Another embodiment of the invention relates to an ophthalmic aqueous composition in the form of solution comprising 0.005% to 0.18% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, from 0.5% w/w to 1.5% w/w macrogol 15 hydroxystearate wherein macrogol 15 hydroxystearate is the only solubilizing agent, for use in the treatment of ocular hypertension, glaucoma or for reducing intraocular pressure.

Another embodiment of the invention relates to an ophthalmic aqueous composition in the form of solution comprising 0.005% to 0.10% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, from 0.5% w/w to 1.5% w/w macrogol 15 hydroxystearate wherein macrogol 15 hydroxystearate is the only solubilizing agent, for use in the treatment of ocular hypertension, glaucoma or for reducing intraocular pressure.

Another embodiment of the invention relates to a method of treating ocular hypertension or glaucoma or to a method of reducing intraocular pressure comprising administering to a patient in need thereof a therapeutically effective amount of the above defined ophthalmic aqueous composition in the form of solution.

Another embodiment of the invention relates to a method of treating ocular hypertension or glaucoma or to a method of reducing intraocular pressure comprising administering to a patient in need thereof a therapeutically effective amount of an ophthalmic aqueous composition in the form of solution comprising 0.005% w/w to 0.065% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, from 0.5% w/w to 1.5% w/w macrogol 15 hydroxystearate and a pharmaceutically acceptable aqueous vehicle, wherein macrogol 15 hydroxystearate is the only solubilizing agent.

Another embodiment of the invention relates to a method of treating ocular hypertension or glaucoma or to a method of reducing intraocular pressure comprising administering to a patient in need thereof a therapeutically effective amount of an ophthalmic aqueous composition in the form of solution comprising from 0.005% w/w to 0.065% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, 1.0% w/w macrogol 15 hydroxystearate, 0.016% w/w benzalkonium chloride, 0.05% w/w ethylenediaminetetraacetic acid disodium salt dihydrate, sodium phosphate dibasic heptahydrate and boric acid and water, wherein the pH of the ophthalmic solution is 6 and wherein macrogol 15 hydroxystearate is the only solubilizing agent; preferably the amount of hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester in the ophthalmic solution is from 0.01% w/w to 0.065% w/w, most preferably is 0.042% w/w, 0.021% w/w or 0.065% w/w; optionally the ophthalmic solution further comprises HCl 1.2M / NaOH 1M to adjust the pH to pH 6.0.

CLAIMS

1. A~~n~~ preservative free ophthalmic aqueous composition in the form of solution comprising 0.005% to 0.18% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, from 0.5% w/w to 1.5% w/w macrogol 15 hydroxystearate, wherein macrogol 15 hydroxystearate is the only solubilizing agent.

~~2. An ophthalmic aqueous composition according to claim 1 comprising 0.005% to 0.10% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, from 0.5% w/w to 1.5% w/w macrogol 15 hydroxystearate.~~

~~3. An ophthalmic aqueous composition according to claim 2 comprising 0.005% to 0.065% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, from 0.5% w/w to 1.5% w/w macrogol 15 hydroxystearate.~~

~~4~~2. The preservative free ophthalmic aqueous composition according to claim 1, wherein the amount of hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester is 0.~~021% w/w, 0.042% w/w, 0.065% w/w or~~ 005% to 0.10% w/w.

3. A preservative free ophthalmic aqueous composition according to claim 1 or 2, further comprising a buffer selected from a mixture of sodium phosphate dibasic heptahydrate and boric acid or a mixture of citric acid and sodium phosphate dibasic heptahydrate, a tonicity agent, having a pH in the range from 5.5 to 6.5 and an osmolality from 260 to 340 mOsm/Kg.

4. The preservative free ophthalmic aqueous composition according to claim 3, wherein the tonicity agent is sorbitol or glycerol.

5. The preservative free ophthalmic aqueous composition according to claim 3 or 4, further comprising a viscosity-adjusting agent.

6. The preservative free ophthalmic aqueous composition according to claim 1, comprising 0.005% to 0.10% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, from 0.5% w/w to 1.5% w/w macrogol 15 hydroxystearate, a tonicity agent, sodium phosphate dibasic heptahydrate and boric acid and water, wherein the pH is 6, and wherein macrogol 15 hydroxystearate is the only solubilizing agent.

