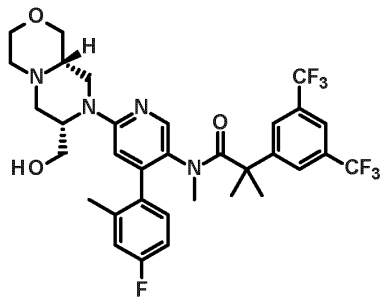
Novel formulation comprising elinzanetant in a solid dispersion

Technical Field

The present invention relates to a pharmaceutical composition comprising a solid dispersion, the solid dispersion comprising elinzanetant and at least one solid dispersion matrix comprising a neutral polymer as a solid dispersion matrix agent, its process of preparation and its use for treating diseases and disorders.

Background of the Invention

The compound 2-[3,5-bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]pyridin-3-yl}-N,2-dimethylpropanamide according to formula (I)



(I)

(herein also referred to by its INN: elinzanetant) is a potent dual specific NK1/3 antagonist that shows high potency in the treatment of different diseases and conditions (WO 2007/028654 A1), including sex-hormone dependent diseases and disorders, such as vasomotor symptoms (WO 2016/184829 A1).

Different approaches have been conducted in order to provide elinzanetant in a form having sufficient pharmacological properties with respect to stability, as well as its dissolution and bioavailability profile. To this end, a crystalline salt form of elinzanetant, a 4-methylbenzenesulfonate salt (tosylate), was initially developed (WO 2010/015626). Even though crystalline forms could be obtained, the disadvantages of the described tosylate salt

are that the crystalline forms were not producible in the desired scale, or the crystalline forms showed high propensity for hydration and solvation with the tendency to switch to other crystalline forms. However, during early clinical Phase I studies the elinzanetant tosylate salt form of the API was used, but only offering an acceptable PK profile when administered as a suspension.

Further, the crystalline anhydrate Form 1 was developed (WO 2011/023733 A1). In WO 2011/023733 A1, page 31, line 6 discloses the formulation of the crystalline anhydrate Form 1 in a solid pharmaceutical composition. To this end, drug substance and excipients were dry mixed and thereafter granulated using water; see WO 2011/023733 A1, page 32, lines 7 to 10. The granules were dried and milled in a conical mill to reduce the size of the granules. The compositions according to WO 2011/023733 A1 exhibit insufficient dissolution in biorelevant media; see e.g. composition 26 of Example 2, Figure 1 and Table 2 of the present disclosure. Therefore, the solid compositions of prior art also exhibit an unfavorable high variability in bioavailability.

To mitigate slow dissolution and provision of a reduced variability in bioavailability a liquid formulation in a soft gelatin capsule was provided (WO 2019/175253 A1). These soft gelatin capsules are used in clinical development and are planned for launch of the commercial drug product. The disadvantage of the capsules described is the fact, that due to the limited drug load, the size of the capsules is large (Size-20) and for a desired daily dose of 120 mg, two soft gelatin capsules containing 60 mg each have to be taken. As this is of low convenience to the patients that have to take the drug, a potential for non-compliance of the patients to the treatment is created.

Today, the majority of new active pharmaceutical ingredients (APIs) in crystalline form shows the properties of poor solubility in water and subsequently reduced bioavailability (D. Alonzo: "Understanding the behavior of amorphous pharmaceutical systems during dissolution." *Pharm. Res.* 27, 608-618 (2010)). One approach to overcome these issues is embedding the API into water-soluble polymers forming an Amorphous Solid Dispersion (ASD). Once these systems get into contact with gastrointestinal media, dissolution will occur to a supersaturated state, which is more or less stabilized by the polymer. This so-called "spring and parachute" approach (C. Brough; "Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery." *Int. J.*

Pharm. 453, 157-166 (2013)) has been shown to significantly enhance the bioavailability of poorly water-soluble APIs. One major challenge in administration of these APIs is the high inter-individual variability of drug performance (M. Herbrink: "Variability in bioavailability of small molecular tyrosine kinase inhibitors." *Cancer Treat. Rev.* 41, 412-422 (2015)). Another inherent issue of amorphous solid dispersions is the instability of the solid state which results in a tendency for recrystallisation of the drug and/or excipients during storage (Andrews et al., *Journal of Pharmacy and Pharmacology*; 62: 1580–1590 (2010)). This may be accompanied by a break-down of dissolution and bioavailability. Moreover, the stability of the API should be preserved, e.g. avoiding degradation or esterification of the API. However, some APIs, like elinzanetant tend to react with the matrix. The inventors have surprisingly found that elinzanetant free base is instable within a matrix of acidic polymer matrix agents. The problem to be solved by the present invention is to provide a pharmaceutical composition containing elinzanetant showing sufficient bioavailability and stability of elinzanetant.

Surprisingly the pharmaceutical composition according to the invention shows desired stabilization of the active ingredient elinzanetant as well as sufficient bioavailability. The inventors have unexpectedly found that the pharmaceutical compositions according to the invention were stable and exhibited increased dissolution behavior in biorelevant media as compared to solid pharmaceutical compositions of prior art, e.g. the ones disclosed in WO 2011/023733 A1. The formulation of WO 2011/023733 A1 relates to a solid pharmaceutical composition not being a solid dispersion, as mixing and wet granulation using water does not lead to embedding of the drug substance into the matrix, i.e. not resulting in a solid dispersion.

Further, it has been shown that the pharmaceutical composition according to the invention shows a pharmacokinetic AUC that is approx. 12% higher than with the formulation (soft gelatin capsules) of prior art used in Phase III clinical studies and used for approval and launch of elinzanetant. This was surprising as the soft gelatin capsules contained elinzanetant in solubilized form. Surprisingly, pharmaceutical compositions according to the present disclosure reach the pharmacokinetic exposures and bioavailability of the soft gelatin capsule formulation as used in clinical Phase III studies at lower doses, such as at a daily dose of 100 mg or higher and lower than 120 mg.

BRIEF DESCRIPTION OF THE INVENTION

The invention pertains to a pharmaceutical composition comprising a solid dispersion comprising elinzanetant or a pharmaceutically acceptable salt thereof.

In an embodiment, the pharmaceutical composition according to the invention comprises elinzanetant or a pharmaceutically acceptable salt thereof, and a solid dispersion matrix; wherein the solid dispersion matrix comprises a neutral polymer as a solid dispersion matrix agent.

The invention further relates to granules, pellets, tablets, dragées, sachets, pills, or melts comprising the pharmaceutical composition according to the invention.

The invention also relates to a method for treating a sex hormone-dependent disease or disorder, comprising administering to a subject in need thereof a pharmaceutical composition according to the invention, or granules, pellets, a tablet, a dragée, a sachet, a pill, or a melt according to the invention, comprising a therapeutically effective dose of elinzanetant.

The invention moreover relates to the pharmaceutical composition according to the invention or the granules, pellets, tablets, dragées, sachets, pills, or melts according to the invention for use in the treatment of a sex hormone-dependent disease.

FIGURE LEGEND

Figure 1 Dissolution of ASD compositions in 2 stage dissolution in biorelevant media; Composition numbers according to Example 1 are indicated

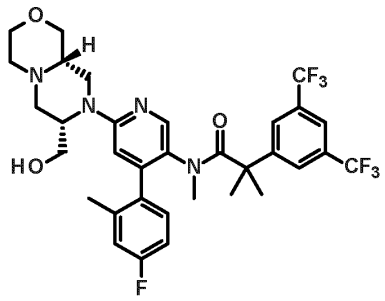
Figure 2 shows the geometric mean and standard deviation (SD) concentration-time profiles of elinzanetant for Reference (circles) and Tablets (rectangles) (N=24).

DETAILED DESCRIPTION OF THE INVENTION

The details and embodiments of the present invention is defined by the disclosure herein. The terms “invention” and “disclosure” are hence used interchangeably herein.

The term “elinzanetant” refers to 2-[3,5-bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-

yl]pyridin-3-yl}-N,2-dimethylpropanamide. In an embodiment, elinzanetant is the compound of formula (I)



(I).

The term “compound of the invention” or “active agent” or “active pharmaceutical ingredient” or “active ingredient” refer to elinzanetant.

Name and meaning of excipients used in the present description are in accordance with the US or European pharmacopoeia.

The term "pharmaceutically acceptable salts" as used herein means salts suitable for medical applications having a pharmaceutically acceptable anion or cation. Such pharmaceutically acceptable salts of elinzanetant include benzenesulfonate salt (besylate), 4-methylbenzenesulfonate salt (tosylate), and hydrochloride salt.

Pharmaceutical compositions according to the disclosure include but are not limited to granules, pellets, tablets, dragées, pills, melts or solid dispersions and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. Preference is given to tablets, solid dispersions, pellets, and granules. Most preferably the pharmaceutically compositions according to the invention is a tablet.

Solid dispersion

The solid dispersion of the present disclosure comprises elinzanetant or a pharmaceutically acceptable salt thereof and a solid dispersion matrix, comprising a solid dispersion matrix agent, and optionally a carrier.

In an embodiment, elinzanetant or the pharmaceutically acceptable salt thereof is present in the solid dispersion in amorphous form. The presence of elinzanetant or the pharmaceutically acceptable salt thereof being in amorphous form in an embodiment means that in the final pharmaceutical composition, the active pharmaceutical ingredient may be molecularly dispersed in the solid dispersion matrix or be present as amorphous particles within the solid dispersion matrix. Such amorphous form within the solid dispersion matrix can be achieved by methods known in the art, such as e.g. solvent evaporation or cooling of the melt. By that the solid dispersion matrix is a very effective solid-state stabilizer. A solid dispersion matrix can be formed by one or more components, such as a solid dispersion matrix agent and optionally a further component, such as a carrier.

A "solid dispersion matrix" according to the present disclosure are polymeric excipients, non-polymeric excipients, or combinations thereof, capable of dissolving or dispersing the active ingredient (I). In the context of the present invention the "solid dispersion matrix" may consist of a "solid dispersion matrix agent", or may consist of the combination of a "solid dispersion matrix agent" and a "carrier" used during the manufacturing process of the amorphous solid dispersion (ASD). The "solid dispersion matrix" and the amorphous elinzanetant or the pharmaceutically acceptable salt thereof become integral parts of the amorphous solid dispersion (ASD).

In context with the present disclosure, it has unexpectedly been found that neutral polymers show superior properties with respect to dissolution behavior and in particular stability of elinzanetant in the pharmaceutical composition. The inventors have surprisingly found that non-neutral solid dispersion matrix agents, such as those comprising recurring carboxylate groups, foster transesterification with elinzanetant and found that neutral polymers as solid dispersion matrix agents unexpectedly increase the chemical and physical stability of elinzanetant in ASD compositions, e.g., as compared to non-neutral solid dispersion matrix agents.

Accordingly, in an embodiment the solid dispersion matrix agent is a neutral polymer.

"Neutral polymer" in context with the present disclosure relate to a polymer containing only non-deprotonable functional groups and/or deprotonable functional groups (contain hydrogen atoms that could potentially be donated) with a pK_a of 7 or more showing

superior properties with respect to dissolution behavior and stability of the pharmaceutical composition.

In the context of the present disclosure, the solid dispersion matrix agent is a pharmaceutically acceptable polymer containing only non-deprotonatable recurring functional groups or deprotonatable recurring functional groups having a pK_a of 7 or more.

In one embodiment of the present disclosure the polymer does not contain a recurring functional group with a pK_a of less than 7, such as a carboxylate group, a sulfonate group, a phosphate group, a sulfate group, and a phosphonate group.

