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[54] **PRESERVATIVE SYSTEMS FOR PHARMACEUTICAL COMPOSITIONS CONTAINING CYCLODEXTRINS**

WO 96/14829 5/1996 WIPO .
 WO 97/10805 3/1997 WIPO .

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[73] Assignee: **Alcon Laboratories, Inc.**, Fort Worth, Tex.

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[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

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[21] Appl. No.: **09/029,943**

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[22] PCT Filed: **Aug. 8, 1997**

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[86] PCT No.: **PCT/US97/14119**

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Related U.S. Application Data

[60] Provisional application No. 60/022,453, Aug. 9, 1996.

[51] **Int. Cl.**⁶ **A61K 47/40**; A61K 47/18

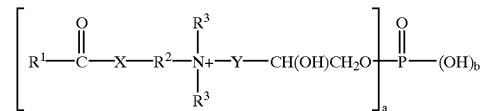
[52] **U.S. Cl.** **424/427**; 514/58; 514/740;
 514/743; 514/553

[58] **Field of Search** 424/427; 514/58,
 514/743, 740, 553

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[57] ABSTRACT

Disclosed are preservative systems useful in aqueous pharmaceutical compositions containing an active agent and a cyclodextrin. The preservative systems comprise boric acid and one or more compounds selected from the group consisting of C₁₆ benzalkonium halide compounds, polymeric quaternary ammonium compounds, and quaternary ammonium alkylene glycol phospholipid derivatives of the following structure



where a+b=3; R¹ is C₈-C₂₂ alkyl or alkene; X is NH, O, or CH₂; R² is C₂-C₆ alkyl; each R³ is independently C₁-C₁₂ alkyl or alkene; and Y is nothing or C₁-C₆ alkyl or alkene; and pharmaceutically acceptable salts thereof.

13 Claims, No Drawings

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[60] Provisional application No. 60/022,453, Aug. 9, 1996.

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 514/743; 514/553

[58] **Field of Search** 424/427; 514/58,
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PRESERVATIVE SYSTEMS FOR PHARMACEUTICAL COMPOSITIONS CONTAINING CYCLODEXTRINS

This application claims priority from U.S. Provisional Application Ser. No. 60/022,453 filed Aug. 9, 1996. This application is also a 371 of PCT/US97/14119 filed Aug. 8, 1997.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to the antimicrobial preservation of aqueous pharmaceutical compositions. In particular, the present invention relates to the antimicrobial preservation of pharmaceutical compositions containing cyclodextrins.

2. Description of Related Art

Cyclodextrins are known to possess a number of uses in pharmaceutical formulations. For example, cyclodextrins are known to increase the solubility of insoluble or poorly soluble drug compounds, to increase the stability of chemically labile drugs in pharmaceutical formulations, and to increase the comfort or mask the taste of active drugs. See, U.S. Pat. No. 4,727,064 (Pitha) and EP 0 149 197 B1 (Janssen Pharmaceutica N.V.).

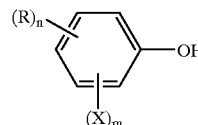
There have been a number of attempts to derivative cyclodextrins in order to decrease toxicity or increase solubility. For example, hydroxy-propyl-beta-cyclodextrin is a derivative which has been shown to have a relatively low toxicity and a high aqueous solubility as compared to the parent compound, beta-cyclodextrin. In addition to hydroxy-propyl derivative of beta cyclodextrin, a number of other cyclodextrin derivatives are known. See, for example, U.S. Pat. Nos. 5,376,645 (Stella et al.) and 4,870,060 (Muller).

Typically, multi-dose pharmaceutical products contain preservatives in order to maintain sterility after opening and during use. Antimicrobial preservation of cyclodextrin-containing formulations can present special problems. For example, Loftsson et al., Drug Development and Industrial Pharmacy, 18 (13), 1477-1484 (1992), have investigated interactions between several commonly used preservatives and 2-hydroxypropyl-β-cyclodextrin (HPβCD). Loftsson et al. report that the interactions were twofold: (i) the preservative molecule can displace a drug molecule from the cyclodextrin cavity, thus reducing the solubilizing effects of the cyclodextrin; and (ii) the antimicrobial activity of the preservative can be reduced by the formation of preservative-cyclodextrin inclusion complexes. Specifically, Loftsson et al. report that chlorobutanol, methylparaben and propylparaben have little or no preservative activity in the tested HPβCD solutions. Additionally, Loftsson et al. found that benzalkonium chloride (with the possible exception of the micro-organism, *Ps. aeruginosa*) and chlorhexidine gluconate did possess significant preservative activity. In contrast, Simpson, FEMS Microbiology Letters, 90, 197-200 (1992), reports that cyclodextrins can inactivate the antimicrobial activity of certain quaternary ammonium compounds. See also, Miyajima et al., Chem. Pharm. Bull., 35(1), 389-393 (1987), regarding the interaction of short-chain alkylammonium salts with cyclodextrins in aqueous solutions, which concluded that α-, β-, and γ-cyclodextrins form complexes with alkylammonium salts having alkyl groups longer than n-butyl, n-hexyl, and n-decyl, respectively.

