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(54) Title: AQUEOUS CEVIMELINE COMPOSITIONS AND METHODS OF USE

(57) Abstract: The invention provides stable aqueous compositions, in particular topical ophthalmic compositions, of cevimeline and sorbic acid or a salt thereof for the treatment of dry eye disease, xerostomia, and/or Sjogren syndrome. The compositions also comprise a water-soluble medium-chain polyunsaturated fatty acid (PUFA) such as sorbic acid, or a pharmaceutically acceptable salt thereof, e.g., potassium sorbate.



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**TITLE: AQUEOUS CEVIMELINE COMPOSITIONS AND METHODS OF USE****Description****BACKGROUND OF THE INVENTION**

The invention relates to compositions, such as topical ophthalmic compositions or topical  
5 compositions for nasal administration, comprising a muscarinic agonist (MRA),  
specifically cevimeline, in combination with a medium-chain (C<sub>6</sub> to C<sub>10</sub>) polyunsaturated  
fatty acid (PUFA; e.g., C<sub>6</sub> to C<sub>12</sub>, or C<sub>6</sub> to C<sub>10</sub>) such as sorbic acid, as well as methods for using  
the same in the treatment of diseases such as dry eye disease (DED), xerostomia and/or  
Sjogren's syndrome. Optionally, the compositions may comprise one or more further active  
10 agents such as steroids, immuno-modulators, hormones, and/or secretagogues.

Xerostomia, or dry mouth, refers to a condition in which the salivary glands in mouth do  
not make enough saliva to keep mouth wet. Xerostomia is often due to the side effect of  
certain medications, Sjogren's disease, or as a result of radiation therapy for cancer.  
Saliva helps prevent tooth decay by neutralizing acids produced by bacteria, limiting  
15 bacterial growth and washing away food particles. Decreased saliva and dry mouth can  
have a major impact to the health of teeth and gums.

Dry eye disease, also called keratoconjunctivitis sicca or dry eye syndrome, is a chronic and  
potentially debilitating condition that involves ocular surface damage, inflammation,  
oxidative stress, and symptoms of irritation including discomfort and reduced visual  
20 quality. It is a multifactorial disorder of the ocular surface affecting an estimated 20 million  
patients in the United States alone. The Dry Eye Workshop (DEWS) has classified dry eye  
diseases based upon two basic causal mechanisms: tear deficiency and evaporative dry eye  
(i.e., a tear film instability due to abnormally rapid tear evaporation). Dry eye disease is  
also associated with localized inflammation of the ocular surface and periocular tissues. It  
25 is unclear whether chronic inflammation leads to the clinical manifestations of dry eye  
disease, or whether, conversely, dry eye disease leads to chronic inflammation. Due to the  
complexity of multifactorial causes of dry eye disease and lack of clear understanding of  
relationship between dry eye disease and inflammation, the attempts in searching for an  
effective dry eye disease treatment have been mostly unsuccessful, leading to  
30 disappointment for both patients and clinicians.

One of the causes of DED, as well as xerostomia, can be Sjogren's syndrome (also known as Mikulicz disease, or Sicca syndrome), an autoimmune disorder in which immune cells attack and destroy the salivary and lacrimal exocrine glands. It affects approx. 4 million people, second only to rheumatic disease. About 90 % of patients are woman above the age of 40, although any age group of men and woman can be affected. It can be primary or developing years, e.g., after rheumatoid arthritis, systemic lupus erythematosus, scleroderma, primary biliary cirrhosis. There is no cure for Sjogren's related dry eye syndrome, and the treatment is palliative and offers at best temporary relief; for instance, artificial tears or goggles to increase local humidity, or punctual plugs inserted to help retain tears.

The pathology of tear deficiencies is a failure to maintain lacrimal gland function in tear secretion. The cause may be due to a failure of the lacrimal glands to produce tears based on a deficiency on the part of the lacrimal glands, an obstruction, systemic drugs that impair the function of the glands, autoimmune disease, or age-related changes in the lacrimal gland. Long-time contact lens wearers and patients who underwent LASIK may also develop deficiencies due to the loss of corneal nerve sensation.

Since most of the tear fluid and its components come from the lacrimal gland, a decrease in its secretion will result in tear deficiency and in corneal epithelium cell damage and inflammation. Moreover, tears secreted from lacrimal gland contains essential enzymes, proteins and antimicrobial components that are crucial to protect and repair corneal epithelium cell damage as a result of dryness of the eye. It is, therefore, rational to target the increase in lacrimal gland secretion as the primary and main treatment of dry eye disease.

Evaporative dry eye is typically caused by Meibomian gland dysfunction and lipid insufficiency that results in increased evaporation and decreased stability of the tear film. Evaporative dry eye causes ocular dry eye symptoms even in the presence of normal tear secretion.

Ocular surface inflammation is among the consequences of tear deficiencies and/or Meibomian gland dysfunction. An immune-based inflammatory response also plays a major part in the corneal epithelial disease and ocular discomfort of dry eye. In light of this, dry eye disease can be thought of as more than a simple deficiency of one or more tear film components; it is also as an ocular surface inflammatory syndrome, and most patients

have a combination of factors that lead to dry eye disease. It is often difficult to point to one particular factor as the cause; instead, dry eye is caused by a cascade of problems or factors that lead to the dry eye disease signs and symptoms.

5 Typical symptoms of dry eye disease include burning, itching, foreign body sensation, stinging, dryness, photophobia, swelling, ocular fatigue, and/or redness. In some cases, patients may report transient blurring of vision. These symptoms are typically worse later in the day and can be triggered or exacerbated by certain environmental conditions such as low humidity environment or wind.

10 Several objective tests are commonly used to diagnose dry eye disease signs. Diagnostic dyes are used to identify and monitor changes in the ocular surface. Tear break-up time (TBUT) is used to assess the stability and performance of the tears. And the Schirmer test is performed to evaluate tear production. In general, dry eye tests do not correlate well with symptoms, but these tests are mainstays in the field and clinicians continue to find their results useful.

15 Current treatment of dry eye diseases includes over-the-counter lubricant eye drops (also referred to as artificial tears) which are used to treat the dryness and irritation associated with deficient tear production in dry eye disease. Mild disease conditions of dry eye disease require the application of lubricant eye drops four times a day while severe cases need greater frequency (10-12 times a day) of administration. Similar treatments and dosing  
20 regimens exist for xerostomia where patients commonly receive artificial saliva compositions based on hydrophilic, swellable polymers.

In addition, punctum plugs, procedures for treating Meibomian gland disorder, nutritional supplements, and a limited number of prescription eye drops are available. Therapeutic agents, or drugs, that are available in form of eye drop preparations for the treatment of  
25 dry eye disease include, for instance, the immunomodulator cyclosporine A (Restasis®), the secretagogues diquafosol sodium (Diquas®) or rebamipide (Mucosta®), and the lymphocyte function-associated antigen 1 (LFA-1) inhibitor lifitegrast (Xiidra®). However, not all of them are approved worldwide due to suboptimal clinical results. Moreover, the effect of the above-mentioned treatments is still far from optimal, and there is a great  
30 demand still for more effective products to be developed for the treatment of dry eye disease, as well as for xerostomia and Sjogren's syndrome.

Owing to their anti-inflammatory and antioxidant properties, recent attempts were focused, for instance, on polyunsaturated fatty acids (PUFAs), including polyunsaturated omega-3 such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), or gamma-linolenic acid (GLA), as well as polyunsaturated omega-6 fatty acids such as linolenic acid (LA) and arachidonic acid (AA). PUFAs have been demonstrated to offer numerous benefits to the eye when given orally in a large amount. For instance, it was reported that long-chain PUFAs (i.e., polyunsaturated fatty acids with 13 C-atoms or more, typically C<sub>13</sub>-C<sub>22</sub>) play important roles in normal human retinal function and visual development, and some epidemiological studies of PUFA-intake suggest a protective role against the incidence of advanced age-related macular degeneration (AMD). It was further reported that high doses of PUFA can alleviate dry eye symptoms, an effect that was confirmed by meta-analysis of the relevant randomized controlled trials.

However, due to their lipophilic and often water-insoluble nature, formulating PUFAs into aqueous compositions for direct application to the eye or other mucosal surfaces, such as eye-drops or nasal sprays, is often challenging. Typically, a surfactant or cosolvent is required to sufficiently solubilize the PUFAs and/or to formulate them into emulsions, which can cause issues, for instance, because some of the most common preservatives for eye drops (e.g., benzalkonium chloride) are not compatible with emulsion formulations. In addition, the surfactants in emulsions can cause blurry vision and/or irritations to the eye. Furthermore, PUFAs are prone to oxidation and therefore require including antioxidant to stabilize them. For instance, US-patent US8957110B2 by TRB Chemedica International S.A discloses a hydrogel-based artificial tears type of eye-drop composition comprising long-chain (here C<sub>16</sub> to C<sub>24</sub>) poly-unsaturated omega-3 and omega-6 fatty acids which enables direct administration of the PUFAs to the eye. The composition comprises vitamin E acetate as an antioxidant as well as gelling polymers such as crosslinked carboxyvinyl polymers as a stabilizer.

Besides the above-mentioned drugs available as prescription eye drops, the U.S. Food and Drug Administration (FDA) also approved cevimeline in the form of an oral preparation for the systemic treatment of dry mouth (xerostomia) in patients with Sjögren's syndrome. Cevimeline (CAS 107233-08-9, or CAS 153504-70-2 for its HCl salt hemihydrate; (2R,2R)-2'-methyl spiro[4-azabicyclo[2.2.2]octane-2,5'-[1,3]oxathiolane]; or cis-2'-methyl spiro[1-aza bicyclo[2.2.2]octane-3,5'-[1,3]oxathiolane] hydrate hydrochloride) is a choli-

nergic agonist which binds to muscarinic receptors, in particular the M<sub>1</sub> and M<sub>3</sub> receptors, and thus is also referred to as a muscarinic receptor agonist (MRA). Cevimeline can increase secretion of exocrine glands, such as salivary and sweat glands. It has further been shown to promote tear production through stimulation of the lacrimal glands. Therefore, the oral cevimeline composition, although not currently approved for this purpose, has also been studied for its benefits in the treatment of dry eye disease. However, while oral cevimeline has shown significant improvement in treating dry eye disease, the treatment has not been widely accepted due to systemic side effects from oral administration, such as sweating, nausea, runny nose, flushing, frequent urge to urinate, dizziness, weakness, diarrhea, and blurred vision.

Furthermore, there are, at present, no marketed topical (i.e., applied to skin- and/or mucosal surfaces), ophthalmic or nasal cevimeline preparations available for the treatment of dry eye disease, xerostomia and/or Sjogren's syndrome.

Cevimeline containing ophthalmic formulations have been suggested, for instance, in US20070053964A1 (US'964) or in WO2020072971A1 (WO'971). US'964 discloses formulations, such as adhesives or ointments, which are adapted for application onto the outer skin surface of the eyelid, and percutaneously deliver the cevimeline from the eyelid-skin into the topical tissue of the eye by transdermal transfer. In addition, US'964 discloses a 20 % eye drop solution formulation of cevimeline that was administered directly into the eye (i.e., to the surface of the eyeball and/or (in)to the inner sides of the eyelids) but that acted only as a comparative example to a 20 % cevimeline ointment formulation. Said eye-drops were found to be inferior to the ointment applied to the eyelid in terms of the amount of lacrimal fluid secretion, and US'964 thus suggested that administration of cevimeline solution directly into the eye is not desirable compared to percutaneous preparations from tear production and side effect perspectives (such as miosis). Miosis is commonly expected to be aggravated when providing an MRA to the anterior segment (cornea) and iris/ciliary body of the eye; hence, these tissues are less desired delivery sites, which might explain US'964 teaching away from dosage forms that are instilled into the eye. Moreover, the 'external' percutaneous formulations described in US'964 are not suitable for direct administration onto the surface of the eye, because the high concentrations of drug and percutaneous absorption enhancer(s), that are required for sufficient transdermal drug transfer, would cause significant eye irritations (e.g., due to their high osmolality), especially when used long-term, as would need to be the case in DED-treatment.

WO'971 describes topical ophthalmic compositions for the treatment of dry eye disease in the form of eye-drops comprising about 0.1-10 % of muscarinic receptor agonists (MRA), such as cevimeline, at a neutral pH range of pH 6-9, and one or more pharmaceutically acceptable excipients. WO'971 also suggests the addition of long-chain polyunsaturated fatty acids (PUFAs), such as EPA, DHA, ALA, GLA, or combinations thereof, to the MRA-composition, with the PUFA(s) being added as an ingredient separate from the MRA, and/or as part of an ion pair comprising the MRA and the PUFA.

Yet, even with WO'971 offering one solution for an aqueous ophthalmic composition of neutral pH and with a well-tolerated drug concentration, there is still an ongoing medical need to develop pharmaceutically stable, comfortable, safe, non-irritating, and effective preparations of muscarinic receptor agonists such as cevimeline, that exhibit less side-effects than prior art compositions and that are suited for direct topical administration to the mucosal surface of the eye and/or nasal cavity for the treatment of dry eye disease, xerostomia and/or Sjogren's syndrome. In case of dry eye disease, goals of treatment include, for instance, to relieve signs and/or symptoms thereof, improve patient comfort, return the ocular surface and tear film to the healthy state, and, whenever possible, prevent corneal damage. Furthermore, the preparations are preferably easier to formulate than prior art compositions, e.g., not requiring antioxidants, surfactants or co-solvents to solubilize and/or stabilize the PUFAs mentioned above.