In one embodiment the polymer does not contain a recurring carboxylate group.

"Recurring group" refers a group present in two or more constitutional repeating units (mer) of the polymer.

"Functional group" - for repeating units of polymers – are attached to their nonpolar core of carbon atoms and thus add chemical character to carbon chains. Functional groups can also be charged, depending on the ambient pH conditions, this is indicated by its pK_a.

Further, it has been unexpectedly found by the inventors, that by using the composition according to the invention, the need for further stabilizing agents or dissolution enhancers, such as surfactants in the solid dispersion is not needed to achieve the desired dissolution and bioavailability profile, thereby, *inter alia*, desirably minimizing the number of excipients and components in the pharmaceutical composition. Accordingly, in an embodiment, the pharmaceutical composition does not contain a surfactant. The presence of an ionic surfactant, such as SDS may interfere with the dissolution behavior. Hence, in an embodiment, the pharmaceutical composition does not contain an ionic surfactant. In an embodiment the pharmaceutical composition does not contain sodium dodecyl sulfate (SDS).

In an embodiment, the solid dispersion matrix agent is selected from the group consisting of polyethylene oxide, polyvinylpyrrolidone (PVP), vinylpyrrolidone/vinylacetate copolymer (copovidone) (e.g. Kollidon VA64), polyalkylene glycol (e.g. polyethylene glycol), hydroxyalkyl cellulose (e.g. hydroxypropyl cellulose), hydroxyalkyl methyl cellulose (e.g. hydroxypropyl methyl cellulose), carboxymethyl cellulose, methacrylester copolymers (such as Eudragit® RS, RL, or NE), aminoalkyl-methacrylate copolymers (such as Eudragit® E), polyvinyl alcohol, polyvinyl acetate, vinyl alcohol/vinyl acetate

copolymer, and combinations thereof. In one embodiment, solid dispersion matrix is selected from the group consisting of polyvinylpyrrolidone (PVP), vinylpyrrolidone/vinylacetate copolymer (copovidone), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), polyethylene glycol and polyethylene oxide.

In an embodiment the neutral polymer is vinylpyrrolidone/vinylacetate copolymer (copovidone).

The inventors have unexpectedly found that the dissolution behavior of the solid pharmaceutical composition according to the present disclosure can be further optimized by adapting the weight ratio of elinzanetant and the solid dispersion matrix agent. In an embodiment, the solid dispersion comprises elinzanetant or the pharmaceutically acceptable salt thereof and the solid dispersion matrix agent in a weight ratio of from 1:0.5 to 1:4, such as from 1:1 to 1:3 or from 1:1.5 to 1:2.5. In an embodiment the solid dispersion comprises elinzanetant or the pharmaceutically acceptable salt thereof and the solid dispersion matrix agent in a weight ratio of 1:2. In an embodiment, the solid dispersion comprises elinzanetant and the solid dispersion matrix agent in a weight ratio of from 1:0.5 to 1:4, such as from 1:1 to 1:3 or from 1:1.5 to 1:2.5. In an embodiment the solid dispersion comprises elinzanetant and the solid dispersion matrix agent in a weight ratio of 1:2.

Carrier

The solid dispersion matrix may optionally further comprise a carrier. In the context of the present disclosure the carrier is selected from the groups of disintegration promoters, fillers, lubricants, sweeteners, antioxidants, plasticizers, flavoring agents and/or colorants or a combination thereof.

In an embodiment, the pharmaceutically acceptable solid dispersion matrix comprises a solid dispersion matrix agent and a carrier.

In an embodiment the solid dispersion matrix consists of a solid dispersion matrix agent and a carrier.

In an embodiment, the carrier according to the present invention is a disintegration promoter. In an embodiment, the carrier is a disintegration promoter selected from the group consisting of cross-linked polyvinylpyrrolidone, maize starch, modified starch, and starch derivatives such as sodium carboxymethyl starch and sodium starch glycolate, cellulose derivatives, such as carmellose calcium (carboxymethylcellulose calcium) and

croscarmellose sodium (cross-linked polymer of carboxymethylcellulose sodium), or microcrystalline cellulose, or a combination of croscarmellose sodium and microcrystalline cellulose, or mixtures thereof.

In one embodiment, the disintegration promoter is croscarmellose sodium or cross-linked polyvinylpyrrolidone. In an embodiment, the disintegration promoter is croscarmellose sodium.

In an embodiment, the carrier according to the present invention is a filler selected from the group consisting of microcrystalline cellulose, cellulose powder, silicified microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, magnesium trisilicate, mannitol, maltitol, sorbitol, xylitol, lactose (anhydrous or as a hydrate, for example monohydrate), dextrose, maltose, sucrose, glucose, fructose or maltodextrins or mixtures thereof. In an embodiment, the filler is microcrystalline cellulose or lactose or a combination thereof.

In an embodiment, the solid dispersion matrix does not contain a filler.

In an embodiment, the solid pharmaceutical composition does not contain a filler.

In an embodiment, the carrier according to the present invention is a lubricant selected from the group consisting of magnesium stearate, sodium stearyl fumarate, stearic acid, glycerin monostearate, glycerin, monobehenate, calcium behenate, hydogenated vegetable fat or oil, polyethylenglycol and talc, or mixtures thereof. In one embodiment the lubricant is selected from the list consisting of magnesium stearate, stearic acid and talc. In one embodiment, the carrier is magnesium stearate.

In an embodiment, the carrier according to the present invention is a sweetener selected from the group consisting of sucralose, saccharin, sodium-, potassium- or calcium saccharin, potassium acesulfame, neotame, alitame, glycyrrhizin or thaumatin, or sugars such as glucose, mannitol, fructose, saccharose, maltose, maltitol, galactose, sorbitol or xylitol, or mixtures thereof. In the context of the present invention sweeteners are added in amounts known for persons skilled in the art.

In an embodiment, the carrier according to the present invention is a flavoring agent selected from the group consisting of synthetic/artificial flavoring agents, such as amyl

acetate (banana flavoring), benzaldehyde (cherry or almond flavor), ethyl butyrate (pineapple), methyl anthranilate (grape), natural flavoring agents such as essential oils and oleoresins, herbs and spices, and natural-identical flavoring agents which are flavoring substances that are obtained by synthesis or are isolated through chemical processes and whose chemical make-up is identical to their natural counterpart, or mixtures thereof. In the context of the present disclosure flavoring agents are added in amounts known to persons skilled in the art according to the desired flavor intensity.

In an embodiment, the carrier according to the present invention is a colorant selected from the group consisting of dyes, lakes, or pigment such as indigo carmine, riboflavin and titanium dioxide, or mixtures thereof. In the context of the present disclosure colorants are added in amounts known for persons skilled in the art according to the desired color and/or color intensity.

In an embodiment, the carrier according to the present invention is an antioxidant selected from the group consisting of citric acid, butylated hydroxyanisole, butylated hydroxytoluene, ethylenediaminetetraacetic acid (EDTA), tocopherol (Vitamine E), ascorbic acid, glutathione, cysteine, sulfite (such as sodium sulfite or sodium hydrogen sulfite), di-sulfite (such as sodium di-sulfite), esters of ascorbic acid, and salts or esters of gallic acid, or mixtures thereof.

In an embodiment, the carrier according to the present invention is plasticizers, selected from the group consisting of polyethylene glycol, propylene glycol, sorbitol, glycerol, maltitol, xylitol, mannitol, erythritol, glycerol trioleate, tributyl citrate, triethyl citrate acetyl triethyl citrate, glyceryl triacetate, stearic acid, medium chain triglycerides or a mixture thereof.

In an embodiment the solid dispersion matrix comprises a mixture of one or more of the above disclosed disintegration promotors, fillers, lubricants, sweeteners, antioxidants, plasticizers, flavoring agents and/or colorants.

Pharmaceutical compositions according to the disclosure is in the form of a solid dispersion or a pharmaceutical composition comprising a solid dispersion. The solid dispersion may be a solid solution, glass solution, glass suspension, amorphous precipitation in a crystalline carrier, eutectic or monotectic, compound or complex formation or combinations thereof.

The inventors have unexpectedly found that the dissolution behavior of the solid pharmaceutical composition according to the present disclosure can be further optimized by adapting the weight ratio of elinzanetant to the solid dispersion matrix agent and to the carrier, or the weight ratio of the sum of elinzanetant and solid dispersion matrix to carrier, or the weight ratio of elinzanetant to carrier.

In an embodiment, the solid dispersion comprises elinzanetant or a pharmaceutically acceptable salt thereof, the solid dispersion matrix agent and the carrier in a weight ratio of from 1:0.5:0.15 to 1:4:10, such as from 1:1:0.5 to 1:3:6 or from 1:1.5:1 to 1:2.5:3.5. In an embodiment the solid dispersion comprises elinzanetant or a pharmaceutically acceptable salt thereof elinzanetant and the solid dispersion matrix agent and the carrier in a weight ratio of 1:2:2. In an embodiment, the solid dispersion comprises elinzanetant, the solid dispersion matrix agent and the carrier in a weight ratio of from 1:0.5:0.15 to 1:4:10, such as from 1:1:0.5 to 1:3:6 or from 1:1.5:1 to 1:2.5:3.5. In an embodiment the solid dispersion comprises elinzanetant and the solid dispersion matrix agent and the carrier in a weight ratio of 1:2:2.

In an embodiment, the solid dispersion comprises elinzanetant or a pharmaceutically acceptable salt thereof, the solid dispersion matrix agent and the carrier in a weight ratio for the sum of elinzanetant or a pharmaceutically acceptable salt thereof and the solid dispersion matrix agent to carrier of from 1:0.1 to 1:2, such as from 1:0.25 to 1:1.5 or from 1:0.4 to 1:1. In an embodiment the solid dispersion comprises elinzanetant and the solid dispersion matrix agent to carrier in a weight ratio of 1:2. In an embodiment, the solid dispersion comprises elinzanetant, the solid dispersion matrix agent and the carrier in a weight ratio for the sum of elinzanetant and the solid dispersion matrix agent to carrier of from 1:0.1 to 1:2, such as from 1:0.25 to 1:1.5 or from 1:0.4 to 1:1. In an embodiment the solid dispersion comprises elinzanetant and the solid dispersion matrix agent to carrier in a weight ratio of 1:2.

In an embodiment, the solid dispersion comprises elinzanetant or a pharmaceutically acceptable salt thereof and the carrier in a weight ratio of from 1:0.15 to 1:10, such as from 1:0.5 to 1:6 or from 1:1 to 1:3.5. In an embodiment the solid dispersion comprises elinzanetant or a pharmaceutically acceptable salt thereof and the carrier in a weight ratio of 1:2. In an embodiment, the solid dispersion comprises elinzanetant and the carrier in a

weight ratio of from 1:0.15 to 1:10, such as from 1:0.5 to 1:6 or from 1:1 to 1:3.5. In an embodiment the solid dispersion comprises elinzanetant and the carrier in a weight ratio of 1:2.

In an embodiment of the pharmaceutical composition, the solid dispersion is substantially homogeneous.

The present invention achieves a stable formulation in which elinzanetant or a pharmaceutically acceptable salt thereof is stabilized in its amorphous form through its shelf life and maintains supersaturation of elinzanetant in solution and resulting in a maximum bioavailability of elinzanetant *in vivo* after administration.