Benzalkonium chloride (BAC) is the most popular preservative for ophthalmic drug preparations. BAC, as defined

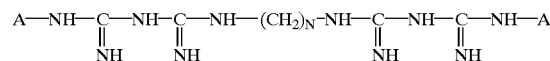
in United States Pharmacopeia XIX, is an alkylbenzyltrimethyl-ammonium chloride mixture with alkyl chains or homologs beginning with n-C₈H₁₇ and extending through higher homologs of C₁₀, C₁₂, C₁₄, and C₁₆-alkyl chains. In our attempts to preserve pharmaceutical formulations containing a cyclodextrin with BAC, however, we have found that cyclodextrin-preservative interactions can significantly reduce or inactivate the preservative efficacy of BAC, when BAC is employed at non-toxic levels.

EP 0 119 737 A2 (Takeda Chem. Ind., Ltd.) discloses aqueous pharmaceutical compositions comprising an active ingredient, a cyclodextrin and a phenol derivative as a preservative. The phenol derivative has the formula



where R is alkyl, X is halogen, n is an integer of 0 to 2, and m is an integer of 1 to 3. According to this reference, formulations containing a cyclodextrin and a paraben preservative (methyl-, ethyl-, propyl-, and butylparaben) suffered a significant decrease in the antimicrobial activity of the preservative, while formulations containing a cyclodextrin and a phenol derivative of the formula above did not.

JP 60149530 A (Takeda Chem. Ind., Ltd.) discloses aqueous compositions of a principal agent and a cyclodextrin where the compositions contain as a preservative a chlorhexidine derivative of the formula



where A is [independently] (un)substituted phenyl; n is 3-9; and the polymethylene chain may be interrupted by an oxygen atom or an aromatic ring.

JP 01016728 A (Santen Seiyaku KK) discloses antiseptic aqueous preparations containing a drug, a cyclodextrin and a cationic surfactant as a preservative. By adding a cyclodextrin or cyclodextrin derivative, cationic surfactants commonly incompatible with certain drugs can be combined. Disclosed cationic surfactants are benzalkonium chloride, benzethonium chloride or chlorhexidine gluconate. Disclosed drugs include sodium hyaluronate, pilocarpine hydrochloride, lysosyme chloride, Na₂ chondroitin sulfate, glycyrrhetinate, pirenixine, sodium chromoglycate, and dimethylisopropylazulene sodium sulfate.

JP 6016547 A (Wakamoto Pharm. Co. Ltd.) discloses eye drop compositions containing diclofenac sodium and a water soluble cyclodextrin compound. The reference also discloses that these compositions can be preserved using benzalkonium chloride, benzethonium chloride and chlorhexidine gluconate as cationic surfactants; methylparaben, ethylparaben, propylparaben and butylparaben as parabens; and phenylethyl alcohol and benzyl alcohol as alcohols.

Even if their antimicrobial preservative efficacy is not significantly reduced by interactions with cyclodextrins, benzyl or phenylethyl alcohol and paraben preservatives may present cytotoxicity, evaporation loss, comfort and/or stability problems. Other compounds or systems capable of effectively preserving pharmaceutical formulations containing cyclodextrins are desirable.

SUMMARY OF THE INVENTION

According to the present invention, aqueous pharmaceutical compositions containing a pharmaceutically active

compound and a cyclodextrin can be preserved using a preservative system comprising a combination of boric acid and one or more compounds selected from the group consisting of C₁₆ benzalkonium halide compounds, polymeric quaternary ammonium compounds, and quaternary ammonium alkylene glycol phospholipid derivatives.

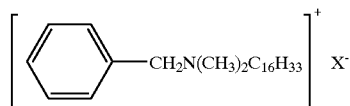
Thus, the present invention relates to aqueous compositions containing a pharmaceutically active drug compound, a cyclodextrin, and a preservative system selected as described above. The present invention also relates to a method of preserving aqueous pharmaceutical compositions containing a cyclodextrin, wherein the method comprises adding to the composition a preservative system of the type described above.

