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.

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 0.042% w/w.

Table 8: Vehicle composition of Formulations 1 and 2

Components (% w/w)	Formulation 1	Formulation 2
Macrogol 15-hydroxystearate	1.0	-
Polysorbate 80	-	1.0
Benzalkonium chloride	0.02	0.02
Boric acid	0.5	0.5
Disodium Edetate dihydrate	0.05	0.05
Sorbitol	2.9	2.9
Sodium phosphate dibasic heptahydrate (Na2HPO4 7H2O)	1.43	1.43
Sodium hydroxide and/or hydrochloric acid	q.s. to pH 6.0	q.s. to pH 6.0
Water for injection	q.s. to 100g	q.s. to 100g

Formulation 3 (Commercially available eyedrop / Lumigan®, Allergan)

Active principle: Bimatoprost 0.03 %;

The concentration 0.042% w/w 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 equimolar with respect to the moles of bimatoprost of the commercially available eyedrop (Formulation 3).

Material

Macrogol 15-hydroxystearate is the commercially available Kolliphor® HS15 (BASF). Polysorbate 80 is the commercially available Polysorbate 80 Super Refined® (Croda).

Experimental procedure

Groups of 10 male naïve Dutch Belted Rabbits were assigned to the study and administered either with Formulations 1 and 2 or Formulation 3 by instillation to each eye at nominal target doses of 12.6 µg/eye for Formulations 1 and 2 and 9 µg/eye for bimatoprost solution. An additional group of 5 males was employed to provide blank control matrix (aqueous humor) for bio-analytical purposes.

During the study, body weight measurements and clinical observations were performed

Tested solutions

Table 10 reports the vehicles of the aqueous ophthalmic solutions containing 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 0.042% w/w.

An additional reference formulation was tested; this formulation is the commercially available eyedrop containing active bimatoprost 0.03 %.

Table 10: Vehicles composition

Components (% w/w)	Vehicle 1	Vehicle 2	Vehicle 3
Polysorbate 80	1.0	1.0	0.5
Macrogol 15-hydroxystearate	-	-	0.5
Benzalkonium chloride	0.02	-	0.02
Glycerol	0.69	0.69	0.69
Citric acid monohydrate	0.34	0.34	0.34
Sodium phosphate dibasic heptahydrate (Na2HPO4 7H2O)	2.26	2.26	2.26
Water for injection	q.s. to 100g	q.s. to 100g	q.s. to 100g
pH	6.7	6.7	6.7

Material

Macrogol 15-hydroxystearate is the commercially available Kolliphor® HS15 (BASF). Polysorbate 80 is the commercially available Polysorbate 80 Super Refined® (Croda).

Experimental procedure

Forty animals were included in the study. They were allocated into four groups of 10 animals/group and were administered with the above reported tested aqueous ophthalmic solutions

All animals included in the study were administered by ocular instillation of both eyes by means of a graduated pipette at a volume of 30 µL/eye. Two animals per formula were sacrificed at 0 h (pre-dose), 1 h, 2 h, 4 h and 8 h, and aqueous humor samples were obtained immediately from both eyes.

Results

CLAIMS

1. 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.

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. The 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 0.10% w/w.

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

6. The ophthalmic aqueous composition according to any one 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 comprising a pH-adjusting agent.

14. The ophthalmic aqueous composition according to any one 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 any one 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 or 0.10% w/w.

18. The ophthalmic aqueous composition according to any one 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. The ophthalmic aqueous composition according to any one of claims 16 to 18, further comprising a pH-adjusting agent selected from hydrochloric acid or sodium hydroxide.

20. The ophthalmic aqueous composition according to any one of the preceding claims, further comprising a viscosity-adjusting agent.

21. The ophthalmic aqueous composition according to claim 2 comprising sodium phosphate dibasic heptahydrate and boric acid and water, wherein the pH of the ophthalmic solution is 6, further comprising a tonicity agent, wherein macrogol 15 hydroxystearate is the only solubilizing agent.

22. The ophthalmic aqueous composition according to claim 21 comprising a pH-adjusting agent.

23. The ophthalmic aqueous composition according to claim 22, wherein the viscosity-adjusting agent is hydroxypropylmethyl cellulose at a concentration less than 0.5% w/w.

24. The ophthalmic aqueous composition according to any one of claims 1 to 23 for use as medicament.

25. The ophthalmic aqueous composition according to any one of claims 1 to 23 for use in the treatment of ocular hypertension, glaucoma or for reducing intraocular pressure.

26. Use of the ophthalmic aqueous composition according to any one of claims 1 to 23 in the manufacture of a medicament for the treatment of ocular hypertension or glaucoma or for reducing intraocular pressure.

27. A process for manufacturing the ophthalmic aqueous composition according to any one of claims 15 to 18, the process comprising the following steps:

Step 1) 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 of an aqueous solution of the remaining products vehicle ingredients by adding in a manufacturing tank containing water for injection 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 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 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 to the targeted final weight;

Step 4) 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.

28. The process according to claim 27, wherein in Step 3) the pH of the bulk ophthalmic solution is adjusted to pH 6.0 with sodium hydroxide or hydrochloric acid.

29. The process according to claim 17 or 28, 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.

30. The process according to any one of claims 27-29, wherein the sterilized bulk ophthalmic solution of Step 4) is filled in low density polyethylene (LDPE) ophthalmic

primary containers.