Excipients of the pharmaceutical composition outside the solid dispersion

The pharmaceutical composition according to the present disclosure may further comprise pharmaceutically acceptable excipients that do not form integral part of solid dispersion of the solid dispersion matrix and elinzanetant or the pharmaceutically acceptable salt thereof. Such pharmaceutically acceptable excipient may for example be blended with the solid dispersion before further processing of the pharmaceutical composition, such as tableting. In one embodiment the pharmaceutical composition according to the disclosure may comprise further pharmaceutically acceptable excipients, such as selected from the group consisting of fillers, lubricants, disintegration promoters, sweeteners, antioxidants, plasticizers, flavoring agents and/or colorants or a combination thereof. The embodiments for the fillers, lubricants, disintegration promoters, sweeteners, antioxidants, plasticizers, flavoring agents and/or colorants, or mixtures thereof, comprised in the pharmaceutical composition are as disclosed for the respective excipients as carriers in the solid dispersion herein.

In an embodiment the pharmaceutical composition consists of a blend of the solid dispersion according to the present disclosure and one or more further pharmaceutically excipients, altogether mixed and formulated into tablets which are optionally finally coated.

In one embodiment the solid pharmaceutical composition comprises a lubricant. In an embodiment the lubricant is selected from the group consisting of magnesium stearate, stearic acid, lecithin, soy lecithin, mineral oil, carnauba wax, acetylated monoglycerides, and polysorbate; or a mixture thereof. In one embodiment the lubricant is magnesium stearate.

The lubricant may be blended with the solid dispersion comprising elinzanetant and the solid dispersion matrix. In an embodiment the lubricant does not form part of the solid dispersion but is blended with the solid dispersion before further processing of the pharmaceutical composition, such as tableting.

Coating

In one embodiment, the solid pharmaceutical composition is optionally coated. In an embodiment the pharmaceutical composition according to the disclosure is a tablet.

In an embodiment the tablet is coated.

In the context of the present invention the optional coating is carried out with addition of customary coating and film-forming agents familiar to the person skilled in the art, such as hydroxy-propylcellulose, hydroxypropylmethylcellulose (HPMC), ethylcellulose, polyvinyl-pyrrolidone, vinylpyrrolidone-vinyl acetate copolymers (for example Kollidon® VA64, BASF), shellac, acrylic and/or methacrylic acid ester copolymers with trimethylammonium methylacrylate, copolymers of dimethylaminomethacrylic acid and neutral methacrylic acid esters, polymers of methacrylic acid or methacrylic acid esters, ethyl acrylate-methyl methacrylate copolymers, methacrylic acid-methyl acrylate copolymers, propylene glycol, polyethylene glycol (e.g. polyethylene glycol 3350), glycerol triacetate or triethyl citrate, and/or colorants/pigments such as, for example, titanium dioxide, rice starch, calcium sulfate, calcium carbonate, iron oxide (e.g. red iron oxide, yellow iron oxide, black iron oxide), indigotin or suitable color lakes, and/or anti-tacking agents such as talc, and/or opacifiers such as titanium dioxide, rice starch, calcium sulfate, calcium carbonate. An optional coating may comprise HPMC and polyethylene glycol, and iron oxide, such as iron oxide red and/or iron oxide yellow. Optionally the coating may comprise an opacifier, such titanium dioxide or rice starch or calcium sulfate. A mixture of the coating substances mentioned herein may also be used as a ready-to-use coating system such as commercially available coatings.

In an embodiment, the coating is about 0.5% to 10% by weight of the coated tablet, preferably 0.5% to 4.5% by weight of the coated tablet formulation, more preferably about 1.5% to 4.5% by weight of the coated tablet. In an embodiment the solid pharmaceutical composition is coated with a lacquer containing HPMC and polyethylene glycol, and iron

oxide, such as iron oxide red, iron oxide yellow and titanium dioxide. In an embodiment the solid pharmaceutical composition is coated with a lacquer containing HPMC and polyethylene glycol, and iron oxide, such as iron oxide red, iron oxide yellow, and one or more opacifier selected from the group consisting of rice starch, calcium sulfate, and calcium carbonate.

Amount of elinzanetant in the solid pharmaceutical composition

The pharmaceutical composition according to the present invention can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable excipient and a pharmaceutically effective amount of elinzanetant. A pharmaceutically acceptable excipient is any excipient which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of elinzantent is that amount which produces a result or exerts an influence on the particular condition being treated.

The pharmaceutical composition according to the invention demonstrates improved pharmacokinetic properties compared to compositions of prior art, in particular the soft gelatin capsules used in Phase III clinical studies. Specifically, the pharmaceutical composition according to the present invention achieves comparable pharmacokinetic exposure at a reduced dose. Data show that a daily dose of 110 mg of the present invention provides an area under the curve (AUC) equivalent to that achieved with a 120 mg daily dose of the prior art composition. This reduction in required dosage, while maintaining therapeutic levels, offers significant advantages including decreased potential for adverse effects and improved patient compliance.

The total amount of elinzanetant to be administered using the pharmaceutical composition of the present invention will generally range from about 5 mg to about 300 mg per day. The amount of the administered elinzanetant can vary widely according to considerations as the compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient

treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

In an embodiment, the amount of elinzanetant in a dosage unit, such as one tablet, of the pharmaceutical composition is from 5 mg to 300 mg, in an embodiment from 60 to 240 mg, in an embodiment from 90 mg to 160mg, in an embodiment 100 to 160 mg.

In an embodiment, the amount of elinzanetant in a dosage unit of the pharmaceutical composition, such as one tablet, is 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, or 120 mg.

An embodiment of the disclosure is a pharmaceutical composition, such as a tablet, comprising elinzanetant in an amount of 5 mg to 300 mg, such as from 60 to 200 mg, such as from 90 mg to 160 mg, such as from 100 to 160 mg. An embodiment of the disclosure is a pharmaceutical composition, such as a tablet, comprising elinzanetant in an amount of 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, or 120 mg.

In an embodiment, the amount of elinzanetant in a single dosage unit of the pharmaceutical composition, such as a tablet, is 120 mg.

A single dosage unit may comprise the daily dose of elinzanetant.

In one embodiment, the daily dose of elinzanetant is from 40 to 300 mg, such as 60 to 200 mg, such as 60 to 160 mg, e.g. 60, 80, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, 120 mg, or 160 mg.

In an embodiment the daily dose of elinzanetant is 100 mg, 105 mg, 110 mg, 115 mg or 120 mg.

In an embodiment the daily dose of elinzanetant is 100 mg.

In an embodiment the daily dose of elinzanetant is 105 mg.

In an embodiment the daily dose of elinzanetant is 110 mg.

In an embodiment the daily dose of elinzanetant is 115 mg.

In an embodiment the daily dose of elinzanetant is 120 mg.

A single dosage unit may contain an integer fraction of the daily dose of elinzanetant. For illustrative purpose a single dosage unit may contain half of the daily dose so that two dosage units are to be taken for administration of the daily dose. Likewise, a single dosage unit may contain a third of the daily dose so that three dosage units are to be taken for administration of the daily dose, and so on.

Hence, it is also most preferred that the amount of elinzanetant in the pharmaceutical composition is an integer fraction of 120 mg, such as 20 mg, 30 mg, 40 mg, 60 mg, or 120 mg. It is nevertheless a particular embodiment that a single dosage unit of the pharmaceutical composition comprises a daily dose of elinzanetant, preferably 120 mg.

Likewise, it is also preferred that the amount of elinzanetant in the pharmaceutical composition is an integer fraction of 110 mg, such as 55 mg. It is nevertheless a particular embodiment that a single dosage unit of the pharmaceutical composition comprises a daily dose of elinzanetant, preferably 110 mg.

Likewise, it is also preferred that the amount of elinzanetant in the pharmaceutical composition is an integer fraction of 100 mg, such as 50 mg. It is nevertheless a particular embodiment that a single dosage unit of the pharmaceutical composition comprises a daily dose of elinzanetant, preferably 100 mg

The pharmaceutical composition according to the invention is administered once or more daily, such as up to three times daily, or up to two times per day. In one embodiment, the solid pharmaceutical composition is administered once daily. In an embodiment, the pharmaceutical composition is administered via the oral route.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behavior toward the active ingredient, type of preparation and time or interval over which the administration is affected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the

upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

The pharmaceutical composition will be utilized to achieve the desired pharmacological effect by, e.g., oral administration to a patient in need thereof and will have advantageous properties in terms of stability, drug release, bioavailability, and/or compliance in mammals.

A patient, for the purpose of this invention, is a mammal, including and in particular a human, in need of treatment for the particular condition or disease.

The pharmaceutical composition according to the invention is in an embodiment a solid pharmaceutical composition and is administered orally or rectally. The pharmaceutical composition according to the invention is in an embodiment a solid pharmaceutical composition and is administered orally.

Dissolution and Pharmacokinetic Features of the pharmaceutical composition

In an embodiment the pharmaceutical composition, is an immediate release pharmaceutical composition, including an immediate release tablet, immediate release granules, immediate release pellets, immediate release solid mixture immediate release dragées, immediate release sachets, immediate release pills, and immediate release melts.

In one embodiment the pharmaceutical composition is a tablet, such as an immediate release tablet.

"Immediate release" in one embodiment relates to a rapid dissolution of elinzanetant from the composition occurring *in vitro*. When administered, the pharmaceutical composition first enters the acidic environment of the stomach before entering the more neutral environment of the duodenum. Accordingly, it may be desirable for the solid pharmaceutical composition, such as a tablet, to allow dissolution of elinzanetant *in vitro* within a certain time after adding it to a solution of acidic conditions for a certain time and rebuffering from that acidic to a more neutral condition. Accordingly, in an embodiment "rapid dissolution" is defined as the *in vitro* dissolution of elinzanetant is such that at least 50% is dissolved within 120 minutes, as determined by USP XXIII Paddle Method II first

using FaSSGF at pH 2.4 as a medium at 37° and 75 rpm as stirring rate for 30 min and then rebuffering to FaSSIF at a pH 6.5 as a medium at 37° and 75 rpm as stirring rate. In a further embodiment "rapid dissolution" is defined as the *in vitro* dissolution of elinzanetant is such that at least 60% is dissolved within 120 minutes, as determined by USP XXIII Paddle Method II first using FaSSGF at pH 2.4 as a medium at 37° and 75 rpm as stirring rate for 30 min and then rebuffering to FaSSIF at a pH 6.5 as a medium at 37° and 75 rpm as stirring rate.

In an embodiment the *in vitro* dissolution of at least 75% of the comprised elinzanetant within 210 minutes, as determined by USP XXIII Paddle Method II first using FaSSGF at pH 2.4 as a medium at 37°C±0.5°C and 75 rpm as stirring rate for 30 min, and then rebuffering to Fasted State Simulated Intestinal Fluid (FaSSIF) at a pH 6.5 as a medium at 37°C±0.5°C and 75 rpm as stirring rate. In a further embodiment of the solid pharmaceutical composition at least 80% of the comprised elinzanetant is dissolved in vitro within 210 minutes, as determined by USP XXIII Paddle Method II first using FaSSGF at pH 2.4 as a medium at 37°C±0.5°C and 75 rpm as stirring rate for 30 min, and then rebuffering to Fasted State Simulated Intestinal Fluid (FaSSIF) at a pH 6.5 as a medium at 37°C±0.5°C and 75 rpm as stirring rate.