It is thus an object of the present invention to provide a stable aqueous composition that can be instilled into the eye, meaning onto the surface of the eye (e.g., eye drops) or applied topically into the nasal cavity, and which can be used for treating diseases such as dry eye disease, xerostomia and/or Sjogren's syndrome. It is, in particular, an object of the present invention to provide a composition comprising cevimeline and a medium-chain poly-unsaturated fatty acid (PUFA) that promotes tear production and, at the same time, diminishes oxidative stress. A further object of the present invention is to provide methods of treating dry eye disease, xerostomia and/or Sjogren's syndrome by topically applied compositions comprising cevimeline and a medium-chain poly-unsaturated fatty acid (PUFA).

Further objects of the invention will be clear on the basis of the following description of the invention, examples, and claims.

## SUMMARY OF THE INVENTION

In a first aspect, the invention relates to an aqueous composition comprising from 1 mg/mL to 50 mg/mL of cevimeline, or a pharmaceutically acceptable salt thereof; sorbic acid, or a pharmaceutically acceptable salt thereof; and an aqueous carrier, wherein the pH of the composition is in the range from pH 6.0 to pH 8.0, and wherein the composition comprises from 3 mg/mL to 10 mg/mL of sorbic acid.

In a second aspect, the invention relates to a method of treating one or more of dry eye disease, xerostomia, or Sjogren syndrome, the method comprising a step of topically administering the composition according to the first aspect of the invention to a subject suffering from dry eye disease, xerostomia, and/or Sjogren syndrome.

In a third aspect, the invention relates to an ophthalmic composition comprising 2 mg/mL to 50 mg/mL cevimeline or a pharmaceutically acceptable salt thereof, 4.7 mg/mL potassium sorbate, sodium phosphate buffer, sodium chloride, and water.

In a further aspect, the invention relates to a method of treating one or more of dry eye disease, xerostomia, or Sjogren syndrome, the method comprising a step of administering an aqueous composition comprising cevimeline to the nasal mucosa of a subject suffering from dry eye disease, xerostomia, and/or Sjogren syndrome.

## DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the invention relates to an aqueous composition comprising from about 1 mg/mL to 50 mg/mL of cevimeline, or a pharmaceutically acceptable salt thereof; sorbic acid, or a pharmaceutically acceptable salt thereof; and an aqueous carrier, wherein the pH of the composition is in the range from about pH 6.0 to pH 8.0, and wherein the composition comprises from about 3 mg/mL to 10 mg/mL of sorbic acid, or a pharmaceutically acceptable salt thereof.

As used herein the expression 'compound X, or a pharmaceutically acceptable salt thereof' includes said compound X as well as its pharmaceutically acceptable salts, both in anhydrous form as well as e.g., hydrates thereof. For instance, cevimeline can be employed as such (i.e., in its free base form), as its hydrochloride salt (cevimeline HCl), as well as in its hydrate-forms such as cevimeline hydrochloride hemihydrate (cevimeline HCl x 0.5 H<sub>2</sub>O). Optionally, mixtures thereof can be used; for instance, the cevimeline may

be present as the free base form, salt form, or a combination of free base and salt form. Thus, unless specified otherwise, the term 'cevimeline' means the free base form, the salt form, or combinations thereof.

Moreover, as used herein the expression 'compound X, or a pharmaceutically acceptable salt thereof' in combination with a concentration provision shall be understood in such a way that the concentration refers to compound X; this means that in case of working with the heavier salts and/or hydrate forms of a compound X, a respectively higher amount of the salt shall be used to achieve a given concentration of X.

Terms such as 'about', 'approximately', or 'ca.' are meant to compensate for the variability allowed for in the technical field concerned and inherent in the respective products (e.g., in the pharmaceutical industry), such as differences in content due to manufacturing variation, measurement variations, and/or time-induced product degradation. The terms in connection with an attribute or value include the exact attribute or the precise value, as well as any attribute or value typically considered to fall within a normal range or variability accepted in the technical field concerned. A variability range of up to  $\pm 10\%$  is common in e.g., the pharmaceutical industry.

The expression 'pharmaceutically acceptable' as used herein refers to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings, and optionally other animals, without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Sorbic acid is a hexadienoic acid with double bonds at C<sub>2</sub> and C<sub>4</sub>, and with four geometrical isomers, the trans, trans-form of which is occurring naturally. Sorbic acid is also a medium-chain fatty acid (i.e., C<sub>6</sub> to C<sub>12</sub>, or C<sub>6</sub> to C<sub>10</sub>), and more specifically a medium-chain polyunsaturated fatty acid (PUFA).

As illustrated in the examples below, the inventors surprisingly found that the addition of sorbic acid to an aqueous cevimeline composition according to the first aspect of the invention (e.g., eye-drops for instillation into the eye) increases the cevimeline exposure of the desired target tissues, mainly the lacrimal glands, while at the same time decreasing cevimeline exposure of eye-tissues such as the cornea and/or the iris/ciliary body. In contrast to the targeted lacrimal glands, the latter tissues are undesired sites for cevimeline exposure insofar as these tissues are responsible for side-effects such as miosis.

The aqueous composition according to the first aspect of the invention is characterized in that it contains from 3 mg/mL to 10 mg/mL of sorbic acid, or a pharmaceutically acceptable salt thereof. Sorbic acid and its salts, such as potassium sorbate, are known antimicrobial preservatives, with both antibacterial and antifungal properties, that are inter alia used in pharmaceuticals preparations. According to the literature, sorbic acids and salts thereof are generally used at concentrations of 0.1-0.2 % in oral or topical formulations (i.e., approx. 1-2 mg/mL in aqueous compositions).

However, both sorbic acid and salts like potassium sorbate are known to exhibit only minimal antibacterial properties in formulations above pH 6. Moreover, the concentration used for the aqueous composition according to the first aspect of the invention is higher than the concentrations recommended in the respective literature for use of sorbic acid or salts thereof as antimicrobial preservatives in topical compositions. This is due to the fact that according to the present invention, sorbic acid, or its salts, are not used, or at least not predominantly or purposefully used, based on its function as an antimicrobial preservative but instead due to its nature as a polyunsaturated acid (PUFA), specifically a water-soluble, medium-chain polyunsaturated acid.

One of the main advantages is that due to its water-solubility, the PUFA sorbic acid does not require surfactants and/or co-solvents in order to be solubilized into an aqueous composition. Moreover, the PUFA sorbic acid is less sensitive to oxidative degradation than long-chain PUFAs such as the above-mentioned eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), gamma-linolenic acid (GLA), linolenic acid (LA), or arachidonic acid (AA). Therefore, the aqueous composition does not necessarily require the presence of an antioxidant. Thus, in one embodiment, the composition is free of, or essentially free of, added antioxidants. As used herein, the term 'antioxidant' is intended to mean an agent that inhibits oxidation and thus is used to prevent the deterioration of the composition, or components thereof, by the oxidative process. As used herein, the terms 'free of X' or 'essentially free of X' means that the respective material (e.g., a chemical compound or a composition) contains less than a functional amount of the ingredient 'X', typically less than 2 wt.-%, or less than 1 wt.-%, preferably less than 0.1 wt.-% or even less than 0.01 wt.-%, and also including 0 wt.-% of the ingredient 'X'.

In an optional embodiment, the composition according to the first aspect of the invention is free of, or essentially free of, long-chain PUFAs (i.e., PUFAs with  $\geq 13$  C-atoms, typically  $C_{13}$ - $C_{22}$ ).

5 In one embodiment, the composition according to the first aspect of the invention comprises no antimicrobial preservative; or, more specifically, no further antimicrobial preservative, in case the sorbic acid or salts thereof are still considered antimicrobial preservatives, despite their reduced antibacterial activity at pH-values above 6.0, such as 6.0 to 8.0. Exemplary preservatives include, but are not limited to, benzalkonium chloride (BAK), benzethonium chloride, p-oxybenzoates such as methyl p-oxybenzoate or  
10 ethyl p-oxybenzoate, benzyl alcohol, phenethyl alcohol, citric acid or salts thereof, thimerosal, chlorobutanol, quaternary amine, chlorhexidine gluconate, stabilized oxychloro complex, or combinations thereof. The (further) preservative, if included, will be present in an amount or concentration required to pass USP and/or Ph. Eur. antimicrobial preservative effective test required for eye drops. For instance, BAK can be  
15 used at a concentration of 0.002-0.02 % (w/v), typically 0.005-0.01 % (w/v).

In one embodiment, the composition is provided in the form of a clear solution. As used herein, the term 'clear' refers to transparent, or see-through, liquids or solutions free of any droplets or other suspended particles that are visible to the naked human eye; said clear liquids or solutions are not opalescent or 'milky' white like most common emulsions,  
20 for instance. Optionally, the clear solution is also colorless.

In a further embodiment, the composition comprises water as a sole solvent, or in other words, water is the aqueous carrier, or at the main component. In a yet further embodiment, the composition comprises no co-solvent. Advantageously, no co-solvent, or no solvent other than water, is needed to solubilize the PUFA when choosing sorbic acid  
25 as the PUFA.

In one embodiment, the composition comprises from 2 mg/mL to 50 mg/mL of cevimeline, or a pharmaceutically acceptable salt thereof. In more specific embodiments, the composition comprises from 2 mg/mL to 40 mg/mL of cevimeline, or a pharmaceutically acceptable salt thereof; or from 2 mg/mL to 20 mg/mL; or from 2 mg/mL to 10 mg/mL; or  
30 from 2 mg/mL to 6 mg/mL.

In one embodiment, the composition comprises from 3 mg/mL to 8 mg/mL of sorbic acid, or a pharmaceutically acceptable salt thereof; or from 3 mg/mL to 6 mg/mL. In one of the preferred embodiments, the composition comprises 3.7 mg/mL to 5.7 mg/mL, or 4.2 mg/mL to 5.2 mg/mL of sorbic acid, or a pharmaceutically acceptable salt thereof, e.g., 4.7 mg/mL.

Optionally, the cevimeline and sorbic acid are provided in the form of an ion-pair.

Optionally, the composition further comprises a complexing agent. In a specific embodiment, the complexing agent comprises, or consists of, a cyclodextrin; or, in other words, the composition further comprises a cyclodextrin. Examples of cyclodextrins include, but are not limited to, derivatives of alpha-, beta-, and gamma-cyclodextrins or combinations thereof. The composition typically comprises less than 100 mg/mL, less than 50 mg/mL, less than 20 mg/mL, or less than 10 mg/mL of cyclodextrin(s). In a more specific embodiment, the cyclodextrin is hydroxypropyl-beta-cyclodextrin (HP- $\beta$ -CD), such as commercially available under the tradename Kleptose®. In a more specific embodiment, the cyclodextrin is present at an amount or concentration in the range from 2 mg/mL to 100 mg/mL, or from 2 mg/mL to 50 mg/mL, or from 2 mg/mL to 40 mg/mL. It should be understood, though, that the composition according to the first aspect of the invention does not necessarily require the presence of a complexing agent such as cyclodextrins. Thus, some embodiments of the invention are free of, or essentially free of, a complexing agent, or more specifically free of, or essentially free of, a cyclodextrin; or, in other words, some embodiments of the invention exclude a complexing agent, or more specifically some embodiments of the invention exclude cyclodextrin.

In one embodiment, the composition further comprises a viscosity-enhancing agent, typically a hydrophilic polymer that is added to the aqueous composition of the invention to increase its viscosity so as to (i) control the rate at which the composition, e.g., eye drops, flows out of its container (thereby enhancing ease of application), and to (ii) prolong the residence time of the composition within the pre-corneal environment.

Examples of viscosity-enhancing agents include, but are not limited to hyaluronic acid, polyvinyl alcohol (PVA), polyvinylpyrrolidone (or povidone), carboxyvinyl polymers, methylcellulose (MC), carboxymethylcellulose (CMC; or carmellose), hydroxypropyl methylcellulose (HPMC; or hypromellose), hydroxypropyl cellulose (HPC), hydroxyethyl

cellulose (HEC), polyacrylic acid or salts thereof, xanthan gum, guar gum, chondroitin sulfate, polyethylene glycol, propylene glycol, or combinations thereof.

In a specific embodiment composition further comprises a viscosity-enhancing agent selected from hyaluronic acid, povidone, hypromellose, carmellose, or combinations thereof.

In one embodiment, the composition further comprises one or more excipients selected from tonicity adjusting agents, buffering agents, and pH-adjusting agents.

Examples of tonicity-adjusting agents include, but are not limited to mannitol, sorbitol, potassium chloride, sodium chloride, glycerin, trehalose, combinations thereof, and the like. The amount of tonicity-adjusting agent in the composition is chosen in such a way as to render the composition's tonicity to fall within the isotonic range, e.g., isotonic with lacrimal fluid. In one of the preferred embodiments, the tonicity adjusting agent is sodium chloride.

Exemplary buffering agents include, but are not limited to, phosphate salt, berate salt, citrate salt, acetate salt, carbonate salt, bicarbonate salt, borate-polyol complexes, boric acid, sodium acetate, amino acid, Tris, bicarbonate, BIS-Tris, or salt thereof, combinations thereof and the like. In one of the preferred embodiments, the buffering agent is a sodium phosphate buffer, for instance, a buffer of sodium phosphate monobasic mono- or dihydrate and sodium phosphate dibasic heptahydrate. In a specific embodiment, the phosphate buffer uses 0.54 mg/mL of sodium phosphate monobasic monohydrate (alternatively, 0.61 mg/mL sodium phosphate monobasic dihydrate) and 1.63 mg/mL of sodium phosphate dibasic heptahydrate.

