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(54) **AQUEOUS LIQUID BROMFENAC COMPOSITION HAVING PRESERVATIVE EFFICACY**

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See application file for complete search history.

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(57) **ABSTRACT**

An aqueous liquid bromfenac composition containing (a) bromfenac or a salt thereof and (b) benzalkonium chloride, characterized by that the composition has preservative efficacy and that the concentration of (b) benzalkonium chloride is higher than 0.0005% and lower than 0.005%.

9 Claims, No Drawings

AQUEOUS LIQUID BROMFENAC COMPOSITION HAVING PRESERVATIVE EFFICACY

TECHNICAL FIELD

The present invention relates to an aqueous liquid bromfenac composition in which a base containing a low concentration of benzalkonium chloride is used and which has preservative efficacy and stability. The present invention also relates to a method for preparing an aqueous liquid bromfenac composition having preservative efficacy by combining bromfenac and an aqueous base composition which contains benzalkonium chloride but does not have sufficient preservative efficacy. The present invention also relates to a method for enhancing the preservative efficacy of an aqueous solution.

BACKGROUND ART

Generally, a preservative is indispensable in (multidose) aqueous liquid compositions. A representative of such a preservative is Benzalkonium chloride. However, frequent application of an ophthalmic solution containing benzalkonium chloride or application thereof to those who have corneal injury or abnormal tear dynamics such as dry eye syndrome causes side effects and corneal damage (Non Patent Literature 1 and 2). Therefore, it is desirable that the concentration of benzalkonium chloride added to ophthalmic solutions etc. is low. Considering both preservative efficacy and safety, a desirable concentration of benzalkonium chloride added to an ophthalmic solution is said to be 0.002% to 0.005% (Non Patent Literature 1). Aqueous liquid bromfenac compositions containing 0.001% or 0.005% benzalkonium chloride are known (Patent Literature 1 to 7). However, the preservative efficacy of the compositions is unknown.

Bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid) is a non-steroidal anti-inflammatory drug of which the preservative efficacy is unknown.

Benzalkonium chloride is a cationic surfactant which is widely used as a preservative for topical aqueous liquids as mentioned above. A preferred concentration of benzalkonium chloride, in particular in ophthalmic solutions, is 0.002% to 0.005%, but the preservative efficacy of benzalkonium chloride can decline under the influence of other substances in an aqueous base. For example, a large amount of a non-ionic surfactant added to an aqueous liquid impairs the preservative efficacy of benzalkonium chloride (Patent Literature 8). It is also known that benzalkonium chloride forms complexes with other substances in an aqueous liquid, resulting in impaired preservative efficacy. In particular, it is reported that a combination of a non-steroidal anti-inflammatory drug (NSAID) and a quaternary ammonium salt such as benzalkonium chloride forms a complex, resulting in decline in the preservative efficacy (Patent Literature 9 and 10).

No aqueous liquid bromfenac composition which has sufficient preservative efficacy and stability as a result of combining bromfenac and a base which contains benzalkonium chloride but does not have sufficient preservative efficacy has so far been reported.

CITATION LIST

Patent Literature

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[PTL 4] JP 2005-046700 W (U.S. Pat. No. 7,829,544)

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[PTL 6] JP Pat. No. 2683676 (U.S. Pat. No. 4,910,225)

[PTL 7] CN 101313899 A

[PTL 8] JP 10-109930 A

[PTL 9] JP 02-286627 A (U.S. Pat. No. 5,414,011)

[PTL 10] JP Pat. No. 2954356 (WO 96/14829)

Non Patent Literature

[NPL 1] *Ophthalmology* Vol. 31 43-48, 1989 (published by Kanehara & Co., Ltd.)

[NPL 2] *Ophthalmology* Vol. 33 533-538, 1991 (published by Kanehara & Co., Ltd.)

SUMMARY OF INVENTION

Technical Problem

In view of the above problems, an object of the present invention is to provide an aqueous liquid bromfenac composition having preservative efficacy and stability by combining bromfenac and an aqueous base which contains benzalkonium chloride but does not have sufficient preservative efficacy. Another object of the present invention is to provide a method for preparing an aqueous liquid bromfenac composition having preservative efficacy by combining bromfenac and an aqueous base which contains benzalkonium chloride but does not have sufficient preservative efficacy. Still another object of the present invention is to provide a method for enhancing the preservative efficacy of an aqueous solution for use in ophthalmic solutions, etc.