An object of the present disclosure is the provision of a solid pharmaceutical composition having the desired bioavailability. Bioavailability in one embodiment is defined as the fraction (percentage) of an administered dose or the concentration (µg drug per L blood) of elinzanetant that reaches the blood stream (systemic circulation) within a time period after administration of the pharmaceutical composition, e.g. the solid pharmaceutical composition according to the present disclosure. T_{max} is the time where the highest concentration of elinzanetant is found in the bloodstream after administration, whereas C_{max} is the maximum concentration of elinzanetant found in the bloodstream after administration. The area under the curve (AUC(0-t_{last})) represents the total amount of elinzanetant which was in the bloodstream over the period studied, or extrapolated to infinity to obtain the total AUC. In one embodiment, the present disclosure relates to a pharmaceutical composition, such as a solid pharmaceutical composition, comprising elinzanetant or a pharmaceutical acceptable salt thereof, wherein the pharmaceutical composition essentially exhibits a bioavailability of elinzanetant as a solid pharmaceutical

composition according to the present disclosure, such as tablets having the composition of Composition 5 of Example 1 of the present disclosure.

"Essentially" in context with the present disclosure refers to values that are within a range of ±30% from the respective value, such as within a range of ±25% from the respective value. In one embodiment "essentially" refers to bioequivalence, such as the bioequivalence according to the US Food and Drug Administration (FDA), e.g. a range between -20% and +25% from the respective value, in other words between 80% and 125% of the respective value. According to the Guidelines of the FDA the upper and lower 90% confidence intervals of the mean value is within the ranges. Hence, in one embodiment the upper and lower 90% confidence intervals of the mean value are within the range of -20% and +25% from the respective value, in other words between 80% and 125% of the respective value.

Bioavailability is in one embodiment evaluated by determining C_{max} and/or total AUC after administration of the pharmaceutical composition to a subject, such as a human subject. In an embodiment administration for determining is performed in the morning, during the day or in the evening. In an embodiment, administration for determining is performed under fasted conditions, such as in the morning before food uptake.

In one embodiment, the pharmaceutical composition of the present disclosure, when administered at a single dose of 120 mg under fasted conditions, exhibits a C_{max} of between 600 µg/L and 1200 µg/L, such as between 650 µg/L and 1150 µg/L. In one embodiment the C_{max} is 901 µg/L ±25%, such as between 80% and 125% of 901 µg/L.

In one embodiment, the pharmaceutical composition of the present disclosure, when administered at a single dose of 120 mg under fasted conditions, exhibits a geometric mean of C_{max} of between 600 µg/L and 1200 µg/L, such as between 650 µg/L and 1150 µg/L. In one embodiment the C_{max} is 941 µg/L ±25%, such as between 80% and 125% of 941 µg/L.

In one embodiment the pharmaceutical composition of the present disclosure, when administered at a single dose of 120 mg, exhibits a C_{max} of between 80% and 125% of the C_{max} as observed after a single dose of 120 mg with a tablet of Composition 5 of Example 1 of the present disclosure. In one embodiment the single doses are administered under fasted conditions.

In one embodiment, the pharmaceutical composition, when administered at a single dose of 120 mg fasted conditions, exhibits a total AUC of between 5000 µg*h/L and 10000 µg*h/L, such as between 5700 µg*h/L and 9600 µg*h/L. In one embodiment the total AUC is 7602 µg*h/L ±25%, such as between 80% and 125% of 7602 µg*h/L.

In one embodiment, the pharmaceutical composition, when administered at a single dose of 120 mg fasted conditions, exhibits a geometric mean of total AUC of between 5000 µg*h/L and 10000 µg*h/L, such as between 5700 µg*h/L and 9600 µg*h/L. In one embodiment the total AUC is 7480 µg*h/L ±25%, such as between 80% and 125% of 7480 µg*h/L.

In an embodiment the pharmaceutical composition of the present disclosure, when administered at a single dose of 120 mg, exhibits a total AUC of between 80% and 125% of the total AUC as observed after a single dose of 120 mg with a tablet of Composition 5 of Example 1 of the present disclosure. In one embodiment the single doses are administered under fasted conditions.

In an embodiment the pharmaceutical composition of the present disclosure, when administered at a single dose of 110 mg, exhibits a total AUC of between 80% and 125% of the total AUC as observed after a single dose of 100 mg, 105 mg,110 mg, or 115 mg with a tablet of Composition 5 of Example 1 of the present disclosure.

In one embodiment the values herein for C_{max} and total AUC refer to the geometric mean.

In one embodiment, the pharmaceutical composition comprises:

(i) elinzanetant at a concentration of 5 % w/w to 50 % w/w,
(ii) copovidone at a concentration of 4% w/w to 77% w/w,
(iii) optionally croscarmellose sodium at a concentration of 4% w/w to 87% w/w, and
(iv) Magnesium stearate at a concentration of 0.1% w/w to 1.5% w/w.

In one embodiment, the pharmaceutical composition comprises:

(i) elinzanetant at a concentration of 5 % w/w to 50 % w/w,
(ii) copovidone at a concentration of 4% w/w to 77% w/w,
(iii) Magnesium stearate at a concentration of 0.1% w/w to 1.5% w/w.

In one embodiment, the pharmaceutical composition comprises:

(i) elinzanetant at a concentration of 5 % w/w to 50 % w/w,

(ii) copovidone at a concentration of 4% w/w to 77% w/w,

(iii) croscarmellose sodium at a concentration of 4% w/w to 87% w/w, and

(iv) Magnesium stearate at a concentration of 0.1% w/w to 1.5% w/w.

In one embodiment, the pharmaceutical composition comprises:

(i) elinzanetant at a concentration of 10 % w/w to 40 % w/w,

(ii) copovidone at a concentration of 30% w/w to 50% w/w,

(iii) croscarmellose sodium at a concentration of 30% w/w to 50% w/w, and

(iv) Magnesium stearate at a concentration of 0.2% w/w to 1.0% w/w.

In one embodiment the pharmaceutical composition comprises:

(i) elinzanetant at a concentration of about 19.9% w/w,

(ii) copovidone at a concentration of about 39.8% w/w,

(iii) croscarmellose sodium at a concentration of about 39.8 % w/w, and

(iv) Magnesium stearate at a concentration of about 0.5 % w/w.

Methods of treatment

Elinzanetant is suited for the treatment of diseases and disorder, such as psychotic disorders (WO 2007/028654 A1), and sex hormone-dependent diseases and disorders (WO 2016/184829 A1). In particular sex hormone-dependent diseases and disorders have been proven to be ameliorated by administration of elinzanetant in various clinical studies.

Accordingly, in a preferred embodiment of the present invention disease or disorder is a sex hormone-dependent disease or disorder. In a particular preferred embodiment, the sex hormone-dependent disease or disorder is selected form the group consisting of vasomotor symptoms, pathological gain of excess body fat and/or excess body weight, insomnia, sleep disturbances, night-time awakenings, anxiety, depression, urinary symptoms of urgency, dysuria.

The term "sex hormone-dependent disease or disorder" as used herein means a disease or disorder which is exacerbated by, or caused by, excessive, inappropriate, or unregulated sex hormone production. Sex hormone-dependent diseases or disorders may occur in both sexes/genders, men and women. Accordingly, in one embodiment of the present invention, the subject is man. In a further embodiment of the present invention the subject is a woman.

Example of such diseases or disorders in men include but are not limited to benign prostatic hyperplasia (BPH), metastatic prostatic carcinoma, testicular cancer, breast cancer, androgen dependent acne, seborrhea, hypertrichosis, male pattern baldness, vasomotor symptoms and in boys' precocious puberty.

Example of such diseases or disorders in women include but not limited to endometriosis, adenomyosis, abnormal puberty, uterine fibroids, heavy menstrual bleeding, hormone-dependent cancers (ovarian cancer, breast cancer), hyperandrogenism, hirsutism, hypertrichosis, female androgenetic alopecia, androgen dependent acne, seborrhea, virilization, polycystic ovary syndrome (PCOS), HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized the ca cells in ovarian stroma), other manifestations of high intra ovarian androgen concentrations (e.g. follicular maturation arrest, atresia, an ovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility), androgen producing tumor (virilizing ovarian or adrenal tumor), pathological gain of excess body fat and/or excess body weight, pre-eclampsia, diabetes, fatigue, irritability, cognitive decline, hair-loss, dry skin, insomnia, sleep disturbances, night-time awakenings, anxiety and depression, decreases in sexual desire, vaginal dryness and pain, connective tissue loss and muscle bulk reduction, urinary symptoms of urgency, hidradenitis suppurativa, dysuria, osteoporosis.

Sex hormone-dependent diseases or disorders may be caused and/or associated with different conditions, which can have natural (such as menopause or adrenopause), surgical (such as bilateral oophorectomy in women, or orchiectomy or prostatectomy in men), radiological (i.e. radiation therapy) or chemical causes (e.g. adjuvant endocrine therapy).

Vasomotor symptoms or sleep disturbances or night-time awakenings can for example be caused by different conditions. In women the condition may be menopause-associated conditions, such as peri-menopause, the menopause, or the post-menopause. When referring to association with menopause herein, it is preferably meant to include peri-menopause, menopause and post-menopause, more preferably peri-menopause and menopause.

In men, sex hormone-dependent diseases or disorders may be associated with adrenopause.

Accordingly, in a preferred embodiment of the present invention, the disease or disorder, preferably the sex hormone-dependent disease or disorder, is a disease or disorder is associated with menopause or adrenopause.

Further, sex hormone-dependent diseases or disorders, e.g., vasomotor symptoms, may be caused in men and women by certain types of therapy interfering with hormone signaling and/or regulation, e.g., adjuvant endocrine therapy, aromatase inhibitors such as anastrozole, exemestane, letrozole and testolactone; gonadotropin-releasing hormone receptor agonists such as such as leuprolide, buserelin, histrelin, goserelin, deslorelin, nafarelin and triptorelin; gonadotropin-releasing hormone receptor antagonists such as ASP1701, elagolix, relugolix and linzagolix (OBE2109); selective estrogen receptor modulators (SERMs) such as bazedoxifene, clomifene, cyclofenil, tamoxifen, ormeloxifene, toremifene, raloxifene, lasofoxifene and ospemifene; selective estrogen receptor degraders (SERDs) such as fulvestrant, brilanestrant and elacestrant; CYP17 AI inhibitors such as abiraterone, ketoconazole and seviteronel; and combined androgen receptor blockers and CYP17 AI inhibitors such as galeterone.

In a particular preferred embodiment of the invention, the disease or disorder is a sex hormone-dependent disease or disorder selected from the group consisting of vasomotor symptoms, insomnia, sleep disturbances, and night-time awakenings. Yet, particularly preferred is the embodiment in which the disease or disorder is vasomotor symptoms.

In a preferred embodiment these sex hormone-dependent diseases or disorders are associated with menopause or caused by adjuvant endocrine therapy. Accordingly, in a preferred wherein the vasomotor symptoms are caused or induced by therapy with an aromatase inhibitor and/or selective estrogen receptor modulators (such as tamoxifen).

Moreover, in a particularly preferred embodiment of the invention the disease or disorder is selected from the group consisting of vasomotor symptoms associated with menopause, insomnia associated with menopause, sleep disturbances associated with menopause, and night-time awakenings associated with menopause. Yet more preferred, the disease or disorder is vasomotor symptoms associated with menopause. Associated with menopause includes peri-menopause, menopause and post-menopause.

Process for manufacturing

The solid dispersion of the invention can be prepared according to methods known to the art for the manufacture of solid dispersions, such as fusion/melt technology, hot melt extrusion, solvent evaporation (i.e. freeze drying, spray drying or layering of powders of granules), coprecipitation, supercritical fluid technology and electrostatic spinning method which are for example described in WO 2006/026500.