Examples of alkaline agents that may be used as pH-adjusting agents, include, but are not limited to, sodium hydroxide (NaOH), potassium hydroxide (KOH), tromethamine, monoethanolamine, sodium bicarbonate ( $\text{NaHCO}_3$ ) and other organic and inorganic bases.

Examples of acidic agents that may be used as pH-adjusting agents include, but are not limited to, hydrochloric acid (HCl), citric acid, tartaric acid, lactic acid, acetic acid, and other organic and inorganic acids and the like and mixtures thereof. In one of the preferred embodiments, the pH-adjusting agent is selected from hydrochloric acid (HCl) or sodium hydroxide (NaOH). It is understood that these pH-adjusting agents can be used to adjust

the pH of the composition as needed (q.s.), e.g., to achieve a specific pH in the pH-range of 6.0 to 8.0, or 6.0 to 7.5, such as about pH 7.4 (pH of lacrimal fluid).

In one embodiment, the composition comprises from 3 mg/mL to 10 mg/mL of potassium sorbate (K-sorbate). In one of the preferred embodiments, the composition comprises  
5 3-8 mg/mL, or 3-6 mg/mL of K-sorbate, or more specifically 3.7-5.7 mg/mL, or 4.2-5.2 mg/mL of K-sorbate, e.g., 4.7 mg/mL.

In a further embodiment, the composition has a pH of about 6.0-7.4. In a more specific embodiment, the composition comprises from 3 mg/mL to 10 mg/mL of potassium sorbate and has a pH of about 6.0-7.4.

10 In one embodiment, the composition is provided in the form of a clear liquid that can be instilled into the eye, i.e., the liquid is applied either directly to the surface of the eyeball and/or (in)to the inner sides of the eyelids, such as into the lacrimal sac. In that regard, it is to be understood that the composition according to the first aspect of the invention can be administered topically directly onto any surface of the eye and/or eye socket (e.g., the  
15 sclera, cornea, conjunctiva, conjunctival sac, etc.) but is not intended for application to the outer surface of the eyelid and percutaneous delivery of cevimeline and/or sorbic acid.

For the purpose of instilling it into the eye, the composition may have a dynamic viscosity in the range of 1 cP to 60 cP, or 1 cP to 50 cP, or 1 cP to 20 cP, for instance, a dynamic viscosity of less than 5 cP. As used herein, the term 'dynamic viscosity' refers to the  
20 dynamic viscosity at room temperature ( $20 \pm 5$  °C) as determined by, or measured using, a Brookfield rotating spindle viscometer which measures the force to turn the spindle in a test sample at a given rotation rate. The test sample is stored at room temperature for about 2 h prior to testing and then placed on the measurement chamber with a pipette. Then a proper rotation speed is selected for the spindle according to the expected viscosity  
25 of the test solution. Furthermore, it is also preferred if the composition is isotonic, or essentially isotonic, with lacrimal fluid (tear fluid). In one embodiment, the composition has an osmolality in the range of about 200-600 mOsm/kg, or about 250-450 mOsm/kg, or about 250-400 mOsm/kg. In some of the preferred embodiments, the liquid composition has an osmolality in the range of about 270-350 mOsm/kg, or about 280-300 mOsm/kg.

Yet further, the composition according to the first aspect of the invention is preferably sterile, especially when intended for – though not only then – for instillation into the eye. In one embodiment, the composition is subjected to sterile filtration, for instance, by passing it through a 0.22 µm filter.

5 In a further specific embodiment, the composition is an ophthalmic composition provided in the form of eye-drops. Occasionally, ophthalmic composition such as eye-drops are also referred to as topical compositions, or topical ophthalmic compositions, since they are applied to skin- and/or mucosal surfaces of the eyes. Assuming concentrations between 1-50 mg/mL of cevimeline for eye-drop compositions according to the first aspect of the  
10 invention, an effective amount of cevimeline can typically be administered with a single drop. The term 'effective amount' refers to the amount or quantity of active ingredient, or drug, (here cevimeline) which is sufficient to elicit the required or desired therapeutic response, or in other words, the amount which is sufficient to elicit an appreciable biological response when administered to a patient.

15 In one embodiment, the composition is not, provided in the form of an ointment, a cream, a paste, an insert, a punctum plug, and/or a plaster. Or in other words, the composition according to the first aspect of the invention excludes compositions in the form of an ointment, a cream, a paste, an insert, a punctum plug, and/or a plaster.

In one embodiment, the composition may optionally comprise one or more further active  
20 agents; for instance, active agents selected from (a) steroids such as loteprednol etabonate, prednisolone acetate, fluticasone, or a combination thereof, (b) immuno-modulators or immunosuppressants such as cyclosporine, tacrolimus, sirolimus, or a combination thereof, (c) hormones such as testosterone, estrogen, or a combination thereof, (d) secretagogues such as rebamipide, diquafosol, or a combination thereof,  
25 (e) lymphocyte function associated antigen-1 (LFA-1) antagonists such as lifitegrast, and/or (f) active ingredients effective for treating Meibomian gland dysfunction.

In an alternative embodiment, the composition is free of, or essentially free of, active agents and/or beneficial agents other than (i) cevimeline, or a pharmaceutically acceptable salt thereof, and/or (ii) sorbic acid as the PUFA, or a pharmaceutically  
30 acceptable salt thereof. In particular, the composition is free of, or essentially free of, insulin, insulin-like growth factor (IGF), somatomedin C, and cycloplegic agent.

In a second aspect, the invention relates to a method of treating one or more of dry eye disease, xerostomia, or Sjogren syndrome, the method comprising a step of topically administering the composition according to the first aspect of the invention to a subject suffering from dry eye disease, xerostomia, and/or Sjogren syndrome. In other words, in this second aspect the invention relates to the composition according to the first aspect of the invention for use in the treatment of one or more of dry eye disease, xerostomia, or Sjogren syndrome. In yet other words, in this second aspect the invention relates to the use of the composition according to the first aspect of the invention in the manufacture of a medicament for the treatment of one or more of dry eye disease, xerostomia, or Sjogren syndrome. Accordingly, any embodiments, or specific or preferred embodiments, disclosed herein in connection with the composition according to the first aspect of the invention, may be applied to the method or use according to the second aspect of the invention.

In one embodiment, the composition may be administered into the eye of the subject, typically, by instilling it into the eye (i.e., applying it either directly to the surface of the eye ball and/or to the inner sides of the eyelids, such as into the lacrimal sac of the eye). In an alternative embodiment, or in addition to the administration into the eye of the subject, the composition may also be administered to the nasal mucosa of the subject, for instance, in the form of an aqueous nasal spray that is to be administered into the nasal cavity.

In one embodiment, the composition is administered once, twice, or three or four times a day. In that regard, the composition is advantageous to, for instance, mere artificial tear- or saliva compositions that need to be applied up to 10-12 times a day.

In one embodiment, the composition is administered over a treatment period of at least 7 days.

Advantageously, the composition does not cause miosis after administration, in particular after administration into the eye.

In a third aspect, the invention relates to an ophthalmic composition comprising 2 mg/mL to 50 mg/mL cevimeline or a pharmaceutically acceptable salt thereof, 4.7 mg/mL potassium sorbate, sodium phosphate buffer, sodium chloride, and water. For instance, in one of the preferred embodiments, the invention relates to an ophthalmic composition comprising 2 mg/mL to 40 mg/mL cevimeline or a pharmaceutically acceptable salt

thereof, 4.7 mg/mL potassium sorbate, sodium phosphate buffer, sodium chloride, and water.

In a further aspect, the invention relates to a method of treating one or more of dry eye disease, xerostomia, or Sjogren syndrome, the method comprising a step of administering  
5 an aqueous composition comprising cevimeline to the nasal mucosa of a subject suffering from dry eye disease, xerostomia, and/or Sjogren syndrome.

The above is a detailed description of particular embodiments of the invention. It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing  
10 from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims. All embodiments disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.

The following examples serve to illustrate the invention; however, they should not be understood as restricting the scope of the invention. All examples used pharmaceutical  
15 grade ingredients in preparing the compositions described below.

## EXAMPLES

### Example 1 (Ex. 1) – Stability of cevimeline/K-sorbate compositions (Panel I)

Several compositions comprising cevimeline (here in its cevimeline HCl x 0.5 H<sub>2</sub>O salt form) as well as the medium-chain polyunsaturated fatty acid sorbic acid (SA; here in its  
20 potassium sorbate salt form) were prepared by mixing the components according to Table 1 below, filtered (0.22 µm), then filled in high density polyethylene (HDPE) eye dropper bottles, and subsequently assessed in terms of stability. The compositions are suited for instillation into the eye, e.g., in the form of eye-drops.

All compositions contained 2 mg/mL cevimeline (free base equivalent) 4.7 mg/mL  
25 potassium sorbate, and sodium chloride as a tonicity agent, except for EY4-11 which was included as a potassium sorbate-free control set to evaluate impact of potassium sorbate on cevimeline stability. Formulation variables evaluated were buffer species and pH (sodium phosphate/ citrate buffer at pH 7.0 and 8.0, citrate buffer at pH 6.0, and borate

buffer at pH 8.0), as well as the effect of the presence of disodium ethylenediamine tetraacetic acid (Na<sub>2</sub>-EDTA) as an antioxidative chelating agent.

Right after preparation, all compositions were clear, colorless solutions free of any oil-films or oil droplets visible to the naked human eye.

- 5 The stability study was conducted at 25 °C / 40 % RH (i.e., 'real time'-stability) and at 40 °C / 25 % RH (accelerated stability). Stability test parameters monitored included percent drug assay (as measured by HPLC), impurity (degradant) content, pH, osmolality, and physical appearance.

| Ingredients [mg/mL]               | EY4-1                                                    | EY4-3 | EY4-7          | EY4-8 | EY4-9         | EY4-11  |
|-----------------------------------|----------------------------------------------------------|-------|----------------|-------|---------------|---------|
|                                   | w/o EDTA                                                 | EDTA  | pH 6 (citrate) | pH 8  | pH 8 (borate) | control |
| Cevimeline                        | 2.0                                                      |       |                |       |               |         |
| K-sorbate                         | 4.7                                                      |       |                |       |               | ---     |
| Citric acid monohydrate           | 0.30                                                     | 0.30  | 0.50           | 0.14  | ---           | 0.30    |
| Na-phosphate dibasic heptahydrate | 3.0                                                      | 3.0   | ---            | 2.68  | ---           | 3.0     |
| Na-citrate dihydrate              | ---                                                      | ---   | 4.5            | ---   | ---           | ---     |
| Boric acid                        | ---                                                      | ---   | ---            | ---   | 6.0           | ---     |
| Na-borate decahydrate             | ---                                                      | ---   | ---            | ---   | 0.45          | ---     |
| Na <sub>2</sub> -EDTA             | ---                                                      | 0.50  |                |       |               | ---     |
| NaCl                              | q.s. for tonicity of 280-300 mOsm/kg (i.e., isotonicity) |       |                |       |               |         |
| Purified water                    | q.s.                                                     |       |                |       |               |         |
| HCl or NaOH (q.s. for pH)         | 7.0                                                      | 7.0   | 6.0            | 8.0   | 8.0           | 7.0     |

- 10 **Table 1:** Exemplary aqueous, liquid cevimeline/K-sorbate-compositions (Panel I)

As can also be seen from Table 2 below, EY4-1 (with sorbate) and EY4-11 (without sorbate) were most stable, indicating that formulating cevimeline in aqueous compositions with potassium sorbate as a PUFA in concentrations above 1-2 mg/mL is feasible.

The EDTA containing formulations EY4-3, -7, -8, and -9 showed discoloration during storage at 40 °C, accompanied by higher drug losses.