Solution to Problem

In view of the above problems, the present inventors made extensive research, and found that an aqueous liquid bromfenac composition having preservative efficacy can be prepared by combining bromfenac sodium and an aqueous base composition which contains up to 0.005% benzalkonium chloride but does not have sufficient preservative efficacy, as the base of the aqueous liquid composition containing bromfenac sodium. The present inventors also found a method for preparing an aqueous liquid bromfenac composition having preservative efficacy by combining bromfenac sodium and the above-mentioned aqueous base composition which contains benzalkonium chloride but does not have sufficient preservative efficacy.

As described above, it is known that a combination of a non-steroidal anti-inflammatory drug (NSAID) and a quaternary ammonium salt forms a complex, resulting in decline in the preservative efficacy. Since bromfenac is a non-steroidal anti-inflammatory drug and benzalkonium chloride is a quaternary ammonium salt, it is expected that combining these two results in dcclinc in the preservative efficacy. However, unexpectedly, a combination of bromfenac and benzalkonium chloride both of which were at a concentration insufficient for exerting preservative efficacy by itself significantly enhanced the preservative efficacy specifically against *Pseudomonas aeruginosa*, that is, provided improved preservative efficacy to the aqueous liquid composition. The obtained aqueous liquid bromfenac composition had also excellent stability.

The present inventors also found that an aqueous liquid

benzalkonium chloride, even when the added amount of benzalkonium chloride is reduced to the minimum. In this way, the side effect of the aqueous liquid bromfenac composition containing benzalkonium chloride can be reduced.

The present inventors also found that bacterial proliferation in an aqueous solution can be suppressed by adding bromfenac or a salt thereof to the solution. Thus, the addition of bromfenac or a salt thereof to an aqueous solution can enhance the preservative efficacy of the solution, and therefore, a small amount of a preservative is sufficient to suppress the proliferation of bacteria or the like in the aqueous solution and hence a highly safe aqueous liquid composition etc. can be obtained.

Based on the above findings, the inventors conducted further research and completed the present invention. That is, the present invention relates to the following (1) to (17).

(1) An aqueous liquid bromfenac composition containing (a) bromfenac or a salt thereof and (b) benzalkonium chloride, characterized by that the composition has preservative efficacy and that the concentration of (b) benzalkonium chloride is higher than 0.0005% and lower than 0.005%.

(2) The aqueous liquid composition of the above (1), wherein the concentration of (a) bromfenac or a salt thereof is 0.01% to 10%.

(3) The aqueous liquid composition of the above (1) or (2), wherein the concentration of (b) benzalkonium chloride is 0.00075% to 0.003%.

(4) The aqueous liquid composition of any one of the above (1) to (3), further containing (c) at least one kind selected from the group consisting of a non-ionic surfactant and a water-soluble polymer.

(5) The aqueous liquid composition of the above (4), wherein the total concentration of (c) at least one kind selected from the group consisting of a non-ionic surfactant and a water-soluble polymer is 0.0001% to 5%.

(6) The aqueous liquid composition of the above (4) or (5), wherein the at least one kind selected from the group consisting of a non-ionic surfactant and a water-soluble polymer is a non-ionic surfactant.

(7) The aqueous liquid composition of any one of the above (4) to (6), wherein the non-ionic surfactant is polysorbate 80.

(8) The aqueous liquid composition of any one of the above (4) to (7), wherein the concentration of the non-ionic surfactant is 0.025% or higher and lower than 0.25%.

(9) The aqueous liquid composition of any one of the above (4) to (8), wherein the concentration of the non-ionic surfactant is 0.025% to 0.15%.

(10) The aqueous liquid composition of any one of the above (4) to (8), wherein the concentration of the non-ionic surfactant is 0.05% or higher and lower than 0.25%.

(11) The aqueous liquid composition of the above (4) or (5), wherein the at least one kind selected from the group consisting of a non-ionic surfactant and a water-soluble polymer is a water-soluble polymer.