Hot melt extrusion or solvent evaporation techniques are preferred processes for preparation of solid dispersion formulations of this invention.

A solvent suitable for manufacture of solid dispersions by solvent evaporation processes such as spray-drying, layering or fluid-bed granulation can be any solvent, wherein the compound of the invention can be dissolved. Preferred solvents include alcohols (e.g. methanol, ethanol, n-propanol, isopropanol, and butanol), ketones (e.g. acetone, methyl ethyl ketone and methyl isobutyl ketone, butanone), esters (e.g. ethyl acetate and propyl acetate) and various other solvents such as acetonitrile, methylene chloride, chloroform, hexane, toluene, tetrahydrofurane, cyclic ethers, and 1,1,1-trichloroethane. Lower volatility solvents, such as dimethyl acetamide or dimethyl sulfoxide can also be used. Mixtures of solvents, such as 20% ethanol and 80% acetone, can also be used, as can mixtures with water as long as the drug and if necessary, the solid dispersion matrix agent are sufficiently soluble to make the process practicable.

In a preferred embodiment the solvent used for manufacture of the solid dispersion is methanol, ethanol, n-propanol, isopropanol, acetone or a mixture thereof. In an embodiment a mixture of ethanol and acetone (1:4) is used as solvent. In an embodiment acetone is used as solvent.

The pharmaceutical composition according to the invention is optionally coated according to methods known to the art as described e.g. in WO 2014/039677 like spraying the coating liquid in a pan or perforated drum coater onto the pharmaceutical composition.

Most film coatings are applied as aqueous or organic based or aqueous-organic based polymer solutions. Methods for applying coating polymers are described in e.g. (Bauer et al., Wiss. Verl.-Ges., "Überzogene Arzneiformen", 1988, ISBN 3-8047-0812-9). There are also several solvent-free coating techniques being described or even applied such as compression coating, hot-melt coating, electrostatic spray powder coating, dry powder coating, supercritical fluid-based coating, and photocurable coating. (Pharm. Dev. Tech., 12, "Solventless Pharmaceutical Coating Processes: A Review", 2007, 115-131).

EXAMPLES

Example 1: Preparation of Compositions

Materials and Methods

Elinzanetant-solvent mixture

The crystalline anhydrate Form 1 of elinzanetant and the polymer were dissolved within an organic solvent (acetone, or a mixture of acetone and ethanol (4:1)).

As polymers polyvinylpyrrolidone (PVP), copovidon, hydroxypropylmethylcellulose-phthalate (HPMC-P), HPMC-acetylsuccinate (HPMC AS), Polyacrylic acid and Hydroxypropylcellulose (HPC) were used.

In addition, in indicated cases a surfactant (e.g. Macrogol 15 hydroxystearate, sodium dodecyl sulfate (SDS)) was added to the elinzanetant-polymer solution.

Carrier addition

Croscarmellose sodium was used as carrier. The carrier was added to the compositions either using rotavapor-preparation or fluid bed granulation.

In the case for rotavapor-preparation, croscarmellose sodium was suspended within the elinzanetant-polymer solution and the suspension filled into a round bottomed flask and acetone evaporated on a rotavapor instrument (Büchi, ~40°C,< 100 mbar). Dryed film material was removed from the glass flask and crushed by mortar and pestle or using a

coffee mill (IKA, 8000 rpm, 30 sec) to obtain the amorphous solid dispersion material (ASD material).

In case of a fluid bed granulation process croscarmellose sodium was fluidized within a granulator (Glatt GPCG 2) and the elinzanetant-polymer solution was sprayed onto it and dried to obtain the ASD material as granules. The granules were roller compacted with a Gerteis Minipactor and directly grinded down to granules to increase bulk density, if needed.

Amorphous state of the ASD material was confirmed via DSC and XRPD measurements as follows:

The X-Ray Powder Diffraction (XRPD) data was recorded on a Bruker D2 PHASER diffractometer with a LYNXEYE-2 detector using Cu Kα1 radiation (1.54060 Å). All samples were prepared and measured at ambient temperature, on open Si-single-crystal low background sample holders. The data were collected in the Bragg-Brentano (θ/2θ) horizontal geometry between either 3° and 40° (2Θ) in 0.02° steps at 0.3 s step-1. The X-ray tube was operated at 30 kV and 10 mA.

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) were performed with a Mettler Toledo DSC 3+ or TGA/DSC 3+. The instruments were purged with nitrogen gas at a flow rate of 20 ml min^{-1}. Approximately 1 – 15 mg of each sample was placed into an aluminum crucible and heated at a heating rate of 20 °C min^{-1} starting from 25°C or 30°C. No sample preparation.

Tablets

Tablets with an amount of 120 mg elinzanetant each were prepared and investigated. Tablets were compressed out of the prepared ASD material using either a compression simulator (StylOne Evolution, Medelpharm), an eccentric press (EK2, Korsch), or a rotary die press (Fette 102i, Fette compacting; XL-100, Korsch). Oval tablets with a length between 16 mm and 19 mm length were produced, depending on the composition mass needed to obtain tablets with the indicated amount of elinzanetant. Compression force was set to target a resistance to crushing between 150 N -190 N per tablet, depending on tablet size.

Resistance to crushing of the tablets was tested on a conventional hardness tester (Sotax MT50 und UTS4.1-12FSr Kraemer).

Table 1 Overview ASD tablet compositions

Composition No.	1	2	3	4	5	6	7	8
Elinzanetant	120	120	120	120	120	120	120	120
Copovidone	120	180	240	240	240	240	360	
PVP								120
HPC								
HPMC-P								
HPMC AS								
Macrogol-15-hydroxystearate								
SDS								
Croscamellose sodium	240	300	360	290	240	194	480	240
Magnesium-stearate	3	3.5	4	3	3	3	5	3
Total tablet weight	483	603.5	724	653	603	557	965	483

Composition No.	9	10	11	12	13	14	15	16
Elinzanetant	120	120	120	120	120	120	120	120
Copovidone			120	120	240	240	240	240
PVP								
HPC	120	240						
HPMC-P								
HPMC AS								
Macrogol-15-hydroxystearate			24	60	24		60	
SDS						24		60
Croscamellose sodium	240	360	240	240	360	360	360	360
Magnesium-stearate	3	4	3	3	3	4	3	4
Total tablet weight	483	724	507	543	747	748	783	784

Table 1 (continued)

Composition No.	17	18	19	20	21	22	23	24	25
Elinzanetant	120	120	120	120	120	120	120	120	120
Copovidone									
PVP	240	240							
HPC									
HPMC-P			120	180	240	360			
HPMC AS							120	180	240
Macrogol-15-hydroxystearate									
SDS	24	60							
Croscamellose sodium	360	360	240	300	360	480	240	300	360
Magnesium-stearate	4	4	3	3.5	4	5	3	3	4
Total tablet weight	748	784	483	603.5	724	965	483	603	724

Values for the respective components are in mg/tablet;

Composition 1 Copovidone ASD ratio 1:1:2 (elinzanetant:polymer:carrier)

12.5 g elinzanetant were dissolved in 44.8 g of solvent mixture (acetone/ethanol (4:1)). 12.5 g Copovidone and additional 39 g of solvent mixture were added and heated to 40°C until a clear solution resulted.

Afterwards 25 g croscarmellose sodium was added and flushed with 6.6 g of the organic mixture into the flask. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar. The ASD material was blended with 0.063 g sieved magnesium stearate and compressed into 16*6 mm tablets each with a total weight of 483 mg.

Composition 2 Copovidone ASD ratio 1:1.5:2.5 (elinzanetant:polymer:carrier)

12.6 g copovidone were dissolved in 42 g of acetone. 8.4 g elinzanetant were added and shaken until a clear solution resulted. Afterwards 21 g croscarmellose sodium was added. The solvent was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar. 10.2 g of the ASD material was blended with 0.06 g

sieved magnesium stearate and compressed into 17*7 mm tablets each with a total weight of 603.5 mg.

Composition 3 Copovidone ASD ratio 1:2:3 (elinzanetant:polymer:carrier)

8.3 g elinzanetant were dissolved in 13.7 g of solvent mixture (acetone/ethanol (4:1)). 16.6 g Copovidone and additional 27.5 g of the solvent mixture were added and heated to 40°C until a clear solution resulted. Afterwards 24.9 g croscarmellose sodium were added and dispersed. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar. 10.08 g of the ASD material were blended with 0.056 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 724 mg.

Composition 4 Copovidone ASD ratio 1:2:2.4 (elinzanetant:polymer:carrier)

92.5 g elinzanetant and 184.8g copovidone were dissolved in 369.9 g acetone and added to 223.4 g croscarmellose sodium using fluid bed granulation. 440.7 g of ASD material were blended with 2 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 653 mg.

Composition 5 Copovidone ASD ratio 1:2:2 (elinzanetant:polymer:carrier)

208.44 g elinzanetant and 416.91 copovidone were dissolved in 625.7 g acetone and added to 416.9 croscarmellose sodium using fluid bed granulation. 300 g of the ASD material as granules were blended with 1.5 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 603 mg. Tablets were coated within a drum coater with a yellow HPMC lacquer.

Composition 6 Copovidone ASD ratio 1:2:1.6 (elinzanetant:polymer:carrier)

216.76 g elinzanetant and 433.47 g copovidone were dissolved in 867.5 g acetone and added to 350.37 g croscarmellose sodium using fluid bed granulation. 300.8 g of ASD material were blended with 1.6 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 557 mg.

Composition 7 Copovidone ASD ratio 1:3:4 (elinzanetant:polymer:carrier)

25.2 g copovidone were dissolved in 77 g of acetone. 8.4 g elinzanetant were added and shaken until a clear solution resulted. Afterwards 58.81 g croscarmellose sodium were added. The solvent was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar. 16.32 g of the ASD material was blended with 0.085g sieved magnesium stearate and compressed into 19*8 mm tablets each with a total weight of 965 mg.

Composition 8 PVP ASD ratio 1:1:2 (elinzanetant:polymer:carrier)

12.5 g Polyvinylpyrrolidone (PVP) were dissolved in 101.1 g solvent mixture (acetone/ethanol (4:1)). 12.5 g elinzanetant were added and shaken until a clear solution was obtained. Afterwards 25 g croscarmellose sodium were added and dispersed. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar. 9.9 g of the ASD material was blended with 0.06 g sieved magnesium stearate and compressed into 16*7 mm tablets each with a weight of 483 mg.

Composition 9 HPC ASD ratio 1:1:2 (elinzanetant:polymer:carrier)

7.5 g elinzanetant were dissolved in 10.2 g solvent mixture (acetone/ethanol (4:1)). 7.5 g Hydroxypropylcellulose (HPC) and additional 114.6 g of solvent mixture were added and shaken until a clear solution resulted.

Afterwards 15.1 g croscarmellose sodium were added and dispersed together with 7.2 g solvent mixture. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a coffee mill. 29.65 g of the ASD material were blended with 0.185g sieved magnesium stearate and compressed into 16*7 mm tablets each with a total weight of 483 mg.

