DESCRIPTION

Method and composition for treating ocular hypertension and glaucoma

Technical field of the invention

The present invention relates to a preservative-free ophthalmic aqueous composition containing prostaglandin (PG hereafter) F2α analogues for treating ocular hypertension and glaucoma, to a method for treating ocular hypertension and glaucoma by administering said composition to a subject in need of such treatment, and to a method for increasing aqueous solubility and improving stability of PGF2α analogues in an aqueous composition.

Background of the invention

PGF2α analogues have been widely used for the treatment of glaucoma and ocular hypertension because of their effectiveness in lowering intraocular pressure and their low systemic side effects. PGF2α analogues include all of the known PGF2α analogues for example tafluprost , latanoprost, isopropyl unoprostone, travoprost, bimatoprost and the analogues shown in US 5,886,035, US 5,807,892, US 6,096,783.

Tafluprost is a new-generation, fluorinated PGF2α isopropyl ester analogue, which is a potent ocular hypotensive agent (EP 0 850 926).

A concentration of PGF2α analogues used for a treatment of glaucoma is very low. For example, the effective concentration of tafluprost from 0.0005 to 0.005 (w/v),

preferably about 0.0015%, in an ophthalmic composition has been found to be sufficient for the treatment of ocular hypertension and glaucoma. However, as lipophilic substances PGF2α analogues such as tafluprost are liable to be absorbed to resinous (plastic) containers or bottles commonly used to store ophthalmic solutions, and thus the already low drug concentration in the ophthalmic solution may be further lowered.

Preservatives

Preservatives which exhibit sufficient antimicrobial effect on bacteria and fungi have traditionally been used in ophthalmic compositions. In addition to this, the preservatives are required to be stable and preferably to homogenize and stabilize the composition by interacting with the ingredients, for example by homogeneously dispersing or dissolving the ingredients into the vehicle or base (see EP 0 969 846, EP 1 916 002 and EP 1 547 599). Nowadays the most commonly used preservatives in commercially available ophthalmic solutions are benzalkonium chloride (BAK) and other quaternary ammonium salts. Other pharmaceutically acceptable preservatives for ophthalmic solutions are for example boric acid-polyol-zinc chloride (EP 1 115 406) or chlorine oxide compounds (EP 1 905 453), chlorhexidine gluconate, benzethonium chloride, sorbic acid, potassium sorbate, ethyl p-hydroxybenzoate and butyl p-hydroxybenzoate.

However, preservatives are also known as the major etiology of keratoconjunctive disorders, and for safety purpose, it is preferred that the concentration of a preservative such as benzalkonium chloride (BAK) is as low as possible. Preservative free ophthalmic solutions have also been developed.

On the other hand, BAK has contributed to the prevention of the degradation of prostaglandins and to the inhibition of absorption of prostaglandins to the resinous container walls. The absorption of tafluprost and other PGF2α analogues to the resinous container walls has been a problem especially with containers made of polyethylene. Due to its properties, such as sufficient flexibility, softness, good manufacturability and user-friendliness, polyethylene is the preferred material of choice for packaging of ophthalmic compositions, especially in unit dose form.

In addition, absorption of PGF2α analogues to the resinous container walls depends on surface area of the container walls. A unit dose preparation contains very small amount of ophthalmic compositions and the contact area of the preparation to the container is very large. Thus, absorption of PGF2α analogues to the container walls is a severe problem for unit dose preparations.

Therefore, before the present invention it has in practice been impossible to prepare stable, preservative-free ophthalmic solutions which contain PGF2α analogues and which can be packaged and stored in containers consisting essentially of polyethylene. According to EP 1011728, aqueous prostaglandin compositions packaged in polypropylene containers are more stable than those packaged in polyethylene containers. Based on the stability results of said publication, a skilled person is not encouraged to choose polyethylene but is likely to disallow it as container material, especially for all highly lipophilic compounds such as PGF2α analogues. Polypropylene-polyethylene copolymers comprising polyethylene as a minor component are also

possible but not alluding to polyethylene as the sole material or as a major resin component (EP 1 829 545).