(12) The aqueous liquid composition of any one of the above (4), (5), and (11), wherein the water-soluble polymer is at least one kind selected from the group consisting of hydroxyethyl cellulose and povidone.

(13) The aqueous liquid composition of any one of the above (4), (5), (11), and (12), wherein the concentration of the water-soluble polymer is 0.01% to 1.4%.

(14) The aqueous liquid composition of any one of the above (1) to (13), which is an ophthalmic solution, a nasal solution, or an otic solution.

(15) A method for providing preservative efficacy to an aqueous liquid composition containing bromfenac or a salt thereof, the method comprising combining bromfenac or a salt thereof and an aqueous base which contains benzalkonium chloride but does not have sufficient preservative efficacy.

(16) A method for enhancing the preservative efficacy of an aqueous solution, the method comprising adding bromfenac or a salt thereof to the solution.

(17) The method of the above (16), wherein the enhancement of the preservative efficacy is evidenced by reduction in viable cell count of *Staphylococcus aureus* (*S. aureus*).

The present invention also relates to the following (A1) to (A10).

(A1) An aqueous liquid bromfenac composition containing (a) bromfenac or a salt thereof and (b) benzalkonium chloride, characterized by that the concentration of (b) benzalkonium chloride is higher than 0.0005% and lower than 0.005%.

(A2) The aqueous liquid composition of the above (A1), wherein the concentration of (b) benzalkonium chloride is higher than 0.0005% and lower than 0.002%.

(A3) The aqueous liquid composition of the above (A1) or (A2), which has preservative efficacy.

(A4) The aqueous liquid composition of any one of the above (A1) to (A3), wherein the concentration of (a) bromfenac or a salt thereof is 0.01% to 10%.

(A5) The aqueous liquid composition of any one of the above (A1) to (A4), wherein the concentration of (b) benzalkonium chloride is 0.00075% to 0.0015%.

(A6) The aqueous liquid composition of any one of the above (A1) to (A5), further containing (c) at least one kind selected from the group consisting of a non-ionic surfactant and a water-soluble polymer.

(A7) The aqueous liquid composition of the above (A6), wherein the non-ionic surfactant is polysorbate 80.

(A8) The aqueous liquid composition of the above (A6) or (A7), wherein the concentration of the non-ionic surfactant is 0.001% to 5%.

(A9) The aqueous liquid composition of any one of the above (A1) to (A8), which is an ophthalmic solution, a nasal solution, or an otic solution.

(A10) A method for providing preservative efficacy to an aqueous liquid composition containing bromfenac or a salt thereof, the method comprising combining bromfenac or a salt thereof and an aqueous base which contains benzalkonium chloride but does not have sufficient preservative efficacy.

Advantageous Effects of Invention

According to the present invention, an aqueous liquid bromfenac composition having preservative efficacy and stability can be obtained even when the added amount of benzalkonium chloride is reduced to the minimum. According to the present invention, an aqueous liquid bromfenac composition having preservative efficacy can be provided by combining bromfenac and an aqueous base which contains a low concentration of benzalkonium chloride or contains benzalkonium chloride but does not have sufficient preservative efficacy. The aqueous liquid bromfenac composition has the preservative efficacy which complies with <51> ANTIMICROBIAL EFFECTIVENESS TESTING (preservatives-effectiveness tests) of "Microbiological tests" specified in the United States Pharmacopeia (USP) 32. Therefore, the present invention can provide a bromfenac aqueous liquid composition which causes fewer side effects and is safe and stable.

In addition, according to the present invention, the preservative efficacy of an aqueous solution can be enhanced by

servative is sufficient to suppress the proliferation of bacteria or the like in the aqueous solution and thus a highly safe aqueous liquid composition can be provided.

DESCRIPTION OF EMBODIMENTS

Definitions

As used herein, "Preservatives-Effectiveness Tests" refers to the method specified in the Japanese Pharmacopoeia Fifteenth Edition unless otherwise stated.

In the method, with the use of bacteria, such as *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa*, and fungi, such as *Candida albicans* and *Aspergillus brasiliensis* (*niger*), as test microorganisms, the following procedures (i) to (iv) are performed.