Composition 10 HPC ASD ratio 1:2:3 (elinzanetant:polymer:carrier)

7.5 g elinzanetant were dissolved in 16.8 g of the solvent mixture (acetone/ethanol (4:1)). 15 g Hydroxypropylcellulose (HPC SL) were together with additional 147.2 g solvent mixture added and shaken until a clear solution resulted. Afterwards 22.7 g

croscarmellose sodium were added and dispersed together with 5 g solvent mixture. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask, dried overnight and crushed down using a coffee mill. 41 g of the ASD material was blended with 0.228 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 742 mg.

Composition 11 Copovidone ASD ratio 1:1:2 (elinzanetant:polymer:carrier) with Macrogol-15-hydroxystearate

7.2 g Copovidone were dissolved in 24 g acetone. 7.2 g elinzanetant were added and shaken until a clear solution resulted. Afterward 1.46 g Macrogol-15-Hydroxystearate with 5 g acetone were added and dissolved, succeeded by the addition of 14.4 g croscarmellose sodium. The solvents were removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a coffee mill. 15 g of the ASD material were blended with 0.088 g sieved magnesium stearate and compressed into 16*7 mm tablets each with a total weight of 507 mg.

Composition 12 Copovidone ASD ratio 1:1:2 (elinzanetant:polymer:carrier) with Macrogol-15-hydroxystearate

6.6 g Copovidone were dissolved in 24 g of acetone. 6.6 g elinzanetant were added and shaken until a clear solution resulted. Afterward 3.3 g Macrogol-15 Hydroxystearate and 8 g acetone were added and dissolved, succeeded by the addition of 13.2 g croscarmellose sodium and 2 g acetone. The solvent was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a coffee mill. 15 g of the ASD material was blended with 0.084 g sieved magnesium stearate and compressed into 16*7 mm tablets each with a total weight of 543 mg.

Composition 13 Copovidone ASD ratio 1:2:3 (elinzanetant:polymer:carrier) with Macrogol-15-hydroxystearate

9.6 g Copovidone were dissolved in 22 g acetone. 4.8 g elinzanetant were added and shaken until a clear solution resulted. Afterward 1 g Macrogol-15 Hydroxystearate and 8

g acetone were added and dissolved, succeeded by the addition of 14.4 g croscarmellose sodium and 2 g acetone. The solvent was afterwards removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a coffee mill. 15 g of the ASD material was blended with 0.061 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 747 mg.

Composition 14 Copovidone ASD ratio 1:2:3 (elinzanetant:polymer:carrier) with SDS

16.8 g Copovidone were dissolved in 52.5 g of acetone. 8.4 g elinzanetant were added and shaken until a clear solution resulted. Afterwards 1.68 g SDS suspended within in 13.13 g ethanol were added, succeeded by the addition of 25.2 g croscarmellose sodium. The solvents were removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar and a coffee mill. 13.26 g of the ASD material were blended with 0.068 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 748 mg.

Composition 15 Copovidone ASD ratio 1:2:3 (elinzanetant:polymer:carrier) with Macrogol-15-hydroxystearate

13.69 g Copovidone were dissolved in 24 g of acetone. 6.86 g elinzanetant were added and shaken until a clear solution resulted. Afterward 3.44 g Macrogol-15 Hydroxystearate and 10 g acetone and were added and dissolved, succeeded by the addition of 20.54 g croscarmellose sodium and 5 g acetone. The solvent was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a coffee mill. 25 g of the ASD material was blended with 0.094 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 783 mg.

Composition 16 Copovidone ASD ratio 1:2:3 (elinzanetant:polymer:carrier) with SDS

16.8 g Copovidone were dissolved in 52.5 g of acetone. 8.4 g elinzanetant were added and shaken until a clear solution resulted. 4.2 g SDS were suspended within 13.13 g of

ethanol were added, succeeded by the addition of 25.2 g croscarmellose sodium. The solvents were removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar and a coffee mill. 13.26 g of the ASD material were blended with 0.068 g sieved magnesium stearate and into 18*8 mm tablets each with a total weight of 784 mg.

Composition 17 PVP ASD ratio 1:2:3 (elinzanetant:polymer:carrier) with SDS

16.8 g PVP 25 were dissolved in 52.5 g solvent mixture (acetone/ethanol (4:1)). 8.4 g elinzanetant were added and shaken until a clear solution resulted. The solution was mixed with 1.7 g SDS dissolved in 885.1 g solvent mixture (acetone/ethanol (4:1)), succeeded by the addition of 25.2 g croscarmellose sodium. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar and a coffee mill. 12.7 g of the ASD material was blended with 0.068 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 748 mg.

Composition 18 PVP ASD ratio 1:2:3 (elinzanetant:polymer:carrier) with SDS

16.8 g PVP 25 were dissolved in 52.5 g solvent mixture (acetone/ethanol (4:1)). 8.4 g elinzanetant were added and shaken until a clear solution resulted. 4.2 g SDS were suspended in the solution, succeeded by the addition of 25.2 g croscarmellose sodium. The solvent mixture was afterwards removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar and a coffee mill. 13.26 g of the ASD material was blended with 0.068 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 784 mg.

Comparative Compositions

Composition 19 HPMC-P ASD ratio 1:1:2 (elinzanetant:polymer:carrier)

7.53 g elinzanetant were dissolved in 13.97 g of solvent mixture (acetone/ethanol (4:1)). 7.55 g Hydroxypropylmethylcellulose-phthalate (HPMC-P) and 56.61 g of solvent mixture (acetone/ethanol (4:1)) were added and dissolved. Afterwards 15.15 g croscarmellose

sodium were added with 5.42 g solvent mixture (acetone/ethanol (4:1)) and dispersed. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar. 10.08 g of the ASD material was blended with 0.063 sieved magnesium stearate and compressed into 16*7 mm tablets each with a total weight of 483 mg.

Composition 20 HPMC-P ASD ratio 1:1.5:2.5 (elinzanetant:polymer:carrier)

10.8 g Hydroxypropylmethylcellulose-phthalate (HPMC-P) were dissolved in 91.85 g solvent mixture (acetone/ethanol (4:1)). 7.2 g elinzanetant were added and dissolved. Afterwards 18 g croscarmellose sodium were added and dispersed. The solvent mixture was afterwards removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar. 8.4 g of the ASD material was blended with 0.05 sieved magnesium stearate and compressed into 16*7 mm tablets each with a total weight of 603.5 mg.

Composition 21 HPMC-P ASD ratio 1:2:3 (elinzanetant:polymer:carrier)

5.06 g elinzanetant were dissolved in 11 g solvent mixture (acetone/ethanol (4:1)). 10.07 g Hydroxypropylmethylcellulose-phthalate (HPMC-P) and 56.61 g of the solvent mixture (acetone/ethanol (4:1)) were added and dissolved. Afterwards 15.15 g croscarmellose sodium and 12.78 g solvent mixture (acetone/ethanol (4:1)) were added and dispersed. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a mortar. 10.08 g of the ASD material was blended with 0.056 sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 724 mg.

Composition 22 HPMC-P ASD ratio 1:3:4 (elinzanetant:polymer:carrier)

21.6 g Hydroxypropylmethylcellulose-phthalate (HPMC-P) were dissolved in 110 g acetone. 7.2 g elinzanetant were added and dissolved. Afterwards 28.8 g croscarmellose sodium were added and dispersed. The solvent was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the

formed film was removed from the flask and crushed down using a mortar. 8.4 g of the ASD material was blended with 0.05 sieved magnesium stearate and compressed into 19*8 mm tablets each with a total weight of 965 mg.

Composition 23 HPMC-AS ASD ratio 1:1:2 (elinzanetant:polymer:carrier)

7.57 g elinzanetant were dissolved in 16.65 g solvent mixture (acetone/ethanol (4:1)). 7.57 g HPMC-acetylsuccinate (HPMC-AS) were added with 158.13 solvent mixture (acetone/ethanol (4:1)) and heated to 40°C until a clear solution was obtained. Afterwards 15.12 g croscarmellose sodium and 10.2 g solvent mixture (acetone/ethanol (4:1)) were added and dispersed. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a coffee mill. 26.1 g of the ASD material were blended with 0.16 sieved magnesium stearate and compressed into 16*7 mm tablets each with a total weight of 483 mg.

Composition 24 HPMC-AS ASD ratio 1:1.5:2.5 (elinzanetant:polymer:carrier)

7.57 g elinzanetant were dissolved in 94.67 g solvent mixture (acetone/ethanol (4:1)). 11.34 g HPMC-acetylsuccinate (HPMC-AS) were added and stirred until a clear solution was obtained. Afterwards 18.99 g croscarmellose sodium were added and dispersed. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a coffee mill. 12 g of the ASD material was blended with 0.06 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 603 mg.

Composition 25 HPMC-AS ASD ratio 1:2:3 (elinzanetant:polymer:carrier)

7.6 g elinzanetant were dissolved in 13.4 g solvent mixture (acetone/ethanol (4:1)). 15.2 g HPMC-acetylsuccinate (HPMC-AS) and 164.0 g solvent mixture (acetone/ethanol (4:1)) were added and heated to 40°C until a clear solution was obtained. Afterwards 22.7 g croscarmellose sodium and 20 g solvent mixture (acetone/ethanol (4:1)) were added and dispersed. The solvent mixture was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a coffee mill. 39.9 g of the ASD material

was blended with 0.2 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 724 mg.

Composition 26 crystalline tablet formulation

14.3 g elinzanetant, 9.1 g lactose monohydrate. 6.4 g microcrystalline cellulose. 1.6 g hydroxyproylmethylcellulose, 0.5 g croscarmellose sodium were blended within a high shear granulator and granulated with 6.4 g water. Wet granules were dried with in a fluid bed instrument. This composition was prepared in accordance with WO 2011/023733 A1; page 31 to page 32.

21 g of granules were blended with 4.2 g lactose anhydrate, 6.6 g microcrystalline cellulose and 1g croscarmellose sodium. This blend was mixed with 0.3 g sieved magnesium stearate and compressed into 10 mm round tablets resulting in a resistance to crushing of around 90 N. Tablets were finally coated with a hydroxypropyl methylcellulose based lacquer within a drum coater.

Example 2: Dissolution behavior:

Material and Methods

Dissolution biorelevant media

Fasted State Simulated Intestinal Fluid (Double concentrated FaSSIF; herein referred to as FaSSIF)

Powder (biorelevant.com Ltd)

sodium taurocholate 3.0 mM, lecithin 0.75 mM, sodium chloride 106 mM, monobasic sodium phosphate 28.4 mM, sodium hydroxide 8.7 mM

Buffer

In about 0.9L of purified water 0.84 g of sodium hydroxide, 7.9 g of monobasic sodium phosphate monohydrate, and 12.38 g sodium chloride was dissolved, and adjust the pH to 6.5 with 1 N sodium hydroxide or 1 N hydrochloride acid. Purified water was added to gain a final volume of 1 L at room temperature.

Preparation

4.48 g of Powder was added to about 0.5 L of Buffer, and stirred until powder was completely dissolved. Buffer was added to gain a final volume 1 L with buffer at room temperature and stored at ambient conditions for at least 2 hours.

Fasted State Simulated Gastric Fluid (herein referred to as FaSSGF)

Powder (biorelevant.com Ltd)

Sodium taurocholate 0.08 mM, lecithin 0.02 mM, -sodium chloride 34.2 mM, hydrochloride acid 25.1 mM

Buffer

In about 0.9L of purified water 2.00g sodium chloride was dissolved and adjust the pH to 2.4 with 1N hydrochloride acid. Purified water was added to gain a final volume of 1 L at room temperature.

