1, paragraph 1 page 10, paragraph 3 page 11, paragraph 1 page 14, paragraph 2; table 1	1-30
X	WO 2005/058819 A (TEVA PHARMA [IL]; TEVA PHARMA [US]; MENDELOVICI MARIOARA [IL]; ARONHIM) 30 June 2005 (2005-06-30) page 4, line 1 - page 8, line 7; claims 1,90-94	1-30

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

"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	Date of mailing of the international search report
18 March 2009	30/03/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/051123

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006116953 A	09-11-2006	NONE	
WO 2005058819 A	30-06-2005	CA 2550886 A1	30-06-2005
		EP 1594493 A2	16-11-2005
		JP 2007514000 T	31-05-2007
		KR 20060111675 A	27-10-2006