Furthermore, almost all of PGF2α analogues are practically insoluble in water. It is thus necessary to solve also the problem of solubility to water in order to formulate PGF2α analogues in ophthalmic solutions, especially for unit dose preparations. In EP 1 321 144 and US 2007/248697, a nonionic surfactant has been added to the ophthalmic solution to prevent a prostaglandin derivative from being adsorbed to a resinous container. Other attempts to compensate the difficulties in formulating highly lipophilic prostaglandin analogues in water have been described for example in EP 0 969 846, EP 1 666 043, EP 1 011 728 and WO 2007/042262 but they do not mention any preservative-free composition.

It is therefore an object of the present invention to provide an ophthalmic aqueous solution comprising PGF2α analogues and substantially no preservatives wherein the absorption of PGF2α analogues to the resinous containers consisting essentially of polyethylene is prevented and wherein said analogues remain soluble, stable and bioavailable in a preservative-free preparation. The aqueous ophthalmic solution according to the invention provides a significant clinical advantage as there is currently an unmet clinical need of preservative-free prostaglandin eye drops for glaucoma patients.

Summary of the invention

The present invention relates to an aqueous ophthalmic solution for treating ocular hypertension and glaucoma comprising PGF2α analogue as an active ingredient thereof which solution contains nonionic surfactant, stabilizing agent, and substantially no preservatives in a container consisting essentially of polyethylene.

The present invention also relates to a method for treating ocular hypertension and glaucoma, which method comprises administering an aqueous ophthalmic solution comprising PGF2α analogue as an active ingredient thereof to a subject in need of said treatment, wherein the ophthalmic solution contains nonionic surfactant, stabilizing agent, and substantially no preservatives.

Further, the present invention relates to the use of PGF2α analogue for manufacturing an ophthalmic aqueous solution for the treatment of ocular hypertension and glaucoma, wherein said solution contains nonionic surfactant, stabilizing agent, substantially no preservatives and is stored in a container consisting essentially of polyethylene.

Another object of the invention is a method for increasing aqueous solubility and improving stability of PGF2α analogues in an aqueous ophthalmic solution, comprising the steps of preparing an ophthalmic aqueous solution containing PGF2α analogue, nonionic surfactant, stabilizing agent and substantially no preservatives, and packaging the preservative-free ophthalmic solution in a container consisting essentially of polyethylene.

Within this description, "substantially no preservatives" or "preservative-free" means that the solution contains absolutely no preservatives, or the solution contains preservatives at a concentration that is undetectable or does not provide a preservative effect.

Brief description of the figures

Figures 1-3 show the effect of polysorbate 80 (Tween 80; TW) on the absorption of preservative-free tafluprost to low-density polyethylene containers at three different concentrations of the polysorbate at 5 °C, 25 °C and 40 °C r espectively.

Figure 4 shows concentration of acid form of tafluprost in rabbit aqueous humor after a single instillation of BAK-preserved 0.0015% tafluprost in ophthalmic solution [BAK(+)], non-preserved 0.0015% tafluprost ophthalmic solution containing 0.20% Tween 80 [BAK(-) 0.2% Tween 80], or non-preserved 0.0015% tafluprost ophthalmic solution containing 0.05% Tween 80 [BAK(-) 0.05% Tween 80]. Bars present standard error of the mean of tafluprost acid form concentration at each time point and asterisks represent statistically significant difference in tafluprost acid form concentrations between BAK(-) 0.2% Tween 80 and BAK(-) 0.05% Tween 80 solutions ($p<0.05$ with $N=8$).

Detailed description of the invention

Nonionic surfactants are added to the ophthalmic solution according to the invention for their solubilizing effect and to prevent the absorption of PGF2α analogues to the resinous walls of the container. Examples of nonionic surfactants are polyoxyethylene fatty esters such as polysorbate 80 [poly(oxyethylene) sorbitan monooleate], polysorbate 60 [poly(oxyethylene)sorbitan monostearate], polysorbate 40 [poly(oxyethylene)sorbitan monopalmitate], poly(oxyethylene)sorbitan monolaurate, poly(oxyethylene)sorbitan trioleate and polysorbate 65 [poly(oxyethylene)sorbitan tristearate], polyoxyethylene hydrogenated castor oils such as polyoxyethylene hydrogenated castor oil 10, polyoxyethylene hydrogenated castor oil 40, polyoxyethylene hydrogenated castor oil 50 and polyoxyethylene hydrogenated castor oil 60, polyoxyethylene polyoxypropylene glycols such as polyoxyethylene (160) polyoxypropylene (30) glycol [Pluronic F68], polyoxyethylene (42) polyoxypropylene (67) glycol [Pluronic P123], polyoxyethylene (54) polyoxypropylene (39) glycol [Pluronic P85], polyoxyethylene (196) polyoxypropylene (67) glycol [Pluronic F127] and polyoxyethylene (20) polyoxypropylene (20) glycol [Pluronic L-44], polyoxyl 40 stearate and sucrose fatty esters. The nonionic surfactants can be used solely or in combination. A preferred example of the nonionic surfactants is polysorbate 80 [poly(oxyethylene)sorbitan monooleate]. Other preferred nonionic surfactants are polyoxyethylene hydrogenated castor oil 60 and polyoxyl 40 stearate.