Among other factors, the present invention is based on the discovery that, unlike BAC, C₁₆ benzalkonium halide compounds, polymeric quaternary ammonium compounds and quaternary ammonium alkylene glycol phospholipid derivatives do not interact with cyclodextrins in a way that significantly reduces or eliminates their antimicrobial preservative activity.

DETAILED DESCRIPTION OF THE INVENTION

The aqueous compositions of the present invention comprise a pharmaceutically active drug compound, a cyclodextrin, and a preservative system, wherein the preservative system comprises a combination of boric acid and one or more compounds selected from the group consisting of C₁₆ benzalkonium halide compounds, polymeric quaternary ammonium compounds, and quaternary ammonium alkylene glycol phospholipid derivatives.

The C₁₆ benzalkonium halide compounds useful in the compositions of the present invention have the following structure

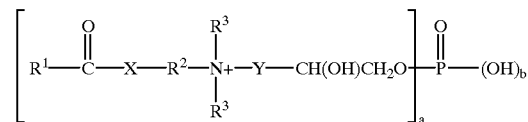


where X=Cl, Br, I, or F. These compounds are known in the art and are either commercially available or can be made using known methods. The most preferred C₁₆ benzalkonium halide compound is C₁₆ benzalkonium chloride. The C₁₆ benzalkonium halide compound is typically used in the compositions of the present invention in an amount from about 0.001 to 1%, preferably from about 0.01 to 0.5%. The most preferred concentration of the C₁₆ benzalkonium halide compounds in the compositions of the present invention is about 0.02%. (Unless indicated otherwise, all percentages referred to herein are on a w/w basis).

The polymeric quaternary ammonium compounds useful in the compositions of the present invention are those which have an antimicrobial effect and which are pharmaceutically acceptable. The most preferred polymeric ammonium compounds are those known as polyquaternium-1, otherwise known as Polyquad® or Onamer M®, with a number average molecular weight between 2,000 to 30,000. Preferably, the number average molecular weight of the polyquaternium-1 is between 3,000 to 14,000.

The polymeric quaternary ammonium compounds are generally used in the compositions of the present invention in an amount from about 0.001 to about 3%, preferably from about 0.001 to about 0.1%. The most preferred concentration of polymeric quaternary ammonium compounds is about 0.01%.

The quaternary ammonium alkylene glycol phospholipid derivatives useful in the compositions of the present invention include those having the structure



where a+b=3; R¹ is C₈-C₂₂ alkyl or alkene; X is NH, O, or CH₂; R² is C₂-C₆ alkyl; each R³ is independently C₁-C₁₂ alkyl or alkene; and Y is nothing or C₁-C₆ alkyl or alkene. In addition to the acid form of the structure shown above, pharmaceutically acceptable salts of the acid form are also within the scope of present invention. Examples of such salts include the sodium chloride, potassium chloride, and calcium and magnesium salts of the structure shown above. Preferred are the following synthetic phospholipids: cocamidopropyl propylene glycol-dimonium chloride phosphate (sodium chloride salt where R¹ is a coconut oil fatty acid alkyl mixture; X is NH; R² is propyl; R³ is methyl; and Y is CH₂); borageamidopropyl phosphatidyl propylene glycol-dimonium chloride (sodium chloride salt where R¹ is a boraginaceae oil fatty acid alkyl mixture; X is NH; R² is propyl; R³ is methyl; and Y is CH₂); and cocophosphatidyl propylene glycol-dimonium chloride (sodium chloride salt where R¹ is a coconut oil fatty acid alkyl mixture; X is O; R² is propyl; R³ is methyl; and Y is CH₂). The phospholipid compounds described above can be synthesized using known techniques. The three preferred phospholipids are commercially available from, for example, MONA Industries, Patterson, N.J.

The amount of quaternary ammonium alkylene glycol phospholipid derivatives in the compositions of the present invention may range from about 0.01 to about 2%, preferably from about 0.03 to 1.5%. When concentrations approaching the upper limits of these ranges are employed in compositions intended for contact with sensitive tissues, such as topically administrable ophthalmic formulations, the comfort of the compositions may be reduced and additional comfort-enhancing ingredients may be needed (such as emollients typical in the ophthalmic industry: polyethylene glycol, hydroxypropylmethylcellulose, polyvinylalcohol, etc.).