Among all buffer species studied, formulations containing phosphate buffer (EY4-1) was most stable and showed promising results in terms of the solution appearance, drug assay, and impurity (degradant) content.

| <b>Panel I<br/>Stability Data</b> | <b>EY4-1</b> | <b>EY4-3</b> | <b>EY4-7</b> | <b>EY4-8</b> | <b>EY4-9</b> | <b>EY4-11</b> |
|-----------------------------------|--------------|--------------|--------------|--------------|--------------|---------------|
| <b>0 months</b>                   |              |              |              |              |              |               |
| <b>Assay % LS</b>                 | <b>94.4</b>  | <b>96.2</b>  | <b>96.6</b>  | <b>95.4</b>  | <b>97.2</b>  | <b>96.9</b>   |
| % total impurities                | 0.15         | 0.15         | 0.15         | 0.15         | 0.15         | 0.15          |
| pH                                | 6.97         | 6.96         | 5.96         | 7.99         | 7.97         | 6.99          |
| osmolality [mOsm/kg]              | 282          | 291          | 283          | 290          | 281          | 280           |
| <b>25 °C / 40 % RH</b>            |              |              |              |              |              |               |
| <b>3 Months</b>                   |              |              |              |              |              |               |
| <b>Assay % LS</b>                 | <b>92.4</b>  | <b>93.2</b>  | <b>89.1</b>  | <b>92.3</b>  | <b>92.1</b>  | <b>95.2</b>   |
| pH                                | 7.13         | 7.14         | 6.15         | 7.89         | 8.16         | 7.19          |
| osmolality [mOsm/kg]              | 277          | 280          | 266          | 281          | 280          | 267           |
| <b>6 Months</b>                   |              |              |              |              |              |               |
| <b>Assay % LS</b>                 | <b>94.5</b>  | n.c.         | n.c.         | n.c.         | n.c.         | <b>97.4</b>   |
| pH                                | 7.10         |              |              |              |              | 7.13          |
| osmolality [mOsm/kg]              | 275          |              |              |              |              | 273           |
| <b>40 °C / 25 % RH</b>            |              |              |              |              |              |               |
| <b>1 Month</b>                    |              |              |              |              |              |               |
| <b>Assay % LS</b>                 | <b>93.6</b>  | <b>94.1</b>  | <b>92.8*</b> | <b>90.3</b>  | <b>87.4</b>  | <b>95.9</b>   |
| pH                                | 6.94         | 6.98         | 6.03         | 7.64         | 8.01         | 7.01          |
| osmolality [mOsm/kg]              | 275          | 273          | 261          | 277          | 277          | 262           |
| <b>3 Months</b>                   |              |              |              |              |              |               |
| <b>Assay % LS</b>                 | <b>92.5</b>  | <b>90.1*</b> | <b>86.7*</b> | <b>84.2*</b> | <b>76.0</b>  | <b>95.5</b>   |
| pH                                | 7.13         | 7.19         | 6.26         | 7.70         | 8.09         | 7.10          |
| osmolality [mOsm/kg]              | 284          | 283          | 269          | 286          | 285          | 271           |
| <b>6 Months</b>                   |              |              |              |              |              |               |
| <b>Assay % LS</b>                 | <b>96.2</b>  | n.c.         | n.c.         | n.c.         | n.c.         | <b>98.7</b>   |
| pH                                | 7.12         |              |              |              |              | 7.09          |
| osmolality [mOsm/kg]              | 290          |              |              |              |              | 275           |

**Table 2:** Summary of stability data cevimeline compositions containing K-sorbate (Panel I)

n.c.: not continued; \* = yellow discoloration; LS = label strength

Example 2 (Ex. 2) – Stability of cevimeline/K-sorbate-compositions (Panel II)

Based on the stability findings from Panel I study, a second panel of formulations was prepared using phosphate as a buffering system, and sodium chloride as a tonicity agent. Aqueous compositions comprising different concentrations of cevimeline (here in its cevimeline HCl x 0.5 H<sub>2</sub>O salt form) as well as the medium-chain polyunsaturated fatty acid sorbic acid (SA; here in its potassium sorbate salt form) were prepared by mixing the components according to Table 3 below, filtered (0.22 µm), then filled in low density polyethylene (LDPE) eye dropper bottles which were further sealed in aluminum pouches, and subsequently assessed in terms of stability. The compositions are suited for instillation into the eye, e.g., in the form of eye-drops.

Formulation variables evaluated were cevimeline concentrations in the range of 2 mg/mL to 40 mg/mL (free base equivalent), pH-values in the range of pH 6.0 to 8.0, and potassium sorbate concentrations in the range of 4.7 mg/mL to 15 mg/mL, with or without the presence of benzalkonium chloride (BAK) as a preservative.

The stability study was conducted at 25 °C / 40 % RH and 40 °C / 25 % RH and 60 °C. Stability test parameters monitored included percent drug assay (as measured by HPLC), impurity (degradant) content, pH, osmolality, and physical appearance.

| <b>Ingredients<br/>[mg/mL]</b>          | <b>EY4-<br/>20</b>                                       | <b>EY4-<br/>21</b> | <b>EY4-<br/>22</b> | <b>EY4-<br/>23</b> | <b>EY4-<br/>24</b> | <b>EY4-<br/>25</b> | <b>EY4-<br/>26</b> | <b>EY4-<br/>27</b> | <b>EY4-<br/>28</b> | <b>EY4-<br/>29</b> | <b>EY4-<br/>30</b> |
|-----------------------------------------|----------------------------------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Cevimeline                              | ---                                                      | 2.0                | 40                 | 10                 | ---                | 2.0                | 2.0                | 2.0                | 2.0                | 2.0                | 2.0                |
| K-sorbate                               | 4.7                                                      | 4.7                | 4.7                | 15                 | ---                | ---                | 4.7                | ---                | ---                | 4.7                | 4.7                |
| Na-phosphate mono-<br>basic monohydrate | 0.54                                                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
| Na-phosphate di-<br>basic heptahydrate  | 1.63                                                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
| BAK                                     | ---                                                      | ---                | ---                | ---                | ---                | ---                | 0.05               | ---                | ---                | ---                | ---                |
| NaCl                                    | q.s. for tonicity of 280-300 mOsm/kg (i.e., isotonicity) |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
| Purified water                          | q.s.                                                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
| HCl or NaOH<br>(q.s. for pH)            | 7.0                                                      |                    |                    |                    |                    |                    |                    | 6.0                | 8.0                | 7.4                | 8.0                |

**Table 3:** Exemplary aqueous, liquid cevimeline/K-sorbate-compositions (Panel II)

| Panel II Stability Data | EY4-20     | EY4-21      | EY4-22       | EY4-23       | EY4-24     | EY4-25      | EY4-26       | EY4-27       | EY4-28      | EY4-29      | EY4-30      |
|-------------------------|------------|-------------|--------------|--------------|------------|-------------|--------------|--------------|-------------|-------------|-------------|
| <b>25 °C / 40 % RH</b>  |            |             |              |              |            |             |              |              |             |             |             |
| <b>0 months</b>         |            |             |              |              |            |             |              |              |             |             |             |
| <b>Assay % LS</b>       | <b>n/a</b> | <b>99.6</b> | <b>100.9</b> | <b>99.5</b>  | <b>n/a</b> | <b>99.2</b> | <b>100.4</b> | <b>100.6</b> | <b>98.8</b> | <b>99.4</b> | <b>99.2</b> |
| % total impurities      | n/a        | 0.17        | 0.17         | 0.12         | n/a        | 0.16        | 0.16         | 0.16         | 0.20        | 0.17        | 0.16        |
| pH                      | 7.03       | 6.99        | 7.01         | 7.00         | 7.01       | 7.00        | 6.99         | 6.03         | 8.01        | 7.41        | 7.99        |
| osmolality [mOsm/kg]    | 281        | 285         | 493          | 305          | 283        | 283         | 286          | 283          | 282         | 283         | 287         |
| <b>3 Months</b>         |            |             |              |              |            |             |              |              |             |             |             |
| <b>Assay % LS</b>       | <b>n/a</b> | <b>97.6</b> | <b>102.2</b> | <b>100.1</b> | <b>n/a</b> | <b>97.9</b> | <b>97.8</b>  | <b>99.4</b>  | <b>94.7</b> | <b>96.6</b> | <b>94.8</b> |
| % total impurities      | n/a        | 0.57        | 0.22         | 0.43         | n/a        | 0.46        | 0.67         | 0.38         | 0.73        | 0.62        | 0.77        |
| pH                      | 6.83       | 6.82        | 6.93         | 6.96         | 6.72       | 6.74        | 6.83         | 6.15         | 7.57        | 7.18        | 7.59        |
| osmolality [mOsm/kg]    | 296        | 286         | 451          | 310          | 281        | 285         | 291          | 294          | 279         | 286         | 290         |
| <b>6 Months</b>         |            |             |              |              |            |             |              |              |             |             |             |
| <b>Assay % LS</b>       | <b>n/a</b> | <b>96.4</b> | <b>101.4</b> | <b>98.0</b>  | <b>n/a</b> | <b>97.2</b> | <b>97.3</b>  | <b>98.8</b>  | <b>92.9</b> | <b>95.0</b> | <b>93.0</b> |
| % total impurities      | n/a        | 1.19        | 0.35         | 0.67         | n/a        | 0.54        | 1.24         | 0.45         | 0.93        | 1.26        | 1.42        |
| pH                      | 6.85       | 6.84        | 6.79         | 6.97         | 6.74       | 6.74        | 6.83         | 6.16         | 7.54        | 7.20        | 7.56        |
| osmolality [mOsm/kg]    | 296        | 294         | 447          | 310          | 293        | 286         | 291          | 294          | 281         | 286         | 287         |
| <b>40 °C / 25 % RH</b>  |            |             |              |              |            |             |              |              |             |             |             |
| <b>1 Month</b>          |            |             |              |              |            |             |              |              |             |             |             |
| <b>Assay % LS</b>       | <b>n/a</b> | <b>93.9</b> | <b>98.6</b>  | <b>95.4</b>  | <b>n/a</b> | <b>94.2</b> | <b>94.6</b>  | <b>98.4</b>  | <b>87.5</b> | <b>89.2</b> | <b>87.7</b> |
| % total impurities      | n/a        | 1.06        | 0.27         | 0.85         | n/a        | 0.85        | 1.20         | 0.51         | 1.21        | 1.31        | 1.54        |
| pH                      | 6.95       | 6.85        | 6.75         | 6.95         | 6.75       | 6.72        | 6.81         | 6.14         | 7.41        | 7.10        | 7.47        |
| osmolality [mOsm/kg]    | 291        | 285         | 447          | 313          | 281        | 284         | 286          | 294          | 281         | 286         | 289         |
| <b>3 Months</b>         |            |             |              |              |            |             |              |              |             |             |             |
| <b>Assay % LS</b>       | <b>n/a</b> | <b>92.8</b> | <b>101.6</b> | <b>96.3</b>  | <b>n/a</b> | <b>94.9</b> | <b>94.3</b>  | <b>98.3</b>  | <b>86.5</b> | <b>90.1</b> | <b>84.8</b> |
| % total impurities      | n/a        | 1.60        | 0.44         | 1.23         | n/a        | 1.07        | 1.55         | 0.74         | 1.44        | 2.01        | 2.31        |
| pH                      | 6.81       | 6.76        | 6.57         | 6.83         | 6.69       | 6.66        | 6.75         | 6.06         | 7.31        | 7.03        | 7.32        |
| osmolality [mOsm/kg]    | 291        | 287         | 450          | 312          | 283        | 285         | 289          | 296          | 281         | 289         | 291         |

| Panel II Stability Data |  | EY4-20 | EY4-21 | EY4-22 | EY4-23 | EY4-24 | EY4-25 | EY4-26 | EY4-27 | EY4-28 | EY4-29 | EY4-30 |
|-------------------------|--|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| <b>6 Months</b>         |  |        |        |        |        |        |        |        |        |        |        |        |
| <b>Assay % LS</b>       |  | n/a    | 91.1   | 99.8   | 91.1*  | n/a    | 91.3   | 90.5   | 96.7   | 79.3   | 86.4   | 79.4   |
| % total impurities      |  | n/a    | 2.41   | 0.58   | 4.58   | n/a    | 1.51   | 2.64   | 1.04   | 2.33   | 2.80   | 3.17   |
| pH                      |  | 6.84   | 6.77   | 6.39   | 6.88   | 6.70   | 6.62   | 6.73   | 6.07   | 7.20   | 7.01   | 7.25   |
| osmolality [mOsm/kg]    |  | 298    | 287    | 448    | 310    | 287    | 285    | 294    | 296    | 282    | 286    | 290    |
| 60 °C                   |  |        |        |        |        |        |        |        |        |        |        |        |
| <b>1 Month</b>          |  |        |        |        |        |        |        |        |        |        |        |        |
| <b>Assay % LS</b>       |  | n/a    | 89.3   | 96.8   | 89.4   | n/a    | 83.3   | 82.3   | 94.2   | 66.8   | 75.8   | 65.7   |
| % total impurities      |  | n/a    | 2.91   | 0.46   | 4.52   | n/a    | 2.22   | 3.22   | 1.50   | 3.66   | 3.83   | 4.62   |
| pH                      |  | 6.80   | 6.73   | 6.13   | 6.66   | 6.63   | 6.64   | 6.68   | 6.05   | 7.01   | 6.88   | 7.08   |
| osmolality [mOsm/kg]    |  | 292    | 287    | 447    | 308    | 283    | 285    | 287    | 296    | 280    | 287    | 290    |
| <b>3 Months</b>         |  |        |        |        |        |        |        |        |        |        |        |        |
| <b>Assay % LS</b>       |  | n/a    | 89.7   | 98.7   | 74.1*  | n/a    | 79.3   | 75.3   | 95.4   | 60.0   | 72.6   | 60.3   |
| % total impurities      |  | n/a    | 5.97   | 1.05   | 34.91  | n/a    | 4.43   | 5.30   | 2.39   | 5.57   | 6.47   | 7.37   |
| pH                      |  | 6.73   | 6.66   | 5.95   | 6.84   | 6.63   | 6.26   | 6.50   | 5.91   | 6.77   | 6.79   | 6.91   |
| osmolality [mOsm/kg]    |  | 296    | 290    | 449    | 299    | 289    | 289    | 289    | 298    | 283    | 289    | 292    |
| <b>6 Months</b>         |  |        |        |        |        |        |        |        |        |        |        |        |
| <b>Assay % LS</b>       |  | n/a    | 89.4   | 95.4   | 53.0*  | n/a    | 75.4   | 62.8   | 94.8   | 51.3   | 61.1   | 50.4   |
| % total impurities      |  | n/a    | 9.65   | 1.40   | 52.60  | n/a    | 7.40   | 10.32  | 3.71   | 8.93   | 11.16  | 12.56  |
| pH                      |  | 6.77   | 6.66   | 5.82   | 6.81   | 6.73   | 6.00   | 6.53   | 5.87   | 6.64   | 6.76   | 6.85   |
| osmolality [mOsm/kg]    |  | 299    | 298    | 454    | 288    | 285    | 291    | 291    | 302    | 283    | 292    | 294    |

**Table 4:** Summary of stability data cevimeline compositions containing K-sorbate (Panel II)

n/a: not analyzed; \* = yellow discoloration

As can also be seen in Table 4 above, stability was found to be dependent on drug concentration, pH, and potassium sorbate concentration. Cevimeline was found to be more stable at higher drug concentration (e.g., EY4-21 vs. EY4-22). Compositions containing a higher concentration of potassium sorbate, on the other hand, were found to be relatively less stable in terms of cevimeline degradation (e.g., EY4-21 vs. EY4-23). For the composition containing 15 mg/mL potassium sorbate (EY4-23), a slight discoloration was only noticed, though, when stored at 40°C for 6 months.