The amount of nonionic surfactant(s) in the ophthalmic solution according to the invention can be chosen depending on the amount and type of prostaglandin analogue and the specific surfactant(s) and is within the skill of a person in the art. For polysorbate 80, the concentration is for example in the range of 0.05 to 0.5% (w/v), even

more preferably 0.05 to 0.1%, and most preferably about 0.075%. It has also been found by the present inventors that a too high concentration of the nonionic surfactant has an irritative effect on the corneal epithelium layer and an adverse effect on the bioavailability of prostaglandin from the ophthalmic solution. For example in the case of tafluprost an upper limit of 0.5% of the nonionic surfactant polysorbate 80 is possible.

The ophthalmic solution according to the invention also contains stabilizing agents to inhibit decomposition of PGF2α analogues in the ophthalmic solution. Preferred examples of stabilizing agents are ethylenediaminetetraacetic acid and salts thereof, such as disodium edetate, and dibutylhydroxytoluene. Also other stabilizing agents, such as sodium nitrite, ascorbic acid, L-ascorbic acid stearate, sodium hydrogensulfite, alphathioglycerin, erythorbic acid, cysteine hydrochloride, citric acid, tocopherol acetate, potassium dichloroisocyanurate, 2,6-di-t-butyl-4-methylphenol, soybean lecithin, sodium thioglycollate, sodium thiomalate, natural vitamin E, tocopherol, ascorbyl pasthyminate, sodium pyrosulfite, butylhydroxyanisole, 1,3-butylene glycol, pentaerythtyl tetrakis[3-(3,5-di-t-butyl-4-hydroxyphenyl)]propionate, propyl gallate, 2-mercaptobenzimidazole and oxyquinoline sulphate, may be used.

The amount of stabilizing agents in the ophthalmic solution according to the invention can be selected depending on the specific stabilizing agent and is within the skill of a person in the art. For example, when the stabilizing agent is disodium edetate, the concentration is usually 0.005 to 0.2% (w/v), preferably 0.01 to 0.1%, even more preferably about 0.05%.

A preferred PGF2α analogue for use in the ophthalmic aqueous solution according to the invention is tafluprost. However, all of the known PGF2α analogues, especially other omega chain phenyl ring-substituted PGF2α analogues such as latanoprost, travoprost and bimatoprost or a mixture of two or more prostaglandins may also be used. Alternative drugs for use in the ophthalmic aqueous solution according to the invention are other prostaglandins and their derivatives such as prostaglandin E and its analogues (see US 6,344,477 and references therein). Combinations of prostaglandins or analogues and other eye drugs, for example β-blocking agents such as timolol, are also possible.

The amount of PGF2α analogues in the ophthalmic solution according to the invention can be selected depending on the specific prostaglandin in question, on the diseases to be treated and their symptoms. For tafluprost, an amount of for example 0.0001 to 0.01%, preferably about 0.0005 to 0.0025%, even more preferably 0.0010 to 0.0025% (w/v) is regarded to be sufficient. Preferable concentrations of other PGF2α analogues for treating glaucoma are 0.001 to 0.004% for travoprost, approximately 0.005% for latanoprost, about 0.03% for bimatoprost and about 0.15% for unoprostone.

The ophthalmic solution according to the invention may also comprise conventional excipients used in ophthalmic compositions, such as buffering agents, solvents, pH adjusters, tonicity agents and the like. Examples of suitable buffering agents include but are not limited to sodium dihydrogen phosphate dihydrate, boric acid, borax, cit-

ric acid, or ε-aminocaproic acid. Specific examples of tonicity agents include but are not limited to glycerol, sorbitol, mannitol and other sugar alcohols, propylene glycol, sodium chloride, potassium chloride and calcium chloride.