Preparation:

Add 0.06 g of Powder was added to about 0.5 L of Buffer, stirred until powder was completely dissolved. Buffer was added to gain a final volume of 1 L at room temperature.

Dissolution test method

Dissolution was tested using USP XXIII Paddle Method II in 500 mL vessels at 37±0.5°C. Rotation speed of the paddles was 75 rpm for tablets. For the 2-stage dissolution set-up for the first 30 min 250 mL Fasted State Simulated Gastric Fluid (FaSSGF) pH 2.4 was used as media and afterward 250 mL double-concentrated Fasted State Simulated Intestinal Fluid (FaSSIF), tempered at 37°C, added. Samples of 5 mL were taken at each sampling point and refilled directly with fresh media.

Prior to HPLC analytics, samples were filtered and diluted 1:1 V/V with isopropanol.

Results

Dissolution of a crystalline IR tablet formulation and ASD tablets was compared in the above described dissolution test method.

The results are shown in Table 2 and Figure 1.

Table 2 Overview release of ASD compositions within 2 stage biorelevant dissolution test in comparison to crystalline composition 26

	1	2	3	5	7	8	9	10	11	12	13	14	15	16	17	18	26
release 120 min [%]	71.9	63.6	73	70.0	56.7	68.6	59.3	68.8	69.2	47.8	71.7	34.6	60.6	67.8	24.1	68.8	23.03
release 210 min[%]	79.5	72.8	79.5	80.6	60.8	77.5	69.95	78.6	77.7	59.9	80.1	51.0	78.4	74.8	37.1	79.4	21.3

Conclusion

Tablets of amorphous solid dispersions showed increased dissolution rates as compared to crystalline IR tablet formulation in the 2-stage biorelevant dissolution set-up resembling the physiological conditions for oral application.

For all neutral polymers, the dissolution rates for a ratio of 1:1 to 1:3 (elinzanetant:polymer) were comparable, with the tendency for lower dissolution rates for ratios of 1:3 (elinzanetant:polymer).

Surprisingly, the dissolution rates using neutral polymers were high and did not increase with the addition of surfactants. Compositions using the neutral polymer copovidone as the solid dispersion matrix agent surprisingly showed the highest combined dissolution rates after 30 min and 210 min in the 2-stage dissolution set-up.

Example 3: Stability:

Stability of ASD compositions comprising neutral polymers or non-neutral polymers (polymers containing recurring functional groups having a pK_a of less than 7), with or without surfactants, was compared.

To investigate the stability of elinzanetant within the solid pharmaceutical compositions ASD material was stored open within a climate chamber at 40°C and 75 % relative humidity (rH) and samples were analyzed with regard to degradation products of elinzanetant and stability of the amorphous state of elinzanetant at different timepoints.

Analysis for degradation products of elinzanetant was performed on a reversed phase HPLC column (ACE 3 - C18; (3 µm, 150 x 4.6 mm)) with UV-detection at 260 nm.

Determination of the amorphous state of elinzanetant within the ASD material and/or tablets was performed using X-Ray Powder Diffraction and Differential Scanning Calorimetry, as disclosed herein above in Example 1.

Results

Detected amounts of degradation products and stability of the amorphous state of elinzanetant are shown in Table 3

Table 3 Overview chemical and physical stability of Compositions, a (amorphous elinzanetant), c (crystalline elinzanetant) pc (partly crystalline elinzanetant), cp (crystalline particles of SDS)

	2 weeks		4 weeks		2 month		3 month		6 month	
No.	Sum of chemical degradation products [%]	solid state	Sum of chemical degradation products [%]	solid state	Sum of chemical degradation products [%]	solid state	Sum of chemical degradation products [%]	solid state	Sum of chemical degradation products [%]	solid state
1	n.d.	n.d.	0.19	a	n.d.	n.d.	0.18	n.d.	n.d.	n.d.
2	n.d.	a	0.14	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3	n.d.	n.d.	0.32	a	n.d.	n.d.	0.31	n.d.	0.27	a
5	n.d.	n.d.	n.d.	n.d.	0.2	a	n.d.	n.d.	n.d.	n.d.
7	n.d.	a	0.19	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
8	n.d.	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.1	a
9	n.d.	a	< 0.05	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
10	n.d.	a	< 0.05	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
11	0.1	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
12	<0.05	c	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
13	0.13	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
14	n.d.	a	0.21	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
15	0.09	pc	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
16	n.d.	a +cp	0.19	a +cp	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
17	n.d.	a	0.07	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
18	n.d.	a +cp	0.08	a +cp	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
19	n.d.	n.d.	3.81	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
20	n.d.	a	5.86	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
21	n.d.	n.d.	8.33	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
22	n.d.	n.d.	13.65	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
23	n.d.	a	0.37	a	n.d.	n.d.	n.d.	a	n.d.	n.d.
24	n.d.	a	0.57	a	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
25	n.d.	a	0.9	a	n.d.	n.d.	n.d.	a	n.d.	n.d.

Conclusion

Solid pharmaceutical compositions comprising an amorphous solid dispersion of elinzanetant and a solid dispersion matrix comprising a neutral polymer showed surprisingly increased stability of elinzanetant, in particular with respect to a surprisingly decreased amounts of degradation products.

Compositions comprising a surfactant showed a higher tendency for recrystallisation of elinzanetant within the ASD. This is also reflected in the tendency of decreased dissolution rates in the compositions comprising a surfactant as compared to the respective compositions without a surfactant.

The effect of reduced degradation of elinzanetant despite the stabilization of the amorphous state is furthermore surprising, as the skilled person would expect an increase of degradation in the disorganized amorphous state as compared to the crystalline structures.

Example 4: Relative Bioavailability between Soft Gelatin Capsule and Tablet according to the present disclosure

Study Design and Method:

A combined single- and multiple-dose, open-label, fixed sequence, crossover study was conducted in healthy female and male participants to investigate the relative bioavailability of elinzanetant using soft gelatin capsules as disclosed herein above and used in phase III clinical studies with a composition according to the present disclosure.

Soft gelatin capsules consisting of a shell and a soft gelatin capsules formulation (fill mass) were used. The composition of the fill mas was as follows: elinzanetant 5.00% w/w; Glycerol Monocaprylocaprate (Capmul MCM) 37.05% w/w; Caprylocaproyl polyoxyl-8 glycerides (Labrasol ALF) 9.50% w/w; Polysorbate 80 (Tween 80) 9.50% w/w; Glyceryl Monooleate (Peceol) 38.00% w/w; and DL-Alpha tocopherol (Vitamin E) 0.95% w/w; with a total amount of 60 mg elinzanetant per capsule. The soft gelatin capsules and manufacture of the same are disclosed in WO 2019/175253 A1 in particular as Example 1a. WO 2019/175253 A1 is incorporated herein by reference.

The above disclosed soft gelatin capsules (Reference) were compared to tablets of Composition no 5, *supra,* (Tablet), coated with a non-functional lacquer. Twenty-four (24) participants received a single dose of two capsules (60 mg elinzanetant in each capsule) of Reference (total dose 120 mg elinzanetant) on Day 1. After a washout phase of 7 days in which frequent blood samples were collected for analyses of concentration of elinzanetant in plasma, all 24 participants received a second single dose of one Tablet (120 mg elinzanetant) followed by a washout phase of 7 days during that frequent blood samples for pharmacokinetic analyses (PK) of elinzanetant were collected. Maximum concentration (C_{max}) and total systemic exposure (AUC, also referred to as total AUC) were calculated for Reference and Tablet to determine relative oral bioavailability.

Results

The geometric mean and standard deviation (SD) concentration-time profiles of elinzanetant using the preliminary results for Reference and Tablet are shown in Figure 2. The geometric mean plasma concentrations and coefficient of variation (CV%) of elinzanetant for C_{max} and total AUC after single dose administration of Reference and Tablet are presented in Table 4.

Table 4 PK exposures of Tablet as compared to Reference (preliminary analysis)

Parameter	Unit	Reference (2x60mg)	Tablet (1x120 mg)
total AUC	µg*h/L	6793 (36.9)	7602 (42.3)
C_{max}	µg/L	1367 (33.9)	901 (77.1)

After availability of the full data set, analysis was conducted and delivered the results of Table 5

Table 5: PK exposures of Tablet as compared to Reference (full data set analysis)

Parameter	Unit	Reference (2x60mg)	Tablet (1x120 mg)
total AUC	µg*h/L	7010 (43.8)	7480 (41.7)
C_{max}	µg/L	1460 (41.1)	941 (69.6)

Conclusions:

Mean total AUC of elinzanetant in the preliminary analysis was 7602 µg*h/L after administration of Tablet and 6793 µg*h/L with Reference. The full analysis confirmed this trend and showed a mean total AUC 7480 µg*h/L for the Tablet and 7010 µg*h/L for the Reference showing surprisingly higher oral bioavailability of the pharmaceutical composition according to the present disclosures as compared to the soft gel capsules of prior art.

Tablet formulation showed a higher oral bioavailability compared to soft gelatin capsule. Hence, surprisingly a lower dose can be administered with the solid pharmaceutical composition according to the disclosure still providing the same oral bioavailability and respective drug exposure in plasma compared to 120 mg dose with Reference formulation. According to the interpolation of the present data, a solid pharmaceutical composition according to the present disclosure would reach the pharmacokinetic exposures and bioavailability of the soft gelatin capsule formulation as used in clinical Phase III studies at a daily dose of between 100 mg to below 120 mg instead of 120 mg.

Example 5: Multiple Dosing

To further investigate the optimal dose (reaching the pharmacokinetic exposures of the soft gelatin capsule formulation of the Phase III clinical studies (Reference)), a clinical study comparing elinzanetant exposures after single administration and after 7 days of once-daily administration of tablets having the relative amounts of the Composition no. 5, *supra*, containing either a 100 mg dose (100 mg Tablet) or a 120 mg dose (120 mg Tablet) of elinzanetant in comparison to once-daily administration of a 120 mg dose elinzanetant (2x60 mg) using Reference formulation (see Example 4) is conducted:

In a combined single- and multiple-dose, open-label, full randomized 3 x 3 crossover study the relative bioavailability of elinzanetant after administration of 100 mg Tablet and 120 mg Tablet against Reference (see Example 4) is investigated in healthy female participants. Steady state Plasma exposures of elinzanetant after multiple dose in terms of $AUC(0\text{-}24)_{ss}$, $C_{max,ss}$, and $C_{min,ss}$ is determined of both Tablet doses and compared against the respective exposures of the 120 mg dose using Reference. Interpolation of the optimal dose is performed by using inverse regression techniques with confidence

regions determined using parametric bootstrap techniques. Using this interpolation, a daily dose of 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, or 119 mg, or one of the tested doses 100 and 120 mg as daily dose is identified to provide exposure values closest to the Reference.

Example 6: Investigation of additional compositions

Further amorphous and crystalline formulations were prepared with compositions listed in Table 6. Amorphous samples were prepared in accordance with Example 1, using a further polymer hydroxypropyl methylcellulose (HPMC). Table 6 presents an overview of the individual compositions.

Solid state (amorphous or crystalline) of elinzanetant in granules or ASD material in this Example was confirmed by XRPD prior to tablet compression as follows:

For X-Ray Powder Diffraction (XRPD) the sample was prepared as a thin layer between two foils, after careful grinding. The measurements were performed at room temperature with a STOE Stadi P Diffractometer (Cu-Kα1/2 = 1.5418 Å, Mythen position sensitive detector) in transmission mode. Data were collected in a two-theta range of either 7° to 30°. The tube voltage and current were set to 40 kV and 40 mA, respectively. “Crystalline form” as used in this example refers to crystalline anhydrate Form 1 as disclosed in WO 2011/023733 A1.