Within the studied pH-range of pH 6.0 to 8.0, cevimeline was relatively more stable at lower pH-values (e.g., EY4-21, -29, and -30). A similar pH effect was also noticed for the formulations that do not contain potassium sorbate (EY4-25, -27, and -28). Lastly, the preservative benzalkonium chloride (BAK) had no significant impact on cevimeline stability (e.g., EY4-21 vs. EY4-26) in this study.

The inventors further found that the total amount of degradation impurities observed in some of the compositions does not correlate with the percent assay loss, suggesting that absorption of cevimeline to the LDPE container may have occurred.

#### Example 3 (Ex. 3) – Stability of cevimeline/K-sorbate-compositions (Panel III)

A third panel of formulations was prepared using phosphate as a buffering system, and sodium chloride as a tonicity agent. Aqueous compositions comprising different concentrations of cevimeline (here in its cevimeline HCl x 0.5 H<sub>2</sub>O salt form) as well as the medium-chain polyunsaturated fatty acid sorbic acid (SA; here in its potassium sorbate salt form) were prepared by mixing the components according to Table 5 below. The compositions, which are suited for instillation into the eye, were filtered (0.22 µm) and filled in eye dropper bottles made of either high density polyethylene (HDPE) (EY4-31 to -37) or polyethylene terephthalate (PET; EY4-38 and -39) to mitigate potential drug absorption (in)to the eye dropper container; both container types were further sealed in an aluminium pouch. Subsequently, the compositions assessed in terms of stability.

Formulation variables evaluated were cevimeline concentrations in the range of 2.0 mg/mL to 6.0 mg/mL (free base equivalent), and pH-values in the range of pH 6.0 to 7.4. Formulations containing polyoxyl 40 hydrogenated castor oil (here

Kolliphor® RH40) and Hydroxypropyl- $\beta$ -Cyclodextrin (HP- $\beta$ -CD; here Kleptose®) were also included in the formulation panel to assess the effect of the two as potential stabilizers.

The stability study was conducted at 25 °C / 40 % RH and 40 °C / 25 % RH and 60 °C. Stability test parameters monitored included percent drug assay (as measured by HPLC), impurity (degradant) content, pH, osmolality, and physical appearance.

| Ingredients<br>[mg/mL]               | EY4-31                                                   | EY4-32 | EY4-33 | EY4-34 | EY4-35 | EY4-36 | EY4-37 | EY4-38 | EY4-39 |
|--------------------------------------|----------------------------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Cevimeline                           | 6.0                                                      |        |        |        |        | ---    | ---    | 2.0    | 6.0    |
| K-sorbate                            | 4.7                                                      |        |        |        | ---    | 4.7    |        |        |        |
| Na-phosphate mono-basic dihydrate    | 0.61*                                                    |        |        |        |        |        |        |        |        |
| Na-phosphate dibasic heptahydrate    | 1.63                                                     |        |        |        |        |        |        |        |        |
| Polyoxyl 40 hydro-genated castor oil | ---                                                      | ---    | 5.0    | ---    | ---    | ---    | 5.0    | ---    | ---    |
| HP-β-Cyclodextrin                    | ---                                                      | ---    | ---    | 40     | ---    | ---    | ---    | ---    | ---    |
| NaCl                                 | q.s. for tonicity of 280-300 mOsm/kg (i.e., isotonicity) |        |        |        |        |        |        |        |        |
| Purified water                       | q.s.                                                     |        |        |        |        |        |        |        |        |
| HCl or NaOH (q.s. for pH)            | 6.0                                                      | 7.0    |        |        |        |        |        | 7.4    | 7.0    |

**Table 5:** Exemplary aqueous, liquid cevimeline/K-sorbate-compositions (Panel III)

\* amount equivalent to 0.54 mg/mL Na-phosphate mono-basic monohydrate

As can also be seen in Table 6 below, drug assays remained unchanged or decreased only marginally in the pouched HDPE-bottles dependent on the pH, whereas the samples stored in the PET-bottles showed seemingly increased drug assays. The increased assays matched with the gravimetric loss of the PET bottles, being 3 % at 25 °C / 40 % RH, 12 % at 40 °C / 25 % RH, and 37 % at 60 °C after 3 months, suggesting significant losses of water in/from the PET bottles. No discoloration was observed for any of the compositions. Both stabilizers investigated did not reduce cevimeline degradation significantly; however, unexpectedly, HP- $\beta$ -CD appears to mitigate the issue of drug absorption (in)to the container, as evidenced by the cevimeline assay of EY4-34 (especially at 40 °C and 60 °C), and further by Example 4.

| Panel III Stability Data |  | EY4-31      | EY4-32      | EY4-33       | EY4-34       | EY4-35       | EY4-36     | EY4-37     | EY4-38       | EY4-39       |
|--------------------------|--|-------------|-------------|--------------|--------------|--------------|------------|------------|--------------|--------------|
| <b>0 months</b>          |  |             |             |              |              |              |            |            |              |              |
| <b>Assay % LS</b>        |  | <b>99.9</b> | <b>99.9</b> | <b>101.7</b> | <b>99.3</b>  | <b>99.0</b>  | <b>n/a</b> | <b>n/a</b> | <b>101.0</b> | <b>98.7</b>  |
| % total impurities       |  | 0.17        | 0.17        | 0.16         | 0.17         | 0.17         | n/a        | n/a        | 0.17         | 0.17         |
| pH                       |  | 5.97        | 7.00        | 7.00         | 6.99         | 6.98         | 7.03       | 7.01       | 7.43         | 7.00         |
| osmolality [mOsm/kg]     |  | 287         | 281         | 284          | 284          | 287          | 282        | 287        | 283          | 284          |
| <b>25 °C / 40 % RH</b>   |  |             |             |              |              |              |            |            |              |              |
| <b>2 Months</b>          |  |             |             |              |              |              |            |            |              |              |
| <b>Assay % LS</b>        |  | <b>98.1</b> | <b>99.2</b> | <b>100.4</b> | <b>100.1</b> | <b>99.3</b>  | <b>n/a</b> | <b>n/a</b> | <b>103.3</b> | <b>102.3</b> |
| % total impurities       |  | 0.20        | 0.20        | 0.15         | 0.22         | 0.15         | n/a        | n/a        | 0.15         | 0.20         |
| pH                       |  | 5.95        | 6.98        | 6.99         | 6.91         | 6.63         | 6.94       | 7.02       | 7.43         | 7.01         |
| osmolality [mOsm/kg]     |  | 290         | 282         | 285          | 282          | 283          | 280        | 284        | 291          | 290          |
| <b>3 Months</b>          |  |             |             |              |              |              |            |            |              |              |
| <b>Assay % LS</b>        |  | <b>97.7</b> | <b>99.4</b> | <b>101.5</b> | <b>98.8</b>  | <b>98.7</b>  | <b>n/a</b> | <b>n/a</b> | <b>104.1</b> | <b>101.8</b> |
| % total impurities       |  | 0.15        | 0.15        | 0.16         | 0.26         | 0.15         | n/a        | n/a        | 0.16         | 0.15         |
| pH                       |  | 6.01        | 7.00        | 7.01         | 6.99         | 6.95         | 7.02       | 7.04       | 7.45         | 7.02         |
| osmolality [mOsm/kg]     |  | 287         | 278         | 287          | 281          | 278          | 277        | 287        | 290          | 290          |
| <b>6 Months</b>          |  |             |             |              |              |              |            |            |              |              |
| <b>Assay % LS</b>        |  | <b>98.9</b> | <b>99.2</b> | <b>100.5</b> | <b>100.7</b> | <b>100.3</b> | <b>n/a</b> | <b>n/a</b> | <b>108.9</b> | <b>107.3</b> |
| % total impurities       |  | 0.16        | 0.21        | 0.15         | 0.27         | 0.15         | n/a        | n/a        | 0.16         | 0.21         |
| pH                       |  | 6.0         | 6.7         | 7.0          | 7.0          | 6.9          | 7.0        | 7.1        | 7.4          | 7.0          |
| osmolality [mOsm/kg]     |  | 289         | 282         | 289          | 283          | 281          | 282        | 293        | 302          | 305          |

**Table 6:** Summary of stability data cevimeline compositions containing K-sorbate (Panel III)

n.c.: not continued; \*\* bottle deformed; n/a: not available

| Panel III Stability Data |                      | EY4-31      | EY4-32      | EY4-33      | EY4-34       | EY4-35      | EY4-36     | EY4-37     | EY4-38       | EY4-39       |
|--------------------------|----------------------|-------------|-------------|-------------|--------------|-------------|------------|------------|--------------|--------------|
| 40 °C / 25 % RH          |                      |             |             |             |              |             |            |            |              |              |
| <b>1 Month</b>           | <b>Assay % LS</b>    | <b>98.8</b> | <b>98.0</b> | <b>99.9</b> | <b>100.4</b> | <b>98.7</b> | <b>n/a</b> | <b>n/a</b> | <b>104.9</b> | <b>103.4</b> |
|                          | % total impurities   | 0.16        | 0.16        | 0.15        | 0.22         | 0.16        | n/a        | n/a        | 0.21         | 0.16         |
|                          | pH                   | 6.00        | 6.95        | 6.97        | 6.95         | 6.89        | 7.03       | 7.03       | 7.41         | 6.99         |
|                          | osmolality [mOsm/kg] | 291         | 294         | 285         | 288          | 282         | 282        | 287        | 296          | 296          |
| <b>2 Months</b>          | <b>Assay % LS</b>    | <b>98.4</b> | <b>98.7</b> | <b>98.1</b> | <b>99.4</b>  | <b>98.4</b> | <b>n/a</b> | <b>n/a</b> | <b>108.2</b> | <b>107.8</b> |
|                          | % total impurities   | 0.21        | 0.31        | 0.16        | 0.31         | 0.15        | n/a        | n/a        | 0.28         | 0.32         |
|                          | pH                   | 5.96        | 6.91        | 6.92        | 6.97         | 6.86        | 6.99       | 7.01       | 7.42         | 7.00         |
|                          | osmolality [mOsm/kg] | 289         | 282         | 284         | 281          | 291         | 279        | 286        | 305          | 305          |
| <b>3 Months</b>          | <b>Assay % LS</b>    | <b>97.5</b> | <b>96.3</b> | <b>97.9</b> | <b>98.8</b>  | <b>96.9</b> | <b>n/a</b> | <b>n/a</b> | <b>112.5</b> | <b>112.2</b> |
|                          | % total impurities   | 0.29        | 0.31        | 0.27        | 0.32         | 0.15        | n/a        | n/a        | 0.31         | 0.29         |
|                          | pH                   | 6.07        | 6.89        | 6.89        | 6.97         | 6.85        | 7.07       | 7.04       | 7.43         | 7.01         |
|                          | osmolality [mOsm/kg] | 283         | 280         | 287         | 279          | 277         | 279        | 289        | 312          | 319          |
| <b>6 Months</b>          | <b>Assay % LS</b>    | <b>97.5</b> | <b>96.5</b> | <b>95.9</b> | <b>98.5</b>  | <b>95.4</b> | <b>n/a</b> | <b>n/a</b> | <b>130.9</b> | <b>129.9</b> |
|                          | % total impurities   | 0.40        | 0.55        | 0.21        | 0.64         | 0.15        | n/a        | n/a        | 0.69         | 0.70         |
|                          | pH                   | 6.1         | 6.9         | 6.9         | 6.9          | 6.8         | 7.1        | 7.1        | n/a          | 7.0          |
|                          | osmolality [mOsm/kg] | 286         | 281         | 290         | 284          | 280         | 282        | 295        | n/a          | 377          |