The pH of the ophthalmic aqueous solution according to the invention is preferably from 4 to 8, more preferably from 5 to 7. As pH adjusters, common pH adjusting agents such as sodium hydroxide and/or hydrochloric acid may be used.

The material of the resinous container consists essentially of polyethylene. The container material may contain minor amounts of other materials than polyethylene, for example polypropylene, polyethylene terephthalate, polyvinyl chloride, acrylic resins, polystyrene, polymethyl methacrylate and nylon 6. The amount of said materials is preferably no more than about 5 to 10% of the total container material.
Polyethylene is classified to several types by the density thereof, namely low density polyethylene (LDPE), middle density polyethylene (MDPE), high density polyethylene (HDPE), etc and these polyethylenes are included in this invention. Preferable polyethylene is LDPE.

Containers for packaging and storing the aqueous ophthalmic solution according to the invention include all container forms suitable for user-friendly topical ophthalmic delivery. Consequently, the containers may be selected for example from the group consisting of bottles, tubes, ampoules, pipettes and fluid dispensers, in single unit dose form or in multidose form. According to a preferred embodiment of the invention, the aqueous ophthalmic solution is in a single dose or unit dose form.

The containers for the ophthalmic solution according to the invention are preferably manufactured by extrusion blow moulding method. Extrusion blow moulding gives smoother inner surface of the container compared to injection blow moulding, which is commonly used to manufacture for example polyethylene multidose bottles. The smoother inner surface gives better chemical stability of prostaglandins in the polyethylene container compared to polyethylene container manufactured by injection blow moulding. Furthermore, when single-dose containers are used, they are sterilized during the moulding process by heat and no additional sterilization of containers is needed, which also improves stability of prostaglandins in a single-dose container (see EP 1 825 855 and EP 1 349 580).

Generally, a unit dose ophthalmic container manufactured by blow moulding method has a volume of about 1 ml and about 0.2 to 0.5 ml of solution is filled. A large variety of shapes are known in such containers. Typical examples are seen in US 5,409,125 and US 6,241,124.

Although unit dose containers are preferred for the purposes of the invention, the aqueous ophthalmic solution according to the invention remains soluble, stable and bioavailable also in fluid dispensers for dispensing of minute amounts of germ-free fluid or in any other container-type wherein the aqueous ophthalmic solution is in contact with container material consisting essentially of polyethylene. Such fluid dispensers are disclosed for example in US 5,614,172.

The preservative-free aqueous ophthalmic solution according to the invention can be stored at room temperature in the above mentioned suitable containers, including unit dose pipettes and dispensers. Stability studies have shown that a preservative-free aqueous ophthalmic tafluprost solution according to the invention is stable in a polyethylene container for a long time, at least for 12 months at 25°C and at least for 30 months at 5°C..

A preferred embodiment according to the invention is an aqueous ophthalmic solution for treating ocular hypertension and glaucoma, which comprises

0.0001 – 0.01% w/v PGF2α analogues;

0.05 – 0.5% w/v non-ionic surfactant,

0.005 – 0.2% w/v stabilizing agent,

substantially no preservatives, and

optionally buffering agents, pH adjusters and tonicity agents conventionally used in ophthalmic solutions, in a container consisting essentially of polyethylene.

The following examples illustrate the invention without limiting the same any way.

Example 1.

The effect of nonionic surfactant on the absorption of preservative-free tafluprost to low density polyethylene containers was studied for 20 weeks at 5 °C ,25 °C and 40 °C. Three different polysorbate 80 (Tween 80) concentrations, namely 0.05%, 0.075% and 0.1% were used. The composition of the preservative-free aqueous ta-

fluprost formulation except polysorbate 80 was 0.0015% tafluprost, 2.25% glycerol, 0.2% sodium dihydrogen phosphate dihydrate, 0.05% disodium edetate and sodium hydroxide and/or hydrochloric acid to adjust the pH to 5.0 – 6.7.

0.3 ml of the composition prepared above was filled in the body part of the unit dose container (LDPE) and sealed by heating with the upper part of the co ntainer (LDPE). The inner volume of the unit dose container was ca. 1 ml. The container was packaged into paper coated aluminium-polyethylene foil and stored in refrigerator or incubator.