(i) Each of the above-mentioned five strains for testing is inoculated onto the surface of a slant agar medium and precultured. As the agar medium for preculture, a soybean casein digest agar medium is used for the bacteria, and a Sabouraud glucose agar medium is used for the fungi. The bacteria are precultured at 30 to 35° C. for 18 to 24 hours, *Candida albicans* is precultured at 20 to 25° C. for 40 to 48 hours, and *Aspergillus brasiliensis* (*niger*) is precultured at 20 to 25° C. for a week or until sufficient sporulation is achieved.

(ii) The aqueous liquid composition to be tested as a sample is dispensed to 5 sterile stoppered test tubes so that each tube contains 10 mL of the sample. To these, test microorganisms of (i) are inoculated at 10^5 to 10^6 cells/mL, and the thus prepared mixed samples are stored at 20 to 25° C. in light-shielded conditions. The test microorganism are not mixed with each other but separately inoculated into the samples.

(iii) From each of the mixed samples, 1 mL is sampled after 1 week, 2 weeks, and 4 weeks of storage, and diluted with 9 mL of physiological saline. The same dilution is further performed twice or 3 times, and 1 mL of each diluent is transferred into separate sterile petri dishes.

(iv) Subsequently, a soybean casein digest agar medium supplemented with 0.1% lecithin and 0.7% polysorbate 80 is poured into the petri dishes containing the bacteria, and a Sabouraud glucose agar medium supplemented with 0.1% lecithin and 0.7% polysorbate 80 is poured into the petri dishes containing the fungi. After culturing under the conditions shown below, the number of the formed colonies is counted, and the theoretical cell count in 1 mL of each mixed sample is calculated.

Culture conditions for bacteria: at 30 to 35° C. for about 3 to 5 days

Culture conditions for fungi: at 20 to 25° C. for about 5 days

After the above (i) to (iv) are completed, the sample is judged as "having preservative efficacy" in cases where the sample satisfies all the following criteria: all the bacterial viable cell counts (*Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa*) in the mixed solutions after 14 days of storage are all reduced to 0.1% of the inoculated cell counts or less, and the bacterial viable cell counts after 28 days of storage are still at the same level as those after 14 days of storage or less; and all the fungal viable cell counts in the mixed solutions after 14 days of storage and after 28 days of storage are all at the same level as the inoculated cell counts or less. In the cases where any one of the above bactcria and fungi does not satisfy the above criteria, the sample is judged as "not having sufficient preservative efficacy".

In the <51> ANTIMICROBIAL EFFECTIVENESS TESTING (preservatives-effectiveness tests) of "Microbio-

is judged as "having preservative efficacy" in cases where the sample satisfies all the following criteria: (1) all the bacterial viable cell counts (*Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa*) in the mixed solutions after 7 days of storage are reduced to 10% of the inoculated cell counts or less, all the viable cell counts after 14 days of storage are reduced to 0.1% of the inoculated cell counts or less, and all the viable cell counts after 28 days of storage remain the same level as those after 14 days of storage or less, and (2) all the fungal viable cell counts in the mixed solutions after 7, 14, and 28 days of storage are at the same level as the inoculated cell counts or less. In the cases where any one of the above bacteria and fungi does not satisfy the above criteria, the sample is judged as "not having sufficient preservative efficacy".

The term "stable" or "having stability" means that the preservative efficacy is retained for, for example, at least 1 year of storage and no changes are observed in the properties.

As used herein, an aqueous liquid composition "having preservative efficacy" is the one that is judged as "having preservative efficacy" in the above-mentioned preservatives-effectiveness tests specified in the Japanese Pharmacopoeia or the United States Pharmacopeia (USP). An aqueous liquid composition "not having sufficient preservative efficacy" is the one that is judged as "not having sufficient preservative efficacy" in the above-mentioned preservatives-effectiveness tests. The term "preservative efficacy" is synonymous with "antiseptic efficacy", and the term "preservative" is synonymous with "antiseptic".