**Table 6 cont.:** Summary of stability data cevimeline compositions containing K-sorbate (Panel III)

n.c.: not continued; \*\* bottle deformed; n/a: not available

| Panel III Stability Data |                      | EY4-31       | EY4-32      | EY4-33      | EY4-34      | EY4-35      | EY4-36     | EY4-37     | EY4-38         | EY4-39         |
|--------------------------|----------------------|--------------|-------------|-------------|-------------|-------------|------------|------------|----------------|----------------|
| 60 °C                    |                      |              |             |             |             |             |            |            |                |                |
| <b>1 Month</b>           | <b>Assay % LS</b>    | <b>97.2</b>  | <b>93.3</b> | <b>93.4</b> | <b>96.6</b> | <b>93.6</b> | <b>n/a</b> | <b>n/a</b> | <b>112.6</b>   | <b>112.3</b>   |
|                          | % total impurities   | 0.49         | 0.66        | 0.68        | 0.66        | 0.16        | n/a        | n/a        | 0.72           | 0.67           |
|                          | pH                   | 6.00         | 6.68        | 6.69        | 6.91        | 6.63        | 7.03       | 7.05       | 7.37           | 6.99           |
|                          | osmolality [mOsm/kg] | 295          | 284         | 285         | 287         | 282         | 283        | 289        | 316            | 318            |
| <b>2 Months</b>          | <b>Assay % LS</b>    | <b>98.7</b>  | <b>90.1</b> | <b>90.4</b> | <b>92.8</b> | <b>91.7</b> | <b>n/a</b> | <b>n/a</b> | <b>125.2**</b> | <b>130.9**</b> |
|                          | % total impurities   | 0.44         | 0.89        | 0.72        | 0.97        | 0.22        | n/a        | n/a        | 1.36           | 1.29           |
|                          | pH                   | 6.19         | 6.59        | 6.60        | 6.66        | 6.36        | 7.06       | 7.10       | 7.37           | 6.95           |
|                          | osmolality [mOsm/kg] | 286          | 284         | 290         | 283         | 282         | 283        | 285        | 354            | 376            |
| <b>3 Months</b>          | <b>Assay % LS</b>    | <b>100.1</b> | <b>90.7</b> | <b>88.5</b> | <b>93.8</b> | <b>89.7</b> | <b>n/a</b> | <b>n/a</b> | <b>143.1**</b> | <b>152.5**</b> |
|                          | % total impurities   | 2.89         | 1.69        | 1.32        | 1.62        | 0.37        | n/a        | n/a        | 2.69           | 2.59           |
|                          | pH                   | 6.35         | 6.60        | 6.52        | 6.44        | 7.18        | 7.16       | 7.10       | 7.38           | 6.94           |
|                          | osmolality [mOsm/kg] | 289          | 277         | 286         | 279         | 277         | 281        | 291        | 400            | 432            |
| <b>6 Months</b>          | <b>Assay % LS</b>    | <b>89.0</b>  | <b>84.1</b> | <b>83.5</b> | <b>90.4</b> | <b>88.6</b> | <b>n/a</b> | <b>n/a</b> | <b>212.1**</b> | <b>433.9**</b> |
|                          | % total impurities   | 7.82         | 3.01        | 4.40        | 2.92        | 0.58        | n/a        | n/a        | 9.44           | 18.74          |
|                          | pH                   | 6.30         | 6.40        | 6.52        | 6.50        | 6.30        | 7.30       | 7.20       | n/a            | 6.90           |
|                          | osmolality [mOsm/kg] | 286          | 279         | 286         | 285         | 283         | 287        | 298        | n/a            | 2252           |

**Table 6 cont.:** Summary of stability data cevimeline compositions containing K-sorbate (Panel III)

n.c.: not continued; \*\* bottle deformed; n/a: not available

Example 4 (Ex. 4) – Container absorption of cevimeline/K-sorbate-compositions with and without HP- $\beta$ -CD at 40 °C (Panel IV)

A fourth panel of formulations was prepared to further investigate the effect of hydroxypropyl-beta-cyclodextrin (HP- $\beta$ -CD) on drug absorption into eyedrop containers.

- 5 For this purpose, formulations according to the present invention, with and without HP- $\beta$ -CD, were investigated in LDPE bottles (EY4-50 to EY4-55). Sorbate-free compositions were prepared as well for comparison.

- 10 Aqueous compositions comprising 2 mg/mL cevimeline (here in its cevimeline HCl x 0.5 H<sub>2</sub>O salt form), which are suited for instillation into the eye, were prepared by mixing the components according to Table 7 below, filtered (0.22  $\mu$ m), and filled in the LDPE eye dropper bottles (3 mL fill). The containers were not sealed in an aluminium pouch for this panel. Formulation variables evaluated were (i) with and without the presence of HP- $\beta$ -CD, and (ii) pH-values in the range of pH 7.0 to 8.0.

- 15 The stability study was conducted at 40 °C / 25 % RH. Stability test parameters monitored included percent drug assay (as measured by HPLC), impurity (degradant) content, pH, osmolality, and physical appearance.

| Ingredients [mg/mL]               | EY4-50                                                   | EY4-51 | EY4-52 | EY4-53 | EY4-54 | EY4-55 | EY4-56 | EY4-57 |
|-----------------------------------|----------------------------------------------------------|--------|--------|--------|--------|--------|--------|--------|
| Cevimeline                        | 2.0                                                      |        |        |        |        |        |        |        |
| K-sorbate                         | 4.7                                                      |        |        |        |        |        | 0      |        |
| Na-phosphate monobasic dihydrate  | 0.61*                                                    |        |        |        |        |        |        |        |
| Na-phosphate dibasic heptahydrate | 1.63                                                     |        |        |        |        |        |        |        |
| HP-β-Cyclodextrin                 | ---                                                      | ---    | ---    | 40     | 40     | 40     | ---    | 40     |
| NaCl                              | q.s. for tonicity of 280-300 mOsm/kg (i.e., isotonicity) |        |        |        |        |        |        |        |
| Purified water                    | q.s.                                                     |        |        |        |        |        |        |        |
| HCl or NaOH (q.s. for pH)         | 7.0                                                      | 7.4    | 8.0    | 7.0    | 7.4    | 8.0    | 7.4    | 7.4    |

**Table 7:** Exemplary aqueous, liquid cevimeline/K-sorbate-compositions (Panel IV)

\* amount equivalent to 0.54 mg/mL Na-phosphate mono-basic monohydrate

| <b>Formulation</b>                                 | <b>HP-<math>\beta</math>-CD</b> | <b>t<sub>0</sub></b> | <b>t<sub>1</sub><br/>(1 month)</b> | <b>t<sub>3</sub><br/>(3 months)</b> | <b>Change<br/>t<sub>3</sub>-t<sub>0</sub></b> |
|----------------------------------------------------|---------------------------------|----------------------|------------------------------------|-------------------------------------|-----------------------------------------------|
| <b>EY4-50</b><br>Assay, % LS<br>% total impurities | No<br>(pH 7.0)                  | <b>99.6</b><br>0.15  | <b>96.3</b><br>0.15                | <b>95.6</b><br>1.60                 | <b>-4.3</b><br>1.45                           |
| <b>EY4-51</b><br>Assay, % LS<br>% total impurities | No<br>(pH 7.4)                  | <b>98.6</b><br>0.14  | <b>95.1</b><br>0.25                | <b>92.7</b><br>2.89                 | <b>-5.9</b><br>2.75                           |
| <b>EY4-52</b><br>Assay, % LS<br>% total impurities | No<br>(pH 8.0)                  | <b>99.0</b><br>0.14  | <b>91.5</b><br>0.18                | <b>88.0</b><br>1.94                 | <b>-11.0</b><br>1.80                          |
| <b>EY4-53</b><br>Assay, % LS<br>% total impurities | Yes<br>(pH 7.0)                 | <b>98.7</b><br>0.14  | <b>99.1</b><br>0.22                | <b>98.5</b><br>1.40                 | <b>0.2</b><br>1.26                            |
| <b>EY4-54</b><br>Assay, % LS<br>% total impurities | Yes<br>(pH 7.4)                 | <b>98.5</b><br>0.13  | <b>98.1</b><br>0.19                | <b>97.3</b><br>1.46                 | <b>-1.2</b><br>1.33                           |
| <b>EY4-55</b><br>Assay, % LS<br>% total impurities | Yes<br>(pH 8.0)                 | <b>98.3</b><br>0.13  | <b>95.9</b><br>0.17                | <b>94.5</b><br>1.59                 | <b>-3.8</b><br>1.46                           |
| <b>EY4-56</b><br>Assay, % LS<br>% total impurities | No<br>(pH 7.4)                  | <b>99.3</b><br>0.14  | <b>95.7</b><br>0.18                | <b>93.6</b><br>1.31                 | <b>-5.7</b><br>1.17                           |
| <b>EY4-57</b><br>Assay, % LS<br>% total impurities | Yes<br>(pH 7.4)                 | <b>99.0</b><br>0.14  | <b>98.6</b><br>0.20                | <b>97.8</b><br>0.98                 | <b>-1.2</b><br>0.84                           |

**Table 8:** Summary of cevimeline assay results from compositions with or without HP- $\beta$ -CD (Panel IV)

As can be seen in Table 8 above, the drug assays confirmed that HP- $\beta$ -CD is able to mitigate cevimeline losses that are associated to absorption to the container, with both the change, or difference, of cevimeline assay between the initial and the 3 months timepoints (t<sub>0</sub> and t<sub>3</sub>) and the increase in impurity contents over time (a sign of drug degradation) being much less for the HP- $\beta$ -CD containing formulations (EY4-53, EY4-54, EY4-55, EY4-57); see, for instance, EY4-50 to EY4-52 compared to their respective HP- $\beta$ -CD containing compositions EY4-53 to EY4-55. Moreover, it could be observed that less drug was lost due to absorption by the container at lower pH-values.

In summary of the compositions exemplified in Examples 1-4 above, it was found that stable aqueous compositions comprising cevimeline (here in its HCl x 0.5 H<sub>2</sub>O salt form) and sorbic acid as a PUFA (here in its potassium sorbate salt form) were successfully developed; for instance, compositions as outlined in Table 9 below. The compositions are suited for instillation into the eye, e.g., in the form of eye-drops. They may comprise a therapeutic effective amount of cevimeline, less than 15 mg/mL, potassium sorbate as the PUFA, a phosphate buffer, and sodium chloride as the tonicity agent. A pH-range of pH 6.0 to 8.0, or pH 6.0 to 7.4, is preferred. The compositions may optionally further contain benzalkonium chloride (BAK) as a preservative and/or HP-β-Cyclodextrin (e.g., Kleptose®). The composition can be filled in a suitable eye-dropper bottle with proven acceptable compatibility where absorption of cevimeline into a primary container housing the composition is mitigated during storage shelf-life (i.e., typically up to 3 years), such as semi-permeable plastic bottles (e.g., high density polyethylene HDPE, low density polyethylene LDPE, polypropylene PP, or cyclic olefin copolymer COC), or similar pharmaceutical primary container closure systems.

| Ingredients                         | Acceptable                                                            | Target                                                         |
|-------------------------------------|-----------------------------------------------------------------------|----------------------------------------------------------------|
| Cevimeline                          | Therapeutic effective range                                           | 2.0–50 mg/mL<br>(e.g., 6 mg/mL, or 20 mg/mL, or 40 mg/mL)      |
| K-sorbate                           | ≤10 mg/mL                                                             | 1–10 mg/mL<br>(e.g., 4.7 mg/mL)                                |
| Na-phosphate mono-basic monohydrate | Typical range for ophthalmic composition                              | 0.41–0.68 mg/mL<br>(e.g., 0.54 mg/mL)                          |
| Na-phosphate dibasic heptahydrate   | Typical range for ophthalmic composition                              | 1.2–2.0 mg/mL<br>(e.g., 1.63 mg/mL)                            |
| BAK                                 | With or without                                                       | With or without                                                |
| NaCl                                | Suitable osmolality for ophthalmic composition, e.g., 200–600 mOsm/kg | 250–450 mOsm/kg<br>(e.g., 270–350 mOsm/kg, or 280–300 mOsm/kg) |
| Purified water                      | q.s.                                                                  | q.s.                                                           |
| Optional excipient(s)               | Cyclodextrin(s)                                                       | HP-β-Cyclodextrin                                              |
| HCl or NaOH (pH-adjustment)         | pH 6.0–8.0 or pH 6.0–7.5                                              | pH 6.0–7.4<br>(e.g., pH 7.0)                                   |

**Table 9:** Summary for aqueous, liquid cevimeline/K-sorbate-compositions

Example 5 (Ex. 5) – Ocular Tolerability Study in New Zealand White Rabbits

The purpose of this study was to evaluate the local and systemic tolerability of cevimeline when applied by topical ocular application 4 times daily, 40 µL to the left eye (right eye not dosed) for 7 consecutive days. The total administered volume was 160 µL/day, the dosing interval was 2 ± 0.5 hr.

Three test compositions (low-, mid-, and high dose), comprising various cevimeline-concentrations (6 mg/mL, 20 mg/mL, and 40 mg/mL, respectively) were tested on a total of 24 experimentally naïve New Zealand White rabbits (12 male, 12 female), all 5 months old and weighing 2.7-3.4 kg at the outset of the study. The components of the cevimeline containing test compositions 1, 2 and 3 (cevimeline here in its cevimeline HCl x 0.5 H<sub>2</sub>O salt form) as well as of the vehicle alone (control), are summarized in Table 10 below. The testing schedule is summarized in Table 11 below.

| Ingredients [mg/mL]               | vehicle | low dose | mid dose | high dose |
|-----------------------------------|---------|----------|----------|-----------|
| Cevimeline (free base equivalent) | 0.0     | 6.0      | 20.0     | 40.0      |
| K-sorbate                         | 4.7     |          |          |           |
| Na-phosphate monobasic dihydrate  | 0.61    |          |          |           |
| Na-phosphate dibasic heptahydrate | 1.63    |          |          |           |
| NaCl (q.s. for 280-300 mOsm/kg)   | 6.2     | 4.5      | 1.0      | 0.0       |
| Purified Water                    | q.s.    |          |          |           |
| HCl or NaOH (q.s. for pH)         | 7.0     |          |          |           |

**Table 10:** Aqueous, liquid cevimeline/K-sorbate test compositions (low-, mid-, and high dose) and vehicle

|                            | Conc.<br>[mg/mL] | Number of Animals |        |
|----------------------------|------------------|-------------------|--------|
|                            |                  | Male              | Female |
| 1. Control group (vehicle) | 0.0              | 3                 | 3      |
| 2 Low-dose group           | 6.0              | 3                 | 3      |
| 3 Mid-dose group           | 20.0             | 3                 | 3      |
| 4 High-dose group          | 40.0             | 3                 | 3      |

**Table 11:** Testing schedule

Mortality/morbidity observations were recorded twice daily, clinical observations once daily. Scoring for ocular irritation according to Draize was performed prior to treatment initiation, on days 1-7 prior to the 1<sup>st</sup> daily dose and after the 4<sup>th</sup> dose, and on day 1 also after the 1<sup>st</sup> dose. In addition, pupil size for each eye was noted as normal, dilated or constricted. Body weights were recorded at the time of randomization/ selection and on days 1 and 7. Food consumption was recorded daily. Ophthalmological examinations were performed for all animals prior to treatment initiation and on day 7. All animals were released from the study and returned to the colony on Day 8 following a final clinical observation.