7. The preservative free ophthalmic aqueous composition according to claim 6, wherein the amount of hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester is 0.021% w/w, 0.042% w/w or 0.065% w/w and the amount of macrogol 15 hydroxystearate is 1.0% w/w, the tonicity agent is sorbitol in an amount of 2.76% w/w, sodium phosphate dibasic heptahydrate is 1.33% w/w and boric acid is 0.5% w/w.

8. The preservative free ophthalmic aqueous composition according to claim 2 having the following composition: 0.10% w/w hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester, 1.5% w/w macrogol 15 hydroxystearate, 0.52% w/w glycerol, 2.33% w/w sodium phosphate dibasic heptahydrate, 0.36% w/w citric acid and water, wherein the pH is 6 and wherein macrogol 15 hydroxystearate is the only solubilizing agent.

~~5. The ophthalmic aqueous composition according to anyone of the preceding claims wherein macrogol 15 hydroxystearate is the only solubilizing agent.~~

~~6. The ophthalmic aqueous composition according to anyone of the preceding~~

~~claims which comprises 0.013% w/w to 0.02% w/w benzalkonium chloride, 0.03% w/w to 0.07% w/w of an edetate salt.~~

~~7. The ophthalmic aqueous composition according to claim 6 wherein the amount of benzalkonium chloride is from 0.013% w/w to 0.02% w/w and the amount of the edetate salt is 0.05% w/w.~~

~~8. The ophthalmic aqueous composition according to claim 7 wherein the amount of benzalkonium chloride is 0.016% w/w and the amount of the edetate salt is 0.05% w/w.~~

~~9. The ophthalmic aqueous composition according to any one of the preceding claims having a pH in the range from 5.5 to 6.5.~~

~~10. The ophthalmic aqueous composition according to any one of the preceding claims having pH 6.~~

~~11. The ophthalmic aqueous composition according to claim 9 or 10, comprising at least a buffer.~~

~~12. The ophthalmic aqueous composition according to claim 11 wherein the buffer is a mixture of sodium phosphate dibasic heptahydrate and boric acid.~~

~~13. The ophthalmic aqueous composition according to claim 11 or 12 further comprises a pH-adjusting agent.~~

~~14. The ophthalmic aqueous composition according to anyone of the preceding claims further comprising a tonicity agent.~~

~~15. The ophthalmic aqueous composition according to claim 14 wherein the tonicity agent is sorbitol or glycerol.~~

~~16. The ophthalmic aqueous composition according to anyone of claims 1-3 wherein the amount of macrogol 15 hydroxystearate is 1.0% w/w and further comprising 0.016% w/w benzalkonium chloride, 0.05% w/w ethylenediaminetetraacetic acid disodium salt dihydrate, 2.76% w/w sorbitol, 1.33% w/w sodium phosphate dibasic heptahydrate, 0.5 % w/w boric acid and water and wherein the pH is 6.~~

~~17. The ophthalmic aqueous composition according to claim 16 wherein the amount of hexanoic acid, 6 (nitrooxy) , (1S,2E) 3 [(1R,2R,3S,5R) 2 [(2Z) 7 (ethylamino) 7-oxo 2 hepten 1 yl] 3,5 dihydroxycyclopentyl] 1 (2 phenylethyl) 2 propen 1 yl ester is 0.021% w/w, 0.042% w/w, 0.065% w/w.~~

~~18. The ophthalmic aqueous composition according to anyone of claims 1 2 wherein the amount of hexanoic acid, 6 (nitrooxy) , (1S,2E) 3 [(1R,2R,3S,5R) 2 [(2Z) 7 (ethylamino) 7 oxo 2 hepten 1 yl] 3,5 dihydroxycyclopentyl] 1 (2 phenylethyl) 2 propen 1 yl ester is 0.1% and the amount of macrogol 15 hydroxystearate is 1.5% w/w and further comprising 0.016% w/w benzalkonium chloride, 0.05% w/w ethylenediaminetetraacetic acid disodium salt dihydrate, 0.52% w/w glycerol, 2.33% w/w sodium phosphate dibasic heptahydrate, 0.36 % w/w citric acid monohydrate and water, and wherein the pH is 6.~~

~~19~~9. The preservative free ophthalmic aqueous composition according to any one of claims ~~16~~ 1 to ~~18~~ 8, further comprising ~~a pH adjusting agent selected from~~ hydrochloric acid or sodium hydroxide as pH adjusting agents.