As used herein, an "aqueous base" refers to an aqueous solution prepared by adding 1 or more additives to water as a vehicle, and "an aqueous liquid" refers to a liquid prepared by adding 1 or more pharmacologically active ingredient to the aqueous base, unless otherwise stated.

As used herein, a "low concentration" refers to a concentration higher than 0.0005% and lower than 0.005%, unless otherwise stated.

As used herein, % means w/v % (g/100 mL), unless otherwise stated.

Herein, as described above, a benzalkonium chloride-containing aqueous base whose efficacy as a preservative has declined under the influence of another substance and has been judged as "not having sufficient preservative efficacy" in the above-mentioned preservatives-effectiveness tests specified in the Japanese Pharmacopoeia or the United States Pharmacopeia (USP) is described as an "aqueous base which contains benzalkonium chloride but does not have sufficient preservative efficacy".

As used herein, a "method for providing preservative efficacy" means a method comprising combining a composition and/or a base both of which were at a concentration insufficient for exerting preservative efficacy by itself to give a composition having preservative efficacy.

The present invention provides an aqueous liquid bromfenac composition containing bromfenac and a low concentration of benzalkonium chloride. The aqueous liquid bromfenac composition of the present invention has preservative efficacy.

The aqueous liquid bromfenac composition of the present invention having preservative efficacy is an aqueous liquid composition containing (a) bromfenac or a salt thereof and (b) benzalkonium chloride, and the concentration of (b) benzalkonium chloride is higher than 0.0005% and lower than 0.005%.

The salt of bromfenac added to the aqueous liquid compo-

the salt include, alkali metal salts, such as sodium salt and potassium salt; alkaline earth metal salts, such as calcium salt and magnesium salt, and these can be used as appropriate unless the objects of the present invention are hindered. Depending on the conditions of synthesis, recrystallization, etc., the above compounds may be obtained in the form of a hydrate, which can be used in the present invention without any inconvenience. Among the salts of bromfenac, preferred is sodium salt.

The concentration of bromfenac or a salt thereof in the aqueous liquid composition of the present invention is usually about 0.001% to 10%, preferably about 0.01% to 10%, more preferably about 0.01% to 1%, still more preferably about 0.02% to 0.15%, and particularly preferably about 0.02% to 0.1%.

In another preferred embodiment of the present invention, the concentration of bromfenac or a salt thereof is preferably about 0.05% to 0.15%.

Bromfenac and a pharmacologically acceptable salt thereof can be appropriately produced by the method according to JP 52-23052 A (corresponding to U.S. Pat. No. 4,045,576) or an equivalent method (for example, FDA Drug Master File #16414, or the like). Depending on the conditions of synthesis, recrystallization, etc., bromfenac and a pharmacologically acceptable salt thereof are usually obtained as hydrates thereof. Examples of the hydrate include ½ hydrate, monohydrate, and 3/2 hydrate, and preferred is 3/2 hydrate.

As used herein, the term benzalkonium chloride has the same meaning as a chloride of benzalkonium.

The generally used benzalkonium chloride, which is represented by the rational formula: $[C_6H_5CH_2N(CH_3)_2R]Cl$, is a mixture of compounds having C_8H_{17} to $C_{18}H_{37}$ as the alkyl group R in the rational formula as described in the pharmacopoeias of Japan, the U.S., and Europe. Shown below are the descriptions of benzalkonium chloride in the pharmacopoeias of Japan, the U.S., and Europe.

Japanese Pharmacopoeia: represented by the formula $[C_6H_5CH_2N(CH_3)_2R]Cl$, in which R is C_8H_{17} to $C_{18}H_{37}$, mainly comprising $C_{12}H_{25}$ and $C_{14}H_{29}$.

The U.S. Pharmacopeia (USP): a mixture of alkylbenzyldimethylammonium chlorides represented by the formula $[C_6H_5CH_2N(CH_3)_2R]Cl$, in which R is a mixture of all or some of alkyl groups equal to or longer than C_8H_{17}, mainly comprising $C_{12}H_{25}$, $C_{14}H_{29}$, and $C_{16}H_{33}$.

European Pharmacopoeia: a mixture of alkylbenzyldimethylammonium chlorides with alkyl chain lengths of C_8 to C_{18}.