It was found that both male and female New Zealand White rabbits tolerated the cevimeline formulations up to the highest concentration of 40 mg/mL when applied topically to their treated eyes 4 times per day for 7 consecutive days. Minor clinical signs were observed sporadically in the cevimeline dose groups, including redness of the eyes/conjunctivae (6, 20 and 40 mg/mL) and squinting (40 mg/mL only). All clinical signs had resolved by the completion of the study on day 8. There were no effects on body weights or food consumption, no mortalities or signs of morbidity, and no effects on pupil size; all pupils were observed to be normal in size following dose administration. All animals survived to the completion of the study on day 8.

At the ophthalmology examination conducted on day 7, minimally hyperemic conjunctiva was noted in 4 of 12 eyes in the low-dose group 2 (6 mg/mL) and 2 of 12 eyes in the mid-dose group 3 (20 mg/mL); however, only 1 of the 4 in group 2 and only 1 of the 2 in group 3 were left (i.e., treated) eyes. Moreover, no hyperemic conjunctiva was found in any animal in the control group 1 or in the high-dose group 4 (40 mg/mL). Since the clinical finding of minimally hyperemic conjunctiva (conjunctival erythema) appeared

(i) sporadically, (ii) in both dosed and un-dosed eyes, (iii) lacked dose-dependence, and (iv) was not correlated with other clinical signs, it was considered procedure-related (scoring/irritation) rather than related to the cevimeline compositions as such. Moreover, only few animals were affected, and the severity score never exceeded 1. There were no effects on pupil size. All pupils were observed to be normal in size following dose administration.

#### Example 6 (Ex. 6) – PK-Study in male New Zealand White Rabbits

The purpose of this study was to evaluate the pharmacokinetic (PK) behavior of cevimeline and exposure of ocular tissues and plasma to cevimeline following a single (i.e., once on day 1) bilateral, topical ocular instillation of four eye-drop test formulations F1-F4 to male New Zealand White rabbits (40 µL into each eye). The testing schedule is summarized in Table 12 below, indicating each test formulation was tested on a total of 16 male and experimentally naïve New Zealand White rabbits.

The test formulations F1-F4 (low-, mid-, and high dose), comprising various cevimeline-concentrations (F1 and F2: 6 mg/mL, F3: 20 mg/mL, and F4: 40 mg/mL, respectively) were prepared by dissolving all components listed in Table 13 in purified water followed by sterile filtration. All test formulations other than the sorbate-free control F1 (i.e., F2-F4) contained 4.7 mg/mL potassium sorbate. Cevimeline was used in the form of its cevimeline HCl x 0.5 H<sub>2</sub>O salt, as obtained from Excella.

After preparation, a fill-volume of 3 mL of each of the tested F1-F4 eye-drop formulations was packaged in 5 mL white HDPE bottles (obtained from Gerresheimer AG; Germany). The bottles, as well as their drop-tips and caps, were sterilized prior to filling (e.g., here by gamma irradiation). At least three bottles per composition were filled; one bottle for the PK-study described in this example, and a further two bottles for a 2-month storage stability test at 25 °C / 40% RH, pre- and post-dosing, as outlined in Example 7.

Blood plasma was collected from two animals/group pre-dose (t<sub>0</sub>), and at approximately 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose. In addition, tissue samples from each eye (namely, cornea, aqueous humor, retina, conjunctiva, iris/ciliary body, lacrimal gland, and sclera) were collected at terminal necropsy from two animals/group at the same time points.

All samples were analyzed for concentrations of cevimeline, and a composite plasma and tissue concentration-time profile was constructed for each dose group and eye from which pharmacokinetic parameters were derived, using model-independent methods. For each dose group, the following pharmacokinetic parameters were determined: maximum cevimeline concentration and the time to reach it ( $c_{\max}$  and  $t_{\max}$ ) in plasma and tissue, and the exposure expressed as the area under the respective concentration-time curves (AUC) in plasma and tissue (both from  $t_0 - t_{24h}$  as well as from  $t_0 - t_{\text{last}}$ , i.e., time of last quantifiable sample). Half-life values ( $t_{1/2}$ ) were determined only if the concentration-time profile had sufficient concentrations in the terminal elimination phase (at least three samples not including  $t_{\max}$ ), an adjusted  $R^2$  of  $\geq 0.9$ , and at least three half-lives of data.

|                                  | Conc.<br>[mg/mL] | Number<br>of animals | Dose/eye<br>[mg] | Dose/day<br>[mg] |
|----------------------------------|------------------|----------------------|------------------|------------------|
| F1: Low-dose group (w/o sorbate) | 6.0              | 16                   | 0.24             | 0.48             |
| F2: Low-dose group               | 6.0              | 16                   | 0.24             | 0.48             |
| F3: Mid-dose group               | 20.0             | 16                   | 0.80             | 1.60             |
| F4: High-dose group              | 40.0             | 16                   | 1.60             | 3.20             |

**Table 12:** Testing overview PK-study

| Ingredients [mg/mL]               | F1<br>(EY4-46) | F2<br>(EY4-47) | F3<br>(EY4-48) | F4<br>(EY4-49) |
|-----------------------------------|----------------|----------------|----------------|----------------|
| Cevimeline (free base equivalent) | 6.0            | 6.0            | 20.0           | 40.0           |
| K-sorbate                         | 0.0            | 4.7            |                |                |
| Na-phosphate monobasic dihydrate  | 0.61           |                |                |                |
| Na-phosphate dibasic heptahydrate | 1.63           |                |                |                |
| NaCl (q.s. for 280-300 mOsm/kg)   | 6.6            | 4.5            | 1.0            | 0.0            |
| Purified Water                    | q.s.           |                |                |                |
| HCl or NaOH (q.s. for pH)         | 7.0            |                |                |                |

**Table 13:** Aqueous, liquid cevimeline/K-sorbate test compositions (low-, mid-, and high dose / low dose with and without K-sorbate)

The PK-study reconfirmed that New Zealand White rabbits tolerated the cevimeline formulations up to the highest concentration of 40 mg/mL when applied topically to the eyes by ocular instillation.

For groups 1-4 (i.e., rabbits receiving test formulations F1, F2, F3 and F4, respectively), AUC<sub>0-24hr</sub> values (i.e., the overall exposure to cevimeline) of the different eye tissues resulted in the following rank order from highest to lowest:

Group 1 / F1 (w/o sorbate):

left lacrimal gland > right lacrimal gland > left cornea > right cornea  
> right conjunctiva > left iris/ciliary body > left conjunctiva > right iris/ciliary body  
> left aqueous humor > right aqueous humor > left sclera > right retina > right sclera  
> left retina;

Group 2 / F2:

right lacrimal gland > left lacrimal gland > right cornea > left cornea  
> right conjunctiva > right iris/ciliary body > right aqueous humor > left iris/ciliary  
body > left aqueous humor > left conjunctiva > left sclera > right retina > right sclera  
> left retina;

Group 3 / F3:

left lacrimal gland > right lacrimal gland > left cornea > right cornea > left iris/  
ciliary body > left aqueous humor > right conjunctiva > right iris/ciliary body  
> left conjunctiva > right aqueous humor > right sclera > left sclera > right retina  
> left retina;

Group 4 / F4:

right lacrimal gland > left cornea > right cornea > left lacrimal gland  
> right conjunctiva > left iris/ciliary body > right iris/ciliary body > left aqueous  
humor > right aqueous humor > left conjunctiva > right sclera > left sclera  
> right retina > left retina.

These results indicate that using the sorbate-containing eye-drop formulations according to the present invention (as exemplified by formulations F1-F4 in this PK-study), cevimeline is predominantly found in or reaching the lacrimal glands of the eyes, which is the target tissue of cevimeline delivery for dry-eye disease treatment.

The results found in plasma versus those found in the highest drug distribution tissues (lacrimal glands and cornea, each as mean value of left and right eyes) for groups 1-4 are summarized in Table 14 below. Comparing the data obtained for the eye tissues to those in plasma, it can be seen that (i) only a very minor cevimeline exposure occurs in the plasma, indicating a negligible risk, if any, for undesirable systemic side-effects; and that (ii) the highest cevimeline exposure (AUC) is found in the lacrimal glands.

|                        | <b>Formulation</b> | <b>C<sub>max</sub></b><br>[ng/mL] | <b>t<sub>max</sub></b><br>[h] | <b>t<sub>last</sub></b><br>[h] | <b>AUC<sub>0-last</sub></b><br>[h*ng/mL] | <b>AUC<sub>0-24h</sub></b><br>[h*ng/mL] | <b>t<sub>1/2</sub></b><br>[h] |
|------------------------|--------------------|-----------------------------------|-------------------------------|--------------------------------|------------------------------------------|-----------------------------------------|-------------------------------|
| <b>Plasma</b>          | <b>F1 / EY4-46</b> | 29.2                              | 0.5                           | 4                              | 29.7                                     | 32.6                                    | 1.10                          |
|                        | <b>F2 / EY4-47</b> | 21.2                              | 0.5                           | 8                              | 31.7                                     | 32.7                                    | NA                            |
|                        | <b>F3 / EY4-48</b> | 80.2                              | 0.5                           | 24                             | 103                                      | 103                                     | NA                            |
|                        | <b>F4 / EY4-49</b> | 135                               | 0.43                          | 24                             | 178                                      | 178                                     | NA                            |
| <b>Lacrimal glands</b> | <b>F1 / EY4-46</b> | 1655                              | 2.0                           | 24                             | 14250                                    | 14250                                   | NA                            |
|                        | <b>F2 / EY4-47</b> | 1880                              | 2.0                           | 24                             | 15200                                    | 15200                                   | 4.78                          |
|                        | <b>F3 / EY4-48</b> | 5290                              | 2.0                           | 24                             | 43750                                    | 43750                                   | 7.28                          |
|                        | <b>F4 / EY4-49</b> | 8180                              | 1.5                           | 24                             | 60900                                    | 60900                                   | NA                            |
| <b>Corneas</b>         | <b>F1 / EY4-46</b> | 10950                             | 0.5                           | 24                             | 11070                                    | 11070                                   | NA                            |
|                        | <b>F2 / EY4-47</b> | 7020                              | 0.5                           | 24                             | 7810                                     | 7810                                    | 6.36                          |
|                        | <b>F3 / EY4-48</b> | 14450                             | 0.75                          | 24                             | 28000                                    | 28000                                   | NA                            |
|                        | <b>F4 / EY4-49</b> | 20200                             | 0.5                           | 24                             | 59650                                    | 59650                                   | NA                            |

**Table 14:** Summary PK-study from test formulations of different cevimeline doses for low-, mid-, and high-dose eye-drop test formulations in plasma or tissue (F2-F4 with K-sorbate; F1 without K-sorbate); NA = not applicable

As can further be seen in Table 14, the time to maximum cevimeline concentration (t<sub>max</sub>) in plasma and cornea was reached within 0.43-0.75 h post-dose for all of groups 1-4, whereas t<sub>max</sub> in the lacrimal glands was a little longer with about 1.5-2 h post-dose for all of groups 1-4. Cevimeline was typically still quantifiable after 24 h in all samples but the

plasma-sample for the low-dose groups 1 and 2 (F1 and F2), where cevimeline could not be detected anymore at the 4- and 8-hour time-points, respectively.

The maximum concentration and exposure values ( $C_{\max}$  and  $AUC_{0-24hr}$ ) of cevimeline increased with increasing doses, both in plasma and in the eye-tissue samples, though not always in a dose-dependent manner. For instance, a 1:3.3:6.7-fold increase in cevimeline dose from 0.48, 1.6, and 3.2 mg per animal resulted in an approximate 1:3.1:3.8-fold or 1:2.5:4.9-fold increase in  $C_{\max}$  values found in the left and right lacrimal glands, respectively; and in an approximate 1:3.1:3.5-fold or 1:2.7:4.5-fold increase in  $AUC_{0-24h}$  values.

- Moreover, comparing compositions with and without K-sorbate (F2 vs. F1, respectively), it was advantageously found that  $C_{\max}$  and  $AUC_{0-24hr}$  of cevimeline were lower in the less desired delivery sites (especially, iris/ciliary body and cornea) when K-sorbate was included in the composition; see Table 15 below (each eye tissue as mean of left and right eyes). In contrast, the desired exposure of lacrimal gland to cevimeline ( $C_{\max}$  and  $AUC_{0-24hr}$ ) was not reduced, but increased instead, by the addition of the potassium sorbate.

|                          | $C_{\max}$ [ng/mL] |              | $AUC_{0-24hr}$ [h*ng/mL] |              |
|--------------------------|--------------------|--------------|--------------------------|--------------|
|                          | F1<br>EY4-46       | F2<br>EY4-47 | F1<br>EY4-46             | F2<br>EY4-47 |
| <b>Plasma</b>            | 29.2               | 21.2         | 32.6                     | 32.7         |
| <b>Aqueous Humor</b>     | 2995               | 2345         | 2440                     | 2295         |
| <b>Conjunctivas</b>      | 676                | 477          | 3960                     | 3375         |
| <b>Corneas</b>           | 10950              | 7020         | 11070                    | 7810         |
| <b>Iris/Ciliary Body</b> | 3590               | 2415         | 3165                     | 2515         |
| <b>Lacrimal Glands</b>   | 1655               | 1880         | 14250                    | 15200        |
| <b>Retinas</b>           | 318                | 223          | 345                      | 376          |
| <b>Scleras</b>           | 204                | 450          | 464                      | 495          |

**Table 15:** Effect of K-sorbate in low-dose cevimeline test formulations (6.0 mg/mL) on  $C_{\max}$  and  $AUC_{0-24hr}$  values (F2 with sorbate and F1 w/o sorbate)

Example 7 (Ex. 7) –Stability of the eye-drop test formulations F1-F4 of Example 6

In addition, to the PK-study outlined in Example 6, the four test formulations F1-F4 were also monitored pre- and post-dosing (pre-dosing =  $t_0$ ; post-dosing = 2 months or  $t_2$ ) for appearance, assay and related substances of cevimeline, assay of sorbate, osmolality and pH-value.