The boric acid used in the compositions of the present invention includes not only boric acid, but also its pharmaceutically acceptable acid addition salts. Accordingly, as used herein, "boric acid" refers to boric acid and its pharmaceutically acceptable acid addition salts. In general, an amount from about 0.3 to about 5% of boric acid is used in the compositions of the present invention. It is preferred to use from about 0.3 to about 3.0%, and it most preferred to use from about 0.5 to about 2.0%.

Suitable cyclodextrins for use in the compositions of the present invention include pharmaceutically acceptable cyclodextrins and cyclodextrin derivatives. Nonionic cyclodextrins are preferred. Most preferred are alkyl derivatives, such as hydroxy-propyl-beta-cyclodextrin. Generally, the concentration of cyclodextrins present in the compositions of the present invention ranges from about 0.5 to about 20%, preferably from about 1 to about 10%.

Any pharmaceutical agent may be included in the compositions of the present invention, particularly both positively-charged and neutral agents (negatively-charged agents may form undesirable complexes with the positively-charged preservative ingredient). For example, pharmaceutically acceptable

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tical agents which may be incorporated into the compositions of the present invention include, but are not limited to, the racemic and enantiomeric forms and pharmaceutically acceptable salts, amides, esters and prodrugs of the following types of drugs: adrenocorticoids; glucocorticoids; anti-coagulants; anticonvulsants; antidepressants; antidiabetics; antihistamines; decongestants; antithyroid agents; antimuscarinics; etc. Preferred are ophthalmic agents including anti-glaucoma agents, such as carbonic anhydrase inhibitors, prostaglandins and prostaglandin derivatives; anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl- alkanolic acids, such as diclofenac, bromfenac, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterial and anti-infective agents, such as sulfacetamide sodium, penicillins and cephalosporins; mydriatic and cycloplegic agents, such as phenylephrine, hydroxyamphetamine, tropicamide; and diagnostic agents such as sodium fluorescein. Combinations of pharmaceutical agents may also be used in the compositions of the present invention.

The aqueous compositions of the present invention may additionally include other pharmaceutically acceptable components. For example, comfort enhancing agents, buffers, surfactants, tonicity agents, antioxidants, chelating agents, binding agents, complexing agents, and viscosity modifying agents, including polymers which will undergo a sol-to-gel

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transition upph exposure to physical or chemical stimuli, such as changes in pH, ion concentration, and/or temperature, may be added to the compositions of the present invention as desired or as necessary.

The compositions of the present invention may be formulated according to techniques known in the art and administered in a variety of ways. For example, the compositions of the present invention may be formulated for parenteral, oral or topical administration. Topically administrable ophthalmic compositions are preferred.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

The following formulations were prepared. In Table 1, below, "BAC" means benzalkonium chloride. "C₁₂ BAC" means the C₁₂ homolog of benzalkonium chloride (dodecyl benzalkonium chloride). "C₁₄ BAC" means the C₁₄ homolog of benzalkonium chloride (tetradecyl benzalkonium chloride). "C₁₆ BAC" means the C₁₆ homolog of benzalkonium chloride (hexadecyl benzalkonium chloride). "HPβD" means hydroxy-propyl-beta-cyclodextrin.

TABLE 1

Ingredient	FORMULATION							
	A	B	C	D	E	F	G	H
Suprofen	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Boric Acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
NaCl	0.7	0.7	0.7	0.7	0.7	0.7	0.6	0.6
Edetate Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
NaOH/HCl	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5
BAC	0.01	—	—	—	—	0.01	0.01	0.01
C ₁₂ BAC	—	0.012	—	—	—	—	—	—
C ₁₄ BAC	—	—	0.012	—	—	—	—	—
C ₁₆ BAC	—	—	—	0.012	0.015	—	—	—
Hamosyl® L	0.03	0.03	0.03	0.03	0.03	—	0.03	—
Monobasic/Dibasic	—	—	—	—	—	—	0.1/ 0.03	0.1/ 0.03
Na Phosphate	—	—	—	—	—	—	—	—
HPβCD	2	2	2	2	2	2	—	—
Glycail	—	—	—	—	—	—	—	—
Polyquaternium-1	—	—	—	—	—	—	—	—
dowicil	—	—	—	—	—	—	—	—
cetrimide	—	—	—	—	—	—	—	—
lysozyme	—	—	—	—	—	—	—	—
phospholipid ¹	—	—	—	—	—	—	—	—