~~20. The ophthalmic aqueous composition according to anyone of the preceding claims further comprising a viscosity adjusting agent.~~

~~21. The ophthalmic aqueous composition according to claim 20 wherein the viscosity adjusting agent is hydroxypropylmethyl cellulose at a concentration less than 0.5% w/w.~~

~~22~~10. The preservative free ophthalmic aqueous composition according to any one of

claims 1 to ~~21~~ 9 for use as medicament.

~~23~~11. The preservative free ophthalmic aqueous composition according to any one of claims 1 to ~~21~~ 9 for use in the treatment of ocular hypertension, glaucoma or for reducing intraocular pressure.

12. Use of the preservative free ophthalmic aqueous composition according to any one of claims 1 to 9 in the manufacture of a medicament for the treatment of ocular hypertension, glaucoma or for reducing intraocular pressure.

~~24~~13. A process for manufacturing the preservative free ophthalmic aqueous composition having pH 6 and osmolality 300 mOsm/kg according to any one of claims ~~15~~ 1 to ~~18~~9, the process comprises the following steps:

Step 1) ~~Preparation~~ preparation of a concentrated solution of hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester which comprise:

1a) heating a mixture of water for injection and polyoxyl 15 hydroxystearate at 32°C until the polyoxyl 15 hydroxystearate is melted;

1b) adding the melted polyoxyl 15 hydroxystearate/water mixture to the pre-weighed hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester;

1c) mixing the obtained mixture until full dissolution of hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester while maintaining the mixture at a temperature of 32°C; wherein the amounts of polyoxyl 15 hydroxystearate and of hexanoic acid, 6-(nitrooxy)-, (1S,2E)-3-[(1R,2R,3S,5R)-2-[(2Z)-7-(ethylamino)-7-oxo-2-hepten-1-yl]-3,5-dihydroxycyclopentyl]-1-(2-phenylethyl)-2-propen-1-yl ester correspond to their amounts in the final formulation and the amount of water for

injection used in Step 1a) is about the 1.5% of the total weight of water used in the preparation;

Step 2) ~~Preparation~~ preparation of an aqueous solution of the remaining products vehicle ingredients by adding in a manufacturing tank containing about 80% to 90% of the total weight of water for injection of the final solution the excipients in the specific following order: ~~edetate disodium dihydrate,~~ the buffer ~~selected from boric acid~~ and ~~sodium phosphate dibasic heptahydrate or citric acid and sodium phosphate dibasic heptahydrate, sorbitol or glycerol and benzalkonium chloride~~ the tonicity agent wherein each excipient being fully dissolved before adding the next excipient and the preparation of the solution is carried out at a temperature from 25°C to 30°C;

Step 3) ~~Preparation~~ preparation of the bulk ophthalmic solution by adding the solution of Step 1 into the manufacturing tank containing the aqueous solution of Step 2 and water for injection ~~till~~ up to the targeted final weight;

Step 4) ~~Sterilization~~ sterilization of the bulk ophthalmic solution by filtering the bulk ophthalmic solution of Step 3 through a Polyethersulfone (PES) filters having pore size of about 0.2 µm.

~~25~~14. The process according to claim ~~24~~ 13 wherein in Step 3) the pH of the bulk ophthalmic solution is adjusted to pH 6.0 with sodium hydroxide 1 M or hydrochloric acid 1.2 M.

~~26~~15. The process according to claim ~~24~~ 13 or ~~25~~ 14 wherein in Step 2) the viscosity adjusting agent is added in the manufacturing tank containing the water for injection as first component and, once it is fully dissolved, the other excipients are added.

~~27. The process according to claims 24-26 wherein the sterilized bulk ophthalmic~~

~~solution of Step 4) is filled in low density polyethylene (LDPE) ophthalmic primary containers.~~