As can be seen in Table 16 below, there was essentially no difference between the pre- and post-dosing analytical results. The eye-drop compositions tested in the PK-study according to Example 6 above were stable over the course of at least two months post-dosing, with assay results ranging between 98.6 % and 101.4 % of label strength for cevimeline (F1-F4) and between 100 % and 102 % of label strength for potassium sorbate (F2-F4). Osmolality was in the range of 278-300 mOsm/kg for the low- and mid-dose formulations F1-3, and 436-441 mOsm/kg for the high-dose formulation F4. The pH was between 6.9 and 7.0 for all formulations F1-F4.

| <b>Formulation</b>                                                                                                       | <b>Sorbate</b> | <b>Pre-dosing<br/>t<sub>0</sub></b>                         | <b>Post-dosing<br/>t<sub>2</sub></b>                         | <b>Change<br/>t<sub>2</sub>-t<sub>0</sub></b>   |
|--------------------------------------------------------------------------------------------------------------------------|----------------|-------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------|
| <b>F1 / EY4-46</b><br>Appearance<br><b>Assay, % LS</b><br>% total impurities<br>Sorbate, %<br>pH<br>Osmolality, mOsm/kg  | No             | clear/colorless<br><b>101.4</b><br>0.14<br>-<br>6.9<br>300  | clear/colorless<br><b>98.6</b><br>0.22<br>-<br>6.9<br>285    | none<br><b>-2.8</b><br>0.08<br>-<br>none<br>-15 |
| <b>F2 / EY4-k47</b><br>Appearance<br><b>Assay, % LS</b><br>% total impurities<br>Sorbate, %<br>pH<br>Osmolality, mOsm/kg | Yes            | clear/colorless<br><b>99.8</b><br>0.14<br>100<br>7.0<br>283 | clear/colorless<br><b>100.3</b><br>0.33<br>101<br>7.0<br>278 | none<br><b>0.5</b><br>0.19<br>1<br>none<br>-5   |
| <b>F3 / EY4-48</b><br>Appearance<br><b>Assay, % LS</b><br>% total impurities<br>Sorbate, %<br>pH<br>Osmolality, mOsm/kg  | Yes            | clear/colorless<br><b>99.1</b><br>0.14<br>100<br>7.0<br>298 | clear/colorless<br><b>99.8</b><br>0.17<br>102<br>7.0<br>294  | none<br><b>0.7</b><br>0.03<br>2<br>none<br>-4   |
| <b>F4 / EY4-49</b><br>Appearance<br><b>Assay, % LS</b><br>% total impurities<br>Sorbate, %<br>pH<br>Osmolality, mOsm/kg  | Yes            | clear/colorless<br><b>99.6</b><br>0.14<br>100<br>6.9<br>441 | clear/colorless<br><b>100.4</b><br>0.16<br>102<br>7.0<br>436 | none<br><b>0.8</b><br>0.02<br>2<br>0.1<br>-5    |

**Table 16:** Summary of cevimeline assay results from compositions with or without sorbate as well as different doses.

The following list of numbered items are embodiments comprised by the present invention:

1. An aqueous composition comprising:
  - (a) from 1 mg/mL to 50 mg/mL of cevimeline, or a pharmaceutically acceptable salt thereof;
  - (b) sorbic acid, or a pharmaceutically acceptable salt thereof; and
  - (c) an aqueous carrier;wherein the pH of the composition is in the range from pH 6.0 to 8.0, or from pH 6.0 to pH 7.5, and
- wherein the composition comprises from 3 mg/mL to 10 mg/mL of sorbic acid, or a pharmaceutically acceptable salt thereof.
2. The composition of item 1, wherein the composition comprises no antimicrobial preservative.
3. The composition of item 1 or 2, wherein the composition is provided in the form of a clear solution.
4. The composition of any one of items 1 to 3, wherein the composition comprises water as a sole solvent.
5. The composition of any one of items 1 to 4, wherein the composition comprises from 2 mg/mL to 50 mg/mL of cevimeline or a pharmaceutically acceptable salt thereof.
6. The composition of any one of items 1 to 5, wherein the composition further comprises a complexing agent.
7. The composition of item 6, wherein the complexing agent comprises, or consists of, a cyclodextrin.
8. The composition of item 7, wherein the cyclodextrin is hydroxypropyl-beta-cyclodextrin (HP- $\beta$ -CD).
9. The composition of item 7 or 8, wherein the cyclodextrin is present at an amount in the range from 2 mg/mL to 100 mg/mL.

10. The composition of any one of items 1 to 9, wherein the composition further comprises a viscosity-enhancing agent.
11. The composition of item 10, wherein the viscosity-enhancing agent is selected from hyaluronic acid, polyvinyl alcohol (PVA), polyvinylpyrrolidone (or povidone),  
5 carboxyvinyl polymers, methylcellulose (MC), carboxymethylcellulose (CMC; or carmellose), hydroxypropyl methylcellulose (HPMC; or hypromellose), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyacrylic acid or salts thereof, xanthan gum, guar gum, chondroitin sulfate, polyethylene glycol, propylene glycol, or combinations thereof.
- 10 12. The composition of item 11, wherein the viscosity-enhancing agent is selected from hyaluronic acid, povidone, hypromellose, carmellose, or combinations thereof.
13. The composition of any one of items 1 to 12, wherein the composition further comprises one or more excipients selected from tonicity adjusting agents such as sodium chloride, buffering agents such as a phosphate buffer, and pH-adjusting  
15 agents.
14. The composition of any one of items 1 to 13, wherein the composition comprises from 3 mg/mL to 10 mg/mL of potassium sorbate.
15. The composition of any one of items 1 to 14, wherein the composition has a pH of about 6.0-7.4.
- 20 16. The composition of any one of items 1 to 15, wherein the composition is provided in the form of a clear liquid that can be instilled into the eye.
17. The composition of any one of items 1 to 16, having a dynamic viscosity in the range of 1 cP to 60 cP, or 1 cP to 50 cP, or 1 cP to 20 cP, for instance, a dynamic viscosity of less than 5 cP.
- 25 18. The composition of any one of items 1 to 17, wherein the composition is an ophthalmic composition provided in the form of eye-drops.

19. The composition of any one of items 1 to 18, wherein the composition is not provided in the form of an ointment, a cream, a paste, an insert, a punctum plug, and/or a plaster.
20. The composition of any one of items 1 to 19, wherein the composition comprises one or more further active agents, optionally, active agents selected from
- 5 (a) steroids,  
(b) immuno-modulators or immunosuppressants,  
(c) hormones,  
(d) secretagogues,  
10 (e) lymphocyte function associated antigen-1 (LFA-1) antagonists, and/or  
(f) active ingredients effective for treating Meibomian gland dysfunction.
21. The composition of any one of items 1 to 19, wherein the composition is free of, or essentially free of, active agents and/or beneficial agents other than (i) cevimeline, or a pharmaceutically acceptable salt thereof, and/or (ii) sorbic acid as the PUFA, or
- 15 a pharmaceutically acceptable salt thereof.
22. The composition of any one of items 1 to 21, wherein the composition is essentially free of insulin, insulin-like growth factor (IGF), somatomedin C, and cycloplegic agent.
23. The composition of any one of items 1 to 22, wherein the absorption of cevimeline from the composition to its primary container is mitigated during storage shelf-life.
- 20 24. The composition of any one of items 1 to 23, wherein the composition is housed in a primary container formed from high density polyethylene (HDPE), low density polyethylene (LDPE), polypropylene (PP), or cyclic olefin copolymer (COC).
- 25 25. A method of treating one or more of dry eye disease, xerostomia, or Sjogren syndrome, the method comprising a step of topically administering the composition of any one of items 1 to 24 to a subject suffering from dry eye disease, xerostomia, and/or Sjogren syndrome.
26. The composition of any one of items 1 to 24 for use in the treatment of one or more of dry eye disease, xerostomia, or Sjogren syndrome.

27. The use of the composition of any one of items 1 to 24 in the manufacture of a medicament for the treatment of one or more of dry eye disease, xerostomia, or Sjogren syndrome.
- 5 28. The method of item 25 or the use of item 26 or 27, wherein the composition is administered into the eye of the subject.
29. The method of item 25 or the use of any one of items 26 to 28, wherein the composition is administered to the nasal mucosa of the subject.
30. The method of item 25 or the use of any one of items 26 to 29, wherein the composition is administered once, twice, or three or four times a day.
- 10 31. The method of item 25 or the use of any one of items 26 to 30, wherein the composition is administered over a treatment period of at least 7 days.
32. The method of item 25 or the use of any one of items 26 to 31, wherein the composition does not cause miosis after administration.
- 15 33. The method or use of item 32, wherein the composition does not cause miosis after administration into the eye.
34. An ophthalmic composition comprising 2 mg/mL to 50 mg/mL cevimeline or a pharmaceutically acceptable salt thereof, 4.7 mg/mL potassium sorbate, sodium phosphate buffer, sodium chloride, and water.
- 20 35. A method of treating one or more of dry eye disease, xerostomia, or Sjogren syndrome, the method comprising a step of administering an aqueous composition comprising cevimeline to the nasal mucosa of a subject suffering from dry eye disease, xerostomia, and/or Sjogren syndrome.

### Claims

1. An aqueous composition comprising:
  - (a) from 1 mg/mL to 50 mg/mL of cevimeline, or a pharmaceutically acceptable salt thereof;
  - (b) sorbic acid, or a pharmaceutically acceptable salt thereof; and
  - (c) an aqueous carrier;wherein the pH of the composition is in the range from pH 6.0 to pH 8.0, and wherein the composition comprises from 3 mg/mL to 10 mg/mL of sorbic acid, or a pharmaceutically acceptable salt thereof.
2. The composition of claim 1, wherein the composition comprises no antimicrobial preservative.
3. The composition of claim 1, wherein the composition is provided in the form of a clear solution.
4. The composition of claim 1, wherein the composition comprises water as a sole solvent.
5. The composition of claim 1, wherein the composition comprises from 2 mg/mL to 50 mg/mL of cevimeline, or a pharmaceutically acceptable salt thereof.
6. The composition of claim 1, wherein the composition further comprises a complexing agent.
7. The composition of claim 6, wherein the complexing agent comprises, or consists of, a cyclodextrin.
8. The composition of claim 7, wherein the cyclodextrin is hydroxypropyl-beta-cyclodextrin.
9. The composition of claim 7, wherein the cyclodextrin is present at an amount in the range from 2 mg/mL to 100 mg/mL.
10. The composition of claim 1, wherein the composition further comprises a viscosity-enhancing agent.

11. The composition of claim 10, wherein the viscosity-enhancing agent selected from hyaluronic acid, polyvinyl alcohol (PVA), polyvinylpyrrolidone (or povidone), carboxyvinyl polymers, methylcellulose (MC), carboxymethylcellulose (CMC; or carmellose), hydroxypropyl methylcellulose (HPMC; or hypromellose), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyacrylic acid or salts thereof, xanthan gum, guar gum, chondroitin sulfate, polyethylene glycol, propylene glycol, or combinations thereof.
12. The composition of claim 1, wherein the composition further comprises one or more excipients selected from tonicity adjusting agents such as sodium chloride, buffering agents such as a phosphate buffer, and pH-adjusting agents.
13. The composition of claim 1, wherein the composition comprises from 3 mg/mL to 10 mg/mL of potassium sorbate
14. The composition of claim 1, wherein the composition has a pH of about 6.0-7.4.
15. The composition of claim 1, having a dynamic viscosity in the range of 1 cP to 60 cP, or 1 cP to 50 cP, or 1 cP to 20 cP.
16. A method of treating one or more of dry eye disease, xerostomia, or Sjogren syndrome, the method comprising a step of topically administering the composition of claim 1 to a subject suffering from dry eye disease, xerostomia, and/or Sjogren syndrome.
17. The method of claim 16, wherein the composition is administered into the eye of the subject.
18. The method of claim 16, wherein the composition is administered to the nasal mucosa of the subject.
19. The method of claim 16, wherein the composition is administered once, twice, or three or four times a day.
20. The method of claim 16, wherein the composition is administered over a treatment period of at least 7 days.
21. The method of claim 16, wherein the composition does not cause miosis.

22. An ophthalmic composition comprising 2 mg/mL to 50 mg/mL cevimeline, or a pharmaceutically acceptable salt thereof, 4.7 mg/mL potassium sorbate, sodium phosphate buffer, sodium chloride, and water.
23. A method of treating one or more of dry eye disease, xerostomia, or Sjogren syndrome, comprising a step of administering an aqueous composition comprising cevimeline to the nasal mucosa of a subject suffering from dry eye disease.