The remaining concentration of tafluprost was measured by HPLC. The results are shown in Figures 1 -3. The results show that the concentration of polysorbate has an influence to the absorption of tafluprost to polyethylene. Polysorbate (0.05 to 0.1%) inhibits the absorption of tafluprost , especially even at an elevated temperature (40°C). An amount of 0.075 to 0.1% of polysorbate shows good inhibition effect of absorption of tafluprost.

Example 2.

The concentration of free acid of tafluprost in rabbit aqueous humor after a single instillation of

1) preserved 0.0015% tafluprost ophthalmic solution containing 0.01% BAK and 0.05% polysorbate 80, or

2) non-preserved 0.0015% tafluprost ophthalmic solution containing 0.20% polysorbate 80, or

3) non-preserved 0.0015% tafluprost ophthalmic solution containing 0.05% polysorbate 80

was studied.

The concentrations of ingredients except polysorbate 80 in non-preserved solutions were the following: 2.25% glycerol, 0.2% sodium dihydrogen phosphate dihydrate, 0.05% disodium edetate and sodium hydroxide and/or hydrochloric acid to adjust the pH to 5.0 – 6.7.

Rabbits received the ophthalmic solutions described above. The rabbits were sacrificed at each time point (4 animals per treatment per time point) and aqueous humor sample was taken. The concentration of tafluprost acid form was measured using the validated LC-MS/MS method.

The results (N= 8 for each test solution per time point) are shown in Figure 4.

From the results it can be seen that the amount of nonionic surfactant has an effect on ocular bioavailability. When the amount of the nonionic surfactant exceeds a certain limit, penetration of the active agent to the aqueous humor starts to decrease. Thus the amount of the nonionic surfactant has to be balanced, on one hand to minimize the absorption of PGF2α analogue to the container walls and, on the other hand, to maximize ocular bioavailability.

Claims

1. An ophthalmic aqueous solution for treating ocular hypertension and glaucoma, comprising PGF2α analogue as an active ingredient, wherein said ophthalmic aqueous solution contains nonionic surfactant, stabilizing agent and substantially no preservatives in a container consisting essentially of polyethylene.

2. The ophthalmic aqueous solution according to claim 1 wherein the PGF2α analogue is selected from the group consisting of latanoprost , isopropyl unoprostone, travoprost, bimatoprost and tafluprost or a mixture of two or more thereof.

3. The ophthalmic aqueous solution according to claim 1 wherein the PGF2α analogue is tafluprost.

4. The ophthalmic aqueous solution according to any one of claims 1 to 3 in a container comprising minor amounts of polypropylene, polyethylene terephthalate, polyvinyl chloride, acrylic resins, polystyrene, polymethyl methacrylate or nylon 6.

5. The ophthalmic aqueous solution according to any one of claims 1 to 4 wherein the nonionic surfactant is selected from the group consisting of polyoxyethylene fatty esters such as polysorbate 80 [poly(oxyethylene) sorbitan monooleate], polysorbate 60 [poly(oxyethylene)sorbitan monostearate], polysorbate 40 [poly(oxyethylene)sorbitan monopalmitate], poly(oxyethylene)sorbitan monolaurate, poly(oxyethylene)sorbitan trioleate and polysorbate 65 [poly(oxyethylene)sorbitan

tristearate], polyoxyethylene hydrogenated castor oils such as polyoxyethylene hydrogenated castor oil 10, polyoxyethylene hydrogenated castor oil 40, polyoxyethylene hydrogenated castor oil 50 and polyoxyethylene hydrogenated castor oil 60, polyoxyethylene polyoxypropylene glycols such as polyoxyethylene (160) polyoxypropylene (30) glycol [pluronic F68], polyoxyethylene (42) polyoxypropylene (67) glycol [Pluronic P123], polyoxyethylene (54) polyoxypropylene (39) glycol [Pluronic P85], polyoxyethylene (196) polyoxypropylene (67) glycol [Pluronic F127] and polyoxyethylene (20) polyoxypropylene (20) glycol [Pluronic L-44], polyoxyl 40 stearate and sucrose fatty esters.

6. The ophthalmic aqueous solution according to claim 5, wherein the nonionic surfactant is polysorbate 80 or castor oil.

7. The ophthalmic aqueous solution according to any one of claims 1 to 6 wherein the amount of the non-ionic surfactant is 0.05 to 0.5% (w/v), preferably 0.05 to 0.1% (w/v), and even more preferably about 0.075% (w/v).