Ingredient	FORMULATION									
	I	J	K	L	M	N	O	P	Q	R
Suprofen	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Boric Acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1.0	0.5
NaCl	0.8	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.3	0.7
Edetate Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
NaOH/HCl	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5
BAC	0.01	—	—	—	—	—	—	—	—	—
C ₁₂ BAC	—	—	—	—	—	—	—	—	—	—
C ₁₄ BAC	—	—	—	—	—	—	—	—	—	—
C ₁₆ BAC	—	—	—	—	—	—	—	—	—	0.015
Hamosyl® L	—	—	—	—	—	—	—	—	—	—
Monobasic/basic	0.1/ 0.03	—	—	—	—	—	—	—	—	—
Na Phosphate	—	—	—	—	—	—	—	—	—	—
HPβCD	—	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Glycail	—	0.03	—	—	—	—	—	—	—	—
Polyquaternium-1	—	—	0.01	0.005	—	—	—	—	—	—
dowicil	—	—	—	—	0.03	—	—	—	—	—

TABLE 1-continued

cetrimide	—	—	—	—	—	0.01	—	—	—	—
lysozyme	—	—	—	—	—	—	0.1	—	—	—
phospholipid ¹	—	—	—	—	—	—	—	1.5	—	0.03

¹cocamidopropyl PG-dimonium chloride phosphate

EXAMPLE 2

In addition to the suprofen formulations appearing in Table 1 above, the betaxolol formulations shown in Table 2, below, were also prepared.

TABLE 2

COMPONENTS	FORMULATION		
	AA	AB	AC
Betaxolol HCl	0.56	0.56	0.56
HPβCD	7.5	7.5	7.5
Boric Acid	0.5	0.5	0.5
Sodium Chloride	0.3	0.3	0.3
EDTA	0.01	0.01	—
BAC	—	0.015	—
Phospholipid ¹	—	—	0.03
POLYQUAD	0.01	—	—
NaOH/HCl QS to pH	7.0	6.6	6.58
Purified Water	QS	QS	QS

¹ = cocamidopropyl PG-dimonium chloride phosphate

EXAMPLE 3

The antimicrobial preservative effectiveness of the compositions of Examples 1 and 2 was determined using an organism challenge test according to the methods described in the United States Pharmacopeia (USP) and European Pharmacopoeia (Ph.Eur.). Samples were inoculated with known levels of gram-positive (*Staphylococcus aureus* ATCC 6538) and gram-negative (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 8739) vegetative bacteria, yeast (*Candida albicans* ATCC 10231) and mold (*Aspergillus niger* ATCC 16404) and sampled at specified intervals to determine if the antimicrobial preservative system was capable of killing or inhibiting the propagation of organisms purposely introduced into the formulation. Despite the fact that the compositions of the present invention are not limited to ophthalmic preparations, USP and/or Ph.Eur. preservative efficacy standards for ophthalmic preparations were used for purposes of comparing the anti-

microbial activity of the test compositions. As shown in Table 3, an abbreviated time pull schedule was employed. Based on the data collected, projected pass/fail determinations were made by comparing the log reductions in the respective organism populations to the standards shown in Table 3.

TABLE 3

Abbreviated Schedule of Compendial Preservative Effectiveness Requirements for Ophthalmic Compositions			
Log Reduction of Organism Population			
Time Pull	USP	Ph. Eur.	Ph. Eur.
		A (Target)	B (Min)
For Bacteria:			
6 hours	—	2	—
24 hours	—	3	1
7 days	3	—	3
For Fungi:			
7 days	—	2	1

— = No requirement at this time pull

The preservative efficacy results for the formulations of Example 1 are shown in Table 4 below, and those for the formulations of Example 2 are shown in Table 5 below.

TABLE 4

Projected Preservative Efficacy Test Results For Formulations of Example 1

Formulation	Log Reduction							Projected Decision		
	6 Hr		24 Hr		Day 7			USP	PhEurA	PhEurB
	Sa	Pa	Sa	Pa	Sa	Pa	An			
A	0.4	0.4	2.1	1.2	ND	ND	ND	—	F	—
B	0.0	0.1	0.0	0.3	ND	ND	ND	—	F	F
C	0.0	0.1	0.0	0.8	ND	ND	ND	—	F	F
D	5.0	1.3	5.0	2.5	ND	ND	ND	—	F	—
E	5.1	2.7	5.1	3.9	5.1	5.0	4.9	P	P	P
F	0.0	0.3	0.2	0.6	ND	ND	ND	—	F	F
G	2.4	5.0	3.7	5.0	5.0	5.0	ND	P	P	P
G(repeat)	0.4	2.0	2.0	2.2	5.1	2.4	3.9	F	F	F
H	2.5	5.0	4.2	5.0	5.0	5.0	ND	P	P	P

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