As used herein, "benzalkonium chloride" usually refers to the mixture of benzalkonium chlorides as described above.

When benzalkonium chloride is designated by the number of carbon atoms, the number denotes the length of the carbon chain of the alkyl group represented by "R" in the above-mentioned pharmacopoeias.

The benzalkonium chloride added to the aqueous liquid composition of the present invention may be one of those represented by the rational formula: $[C_6H_5CH_2N(CH_3)_2R]Cl$ in which the alkyl group R is C_8H_{17} to $C_{18}H_{37}$, or a mixture thereof. Preferred is a mixture represented by the rational formula in which R mainly comprising $C_{12}H_{25}$ and $C_{14}H_{29}$, and more preferred is a mixture represented by the rational formula in which R is a mixture in which the amount of $C_{12}H_{25}$ is about 80 to 85% and the amount of $C_{12}H_{25}$ and $C_{14}H_{29}$ together is about 98% or more.

The lower limit of the concentration of benzalkonium chloride in the aqueous liquid composition of the present invention is usually about 0.0005%, preferably about 0.00075%, particularly preferably about 0.0008%, and most preferably about 0.001%. The upper limit thereof is usually lower than about 0.005%, preferably about 0.004%, more preferably about 0.003%, still more preferably about 0.002%, particularly preferably about 0.0015%, and most preferably about 0.001%. Even when the concentration of benzalkonium chloride is within the above range, such benzalkonium chloride can be combined with bromfenac or a salt thereof to give an aqueous liquid composition having preservative efficacy.

The concentration range of benzalkonium chloride blended in the aqueous liquid composition of the present invention is usually higher than about 0.0005% and lower than about 0.005%, preferably about 0.00075% to 0.003%, and still more preferably about 0.001% to 0.002%.

The aqueous liquid composition of the present invention has preservative efficacy because the composition contains (a) bromfenac or a salt thereof and (b) benzalkonium chloride, the concentration of (b) being higher than 0.0005%. Therefore, the composition need not contain any preservatives other than benzalkonium chloride. The composition may, however, further contain an additional preservative if desired.

As the additional preservative, one or more kinds of, for example, chlorhexidine salt, benzethonium chloride, p-hydroxybenzonates, benzyl alcohol, p-chlorometaxylenol, chlorocresol, phenethyl alcohol, sorbic acid or a salt thereof, thimerosal, chlorobutanol, boric acid, sodium edetate, and the like. The amount of the additional preservative is not particularly limited as long as the effect of the present invention is exerted, and can be determined as appropriate.

The aqueous liquid composition of the present invention can further contain a compound having a surface-activating action. Examples of the compound having a surface-activating action include a non-ionic surfactant, a water-soluble polymer, and the like. Such an aqueous liquid composition further containing at least one kind selected from the group consisting of a non-ionic surfactant and a water-soluble polymer is a preferred embodiment of the present invention. Inter alia, more preferred is the one containing a non-ionic surfactant.

The total concentration of the non-ionic surfactant and the water-soluble polymer in the aqueous liquid composition of the present invention is usually about 0.0001% to 5%, preferably about 0.01% to 3%, more preferably about 0.01% to 1.4%, still more preferably about 0.025% to lower than 0.25%, particularly preferably about 0.025% to 0.15%, and most preferably about 0.05% to 0.15%.

In another preferred embodiment of the present invention, the total concentration of the non-ionic surfactant and the water-soluble polymer is further preferably about 0.05% to 0.3%.

Examples of the non-ionic surfactant in the aqueous liquid composition of the present invention include polyoxyethylene sorbitan fatty acid esters, polyoxyethylene hydrogenated castor oils, alkyl aryl polyether alcohol-type polymers, polyoxyethylene fatty acid esters, polyoxyethylene polyoxypropylene glycols, and sucrose fatty acid esters. Preferred are polyoxyethylene sorbitan fatty acid esters, such as polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, and polyoxyethylene sorbitan tristearate; polyoxyethylene hydrogenated castor oils, such as polyoxyethylene hydrogenated castor oil 10, polyoxyethylene hydrogenated castor oil 40, polyoxyethyl-

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