Amorphous compositions

Composition 27

19.9 g HPMC-P were dissolved in 94.5 g of acetone. 10 g elinzanetant were added and shaken until a clear solution resulted. Afterwards 19.9 g croscarmellose sodium was added. The solvent was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a tube mill (IKA). Crushed material was sieved through a 1.25 mm sieve. 30 g of the ASD material was blended with 0.15 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 603 mg.

Composition 28

19.9 g HPMC were dissolved in 94.5 g of acetone. 10 g elinzanetant were added and shaken until a clear solution resulted. Afterwards 19.9 g croscarmellose sodium was

added. The solvent was removed using a rotavapor under reduced pressure while rotating the flask within a water bath at 40°C. After drying the formed film was removed from the flask and crushed down using a tube mill (IKA). Crushed material was sieved through a 1.25 mm sieve 30 g of the ASD material was blended with 0.15 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 603 mg.

Crystalline compositions

Composition 29 crystalline tablet formulation

10 g elinzanetant, 19.9 g copovidon and 19.9 g croscarmellose sodium were blended
The blend was wet granulated by adding water consistency q.s. in the mortar and blending it manually with a pistil. Wet granules were dried overnight and crushed in a tube mill (IKA) and sieved through a 1.25 mm sieve.
30 g of the granule material was blended with 0.15 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 603 mg.
This composition is the same as Composition 5, with the difference that elinzanetant is crystalline and not embedded in the polymer (not a solid dispersion). The preparation method resembles the preparation of the pharmaceutical compositions disclosed in WO 2011/023733 A1, pages 31 and 32 and does not lead to a solid dispersion.

Composition 30 crystalline tablet formulation

9.96 g elinzanetant, 19.9 g HPMC-P and 19.9 g croscarmellose sodium were blended.
The blend was wet granulated by adding water q.s. in the mortar and blending it manually with a pistil. Wet granules were afterwards dried overnight and crushed in a tube mill (IKA) and sieved though a 1.25 mm sieve.
30 g of the granule material was blended with 0.15 g sieved magnesium stearate and compressed into 18*8 mm tablets each with a total weight of 603 mg.
This composition is the same as Composition 27, with the difference that elinzanetant is crystalline and not embedded in the polymer (not a solid dispersion). The preparation method resembles the preparation of the pharmaceutical compositions disclosed in WO 2011/023733 A1, pages 31 and 32 and does not lead to a solid dispersion.

Table 6 Overview of final tablet compositions

Composition No.	27	28	29	30
Elinzanetant crystalline			120	120
Elinzanetant amorphous	120	120		
Copovidone			240	
HPMC		240		
HPC				
HPMC-P	240			240
Croscamellose sodium	240	240		
Magnesium-stearate	3	3	3	3
Total tablet weight	603	603	603	603

Dissolution behavior was tested as described in Example 3, but with diluting 1 mL of the respective sample with 0.5 mL of an aqueous 10% SDS solution prior to the HPLC analytics instead of diluting it with isopropanol. Table 7 shows the results.

Table 7 Overview release of additional compositions within 2 stage biorelevant dissolution test

	27	28	29	30
release 30 min [%]	2.8	25.3	23.9	6.9
release 120 min [%]	92.9	76.8	23.0	16.7
release 210 min[%]	93.2	86.0	16.2	16.9

The dissolution test shows that providing an amorphous solid dispersion with results in drastically increase dissolution under basic conditions in the two stage biorelevant dissolution test (c.p., e.g., results for Composition 29 with results for Composition 5 (Table 2)). Furthermore, the composition according to the invention (comprising a neutral polymer; Composition 28 in this example) exhibits an increased dissolution rate in gastric environment (release 30 min) as compared to Composition 27.

For the additional compositions, stability was investigated as described in Example 3. Results are presented in Table 8.

Table 8 Overview chemical and physical stability of Compositions, a (amorphous elinzanetant), c (crystalline elinzanetant)

	2 weeks		4 weeks	
Composition No.	Sum of chemical degradation products [%]	solid state	Sum of chemical degradation products [%]	solid state
27	18.1	a	19.4	a
28	<0.05	a	<0.05	a
29	0.1	c	0.1	c
30	25.3	c	25.6	c

Conclusion:

The results unexpectedly show that the combination of providing elinzanetant in an amorphous form in solid dispersion with a neutral polymer provides for a superior pharmaceutical composition with respect to chemical and physical stability and dissolution behavior. Only this combination provides for a suitable pharmaceutical composition to deliver elinzanetant as free base in solid dosage form.

In other words: In order to deliver a composition enabling a superior dissolution rate and stability profile while reaching the bioavailability of the previous Phase III clinical studies soft gelatin capsules, just the combination of embedding elinzanetant free base in its amorphous form within a solid dispersion with neutral polymers was successful.

CLAIMS

1. A pharmaceutical composition comprising a solid dispersion, the solid dispersion comprising elinzanetant or a pharmaceutical acceptable salt thereof and at least one solid dispersion matrix;

wherein the solid dispersion matrix comprises a neutral polymer as a solid dispersion matrix agent.

2. The composition according to claim 1, wherein elinzanetant or the pharmaceutically acceptable salt thereof is present in the solid dispersion in amorphous form.

3. The composition according to claim 1 or 2, wherein the neutral polymer is a pharmaceutically acceptable polymer containing only non-deprotonatable recurring functional groups or deprotonatable recurring functional groups having a pK_a of more than 7.

4. The composition according to any one of claims 1 to 3, wherein the composition comprises elinzanetant and the solid dispersion matrix agent in a weight ratio of 1:0.5 to 1:4, preferably 1:1 to 1:3, more preferably 1:1.5 to 1:2.5, such as 1:2.

5. The composition according to any one of claims 1 to 4, wherein the solid dispersion matrix agent is selected from the group consisting of polyethylene oxide, polyvinylpyrrolidone (PVP), vinylpyrrolidone/vinylacetate copolymer (copovidone) (e.g. Kollidon VA64), polyalkylene glycol (e.g. polyethylene glycol), hydroxyalkyl cellulose (e.g. hydroxypropyl cellulose), hydroxyalkyl methyl cellulose (e.g. hydroxypropyl methyl cellulose), carboxymethyl cellulose, methacrylester copolymers (such as Eudragit® RS, RL, or NE), aminoalkyl-methacrylate copolymers (such as Eudragit® E), polyvinyl alcohol, polyvinyl acetate, vinyl alcohol/vinyl acetate copolymer, and combinations thereof.

6. The composition according to any one of claims 1 to 5, wherein the solid dispersion matrix agent is selected from the group consisting of vinylpyrrolidone/vinylacetate copolymer (copovidone) (e.g. Kollidon VA64), polyvinylpyrrolidone (PVP),

hydroxyalkyl cellulose (e.g. hydroxypropyl cellulose), and hydroxyalkyl methyl cellulose (e.g. hydroxypropyl methyl cellulose); or mixtures thereof.

7. The composition according to any one of claims 1 to 6, wherein the solid dispersion matrix agent is copovidone.

8. The composition according to any one of claims 1 to 7, wherein the solid dispersion matrix further comprises a carrier.

9. The composition according to claim 8, wherein the composition comprises elinzanetant, the solid dispersion matrix agent and the carrier in a weight ratio of 1:0.5:0.15 to 1:4:10, preferably from 1:1:0.5 to 1:3:6 or from 1:1.5:1 to 1:2.5:3.5, more preferably in a weight ratio of 1:2:2.

10. The composition according to claim 8 or 9, wherein the carrier is selected from the group consisting of disintegration promoters, fillers, lubricants, sweeteners, antioxidants, plasticizers, flavoring agents and/or colorants or a combination thereof.

11. The composition according to any one of claims 8 to 10, wherein the carrier is a disintegration promoter.

12. The composition according to claim 11, wherein the disintegration promoter is croscarmellose sodium.

13. The pharmaceutical composition according to any one of claims 1 to 12, wherein the composition is selected from the group consisting of granules, pellets, tablets, dragées, sachets, pills, or melts.

14. The pharmaceutical composition according to any one of claims 1 to 13, wherein the pharmaceutical composition comprises:

(i) elinzanetant at a concentration of 5% w/w to 50% w/w,
(ii) copovidone at a concentration of 4% w/w to 77% w/w,
(iii) optionally croscarmellose sodium at a concentration of 4% w/w to 87% w/w, and
(iv) Magnesium stearate at a concentration of 0.1% w/w to 1.5% w/w.

15. The pharmaceutical composition according to any one of claims 1 to 14, wherein the pharmaceutical composition comprises:

(i) elinzanetant at a concentration of about 19.9% w/w,
(ii) copovidone at a concentration of about 39.8% w/w,
(iii) croscarmellose sodium at a concentration of about 39.8 % w/w, and
(iv) Magnesium stearate at a concentration of about 0.5 % w/w.

16. A tablet comprising a pharmaceutical composition according to any one of claims 1 to 15.

17. The tablet according to claim 16, wherein the tablet further comprises a coating.

18. The tablet according to claim 16 or 17, wherein the *in vitro* dissolution of elinzanetant is such that at least 50% is dissolved within 120 minutes, as determined by USP XXIII Paddle Method II first using FaSSGF at pH 2.4 as a medium at 37° and 75 rpm as stirring rate for 30 min and then rebuffering to FaSSIF at a pH 6.5 as a medium at 37° and 75 rpm as stirring rate.

19. The tablet according to any one of claims 16 to 18, wherein the *in vitro* dissolution of elinzanetant is such that at least 75% is dissolved within 210 minutes, as determined by USP XXIII Paddle Method II first using FaSSGF at pH 2.4 as a medium at 37° and 75 rpm as stirring rate for 30 min and then rebuffering to FaSSIF at a pH 6.5 as a medium at 37° and 75 rpm as stirring rate.

20. The tablet according to any one of claims 16 to 19, wherein the tablet comprises an amount of 10 mg to 320 mg elinzanetant.

21. The pharmaceutical composition according to any one of claims 1 to 15 or the tablet according to any one of claims 16 to 20 for use in the treatment of a sex hormone-dependent disease or disorder.

22. The pharmaceutical composition or the tablet for use according to claim 21, wherein the sex hormone-dependent disease or disorder is selected form the group consisting of vasomotor symptoms, pathological gain of excess body fat and/or excess body

weight, insomnia, sleep disturbances, night-time awakenings, anxiety, depression, urinary symptoms of urgency, dysuria.

23. The pharmaceutical composition or the tablet for use according to claim 21 or 22, wherein the sex hormone-dependent disease or disorder, is a disease or disorder that is associated with menopause and/or adjuvant endocrine therapy.

24. The pharmaceutical composition or the tablet for use according to claim 23, wherein the sex-hormone dependent disease is vasomotor symptoms.

25. The pharmaceutical composition or the tablet for use according to claim 24, wherein the sex-hormone dependent disease is vasomotor symptoms associated with menopause and/or cancer therapy.

26. The pharmaceutical composition or the tablet for use according to claim 24 or 25, wherein the pharmaceutical composition or tablet is administered at a daily dose of 100 mg to 120 mg elinzanetant.

27. The pharmaceutical composition or the tablet for use according to claim 26, wherein the pharmaceutical composition or the tablet is administered at a daily dose selected from the group consisting of 100 mg, 105 mg, 110 mg, 115 mg and 120 mg.