8. The ophthalmic aqueous solution according to any one of claims 1 to 7 wherein the stabilizing agent is selected from the group consisting of ethylenediaminetetraacetic acid and salts thereof, sodium nitrite, ascorbic acid, L-ascorbic acid stearate, sodium hydrogensulfite, alphathioglycerin, erythorbic acid, cysteine hydrochloride, citric acid, tocopherol acetate, potassium dichloroisocyanurate, 2,6-di-t-butyl-4-methylphenol, soybean lecithin, sodium thioglycollate, sodium thiomalate, natural vitamin E, tocopherol, ascorbyl pasthyminate, sodium pyrosulfite, butylhydroxyani-

sole, 1,3-butylene glycol, pentaerythtyl tetrakis[3-(3,5-di-t-butyl-4-hydroxyphenyl)]propionate, propyl gallate, 2-mercaptobenzimidazole and oxyquinoline sulphate.

9. The ophthalmic aqueous solution according to claim 8 wherein the stabilizing agent is disodium edetate.

10. The ophthalmic aqueous solution according to any one of claims 1 to 9 wherein the amount of the stabilizing agent is 0.005 to 0.2%, preferably 0.01 to 0.1%, even more preferably about 0.05% (w/v).

11. The ophthalmic aqueous solution according to claim 1 in a single dose form.

12. The ophthalmic aqueous solution according to any one of claims 1 to 11 comprising at least one further pharmaceutically active substance, such as timolol.

13. An ophthalmic aqueous solution comprising
0.0001 – 0.01% w/v PGF2α analogue;
0.05 – 0.5% w/v non-ionic surfactant,
0.005 – 0.2% w/v stabilizing agent, and
optionally buffering agents, pH adjusters and tonicity agents conventionally used in ophthalmic solutions, and substantially no preservatives, in a container consisting essentially of polyethylene or in contact with container material consisting essentially of polyethylene.

14. An ophthalmic aqueous solution comprising

0.0010 – 0.0015% w/v tafluprost;

0.05 – 0.1% w/v polysorbate 80,

0.01 – 0.1% w/v disodium edetate, and

optionally buffering agents, pH adjusters and tonicity agents conventionally used in ophthalmic solutions, and substantially no preservatives, in a container consisting essentially of polyethylene or in contact with container material consisting essentially of polyethylene..

15. An ophthalmic aqueous solution, comprising

0.0015% w/v tafluprost

0.075% w/v polysorbate 80,

0.05% w/v disodium edetate,

2.25% w/v glycerol,

0.2% w/v sodium dihydrogen phosphate dihydrate,

pH adjusters, and substantially no preservatives, in a container consisting essentially of polyethylene or in contact with container material consisting essentially of polyethylene.

16. The ophthalmic aqueous solution according to any one of claims 13 to 15 in a container comprising minor amounts of polypropylene, polyethylene terephthalate, polyvinyl chloride, acrylic resins, polystyrene, polymethyl methacrylate or nylon 6.

17. The ophthalmic aqueous solution according to any one of claims 13 to 15 in a single dose or unit dose form.

18. The ophthalmic aqueous solution according to any one of claims 13 to 15 in a fluid dispenser form.

19. A method for increasing aqueous solubility and improving stability of PGF2α analogues in an aqueous ophthalmic solution, comprising the steps of preparing an aqueous ophthalmic solution containing PGF2α analogue, nonionic surfactant, stabilizing agent and substantially no preservatives, and packaging the preservative-free ophthalmic solution in a container consisting essentially of polyethylene or in contact with container material consisting essentially of polyethylene.

20. Use of PGF2α analogues for the manufacture of an ophthalmic aqueous solution for the treatment of ocular hypertension and glaucoma, wherein said ophthalmic solution comprises non ionic surfactant, stabilizing agent, and substantially no preservatives.

21. The use according to claim 20, wherein the ophthalmic aqueous solution is packaged in a container consisting essentially of polyethylene or in contact with container material consisting essentially of polyethylene.

22. A method for treating ocular hypertension and glaucoma, which comprises administration of an ophthalmic aqueous solution comprising PGF2α analogue as an

active ingredient thereof to a subject in need of said treatment, wherein said ophthalmic solution comprises nonionic surfactant, stabilizing agent, and substantially no preservatives.

5