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APPENDIX

Hydrophilic Ointment U.S.P. XIX (19)

Methylparaben	0.25	g.
Propylparaben	0.15	g.
Sodium Lauryl Sulfate	10	g.
Propylene Glycol	120	g.
Stearyl Alcohol	250	g.
White Petrolatum	250	g.
Purified Water	370	g.
To make about	1000	g.

Melt the stearyl alcohol and the white petrolatum on a steam bath, and warm to about 75°. Add the other ingredients, previously dissolved in the water and warmed to 75°, and stir the mixture until it congeals.

Hydrophilic Petrolatum U.S.P.XIX(19)

Cholesterol	30	g.
Stearyl Alcohol	30	g.
White Wax	80	g.
White Petrolatum	860	g.
To make	1000	g.

Melt the stearyl alcohol, white wax, and white petrolatum together on a steam bath, then add the cholesterol and stir

until it completely dissolves. Remove from the bath, and stir until the mixture congeals.

Polyethylene Glycol Ointment U.S.P. XIX (19)

Polyethylene Glycol 4000	400	g.
Polyethylene Glycol 400	600	g.

Heat the two ingredients on a water bath to 65°. Allow to cool and stir until congealed. If a firmer preparation is desired, replace up to 100 g. of the polyethylene glycol 400 with an equal amount of polyethylene glycol 4000.

Note. If 6-25 % of an aqueous solution is to be incorporated in polyethylene glycol ointment, replace 50 g. of the polyethylene glycol 4000 with an equal amount of stearyl alcohol.

White Ointment U.S.P. XIX (19)

White Wax	50	g.
White Petrolatum	950	g.
To make	1000	g.

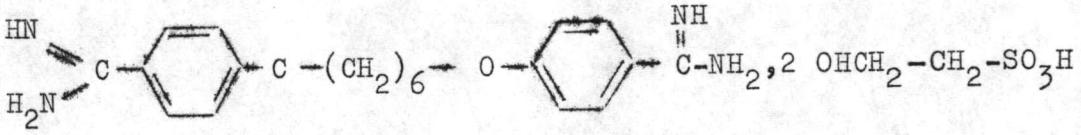
Melt the white wax in a suitable dish on a water bath, add the white petrolatum, warm until liquefied, then discontinue the heating and stir the mixture until it begins to congeal.

Hexamidine (17,26)

Synonyms : Hexomidine, Desomedine, Esomedina, RP,2535

Description : White,odorless, hygroscopic powder(with a water uptake of about 4.5 % within 24 hours at 20°C in an atmosphere of 70 % relative humidity). Hexamidine is an antiseptic with a powerful bactericidal and bacteriostatic action and a noteworthy fungistatic effect, is neither a member of the sulfonamide nor the quarternary ammonium compounds nor of the mercurial derivatives; this is Hexamidine, an antiseptic belonging to the diamidine series. Clinical experimentation confirmed the spectacular laboratory results:at present Hexamidine seems to be the most effective, the safest, and the best tolerated antiseptic available.

Formula : 4, 4′ -diamidino-diphenoxyhexane isethionate



$C_{20}H_{26}N_4O_2 + 2(C_2H_6O_4S)$ M.W. = 354.46 + 252.26

= 606.72

Solubilities at about 20°C

Water, dimethylformamide,methanol .....soluble.

Ethanol .....sparingly soluble

Ethyl ether, acetone,chloroform.....practically insoluble.

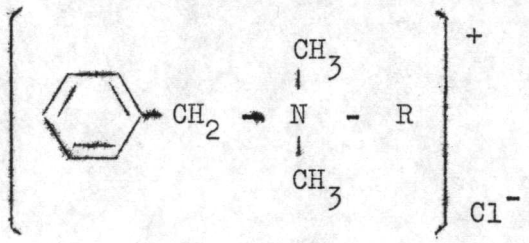
Use : Topical antiseptic.

Benzalkonium Chloride(20,27)

Synonyms : Zephiran chloride, B.T.C.Roccal.

Description : White or yellowish-white amorphous powder or thick gel or gelatinous pieces with an aromatic odor and a very bitter taste. It contains not more than 15 % of water.

Formula :



It is a mixture of alkylbenzyldimethylammoniumchlorides of the general formula $\left[C_6H_5.CH_2.N(CH_3)_2.R \right]$ Cl, in which R. represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$.

Solubilities : Very soluble in water, alcohol, and acetone; practically insoluble in ether. A solution in water is usually slightly alkaline and foams strongly when shaken.

Incompatibilities : Incompatible with soaps and other anionic surfactants, citrates, iodides, nitrates, permanganates, salicylates, silver salts, tartrates, zinc sulfate, ingredients of some commercial rubber mixes, aluminum, fluorescein sodium, hydrogen peroxide, kaolin, hydrous wool fat and some sulfonamides.

Toxic Effects and Treatment : As for cetrimide.

Precautions : Benzalkonium chloride should not be applied repeatedly to the skin and wet dressings should not be left in contact as hypersensitivity may develop.

Uses : Benzalkonium chloride is a quarternary ammonium disinfectant with properties and uses similar to those of the other cationic surfactants as described under Cetrimide.

Doses : A 0.1 to 0.2 % solution of benzalkonium chloride may be used for the pre-operative disinfection of unbroken skin. A 0.1 % solution is used for mucous membranes, denuded skin, wounds and burns. An aqueous solution not stronger than 0.005 % is used for irrigation of the bladder and urethra, and a 0.01 % solution is used as a preservative for eye drops of the B.P.C. and U.S., N.F.

Cetrimide (21,28)

Synonyms : Cetyltrimethylammonium Bromide, Cetrimonium Bromide, Hexadecyltrimethylammonium Bromide, Cetylamine, Cetavlon.

Descriptions : Cetrimide consists chiefly of tetradecyltrimethylammonium bromide together with smaller amounts of dodecyl and hexadecyltrimethylammoniumbromides. It is a white to creamy-white, voluminous, free-flowing, hygroscopic powder with a faint characteristic odor and a bitter soapy taste. A solution in water has a low surface tension and foams on shaking. A 2 % solution is clear or not more than very slightly opalescent.

Formula.

$$\left[CH_3(CH_2)_{15}N(CH_3)_3\right]^+ Br^-$$

It contains not less than 96 % of alkyltrimethylammonium bromides calculated as $C_{17}H_{38}BrN$ = 336.4

Solubilities. Soluble 1 in 2 of water; very soluble in alcohol. A 1 % solution in water has a pH of 5 to 7.5.

Incompatibilities : Incompatible with soaps and other anionic surfactants, bentonite, iodine, phenylmercuric nitrate and alkaline hydroxides, Solutions are sterilised by autoclav-

ing or by filtration. Cetrimide is stable in solution. The B.P.C. states that solutions containing up to 40 % of cetrimide may be stored and subsequently diluted, but in order to guard against contamination with Pseudomonas spp, stock solutions should contain at least 7 % V/V of alcohol or 4 V/V of isopropylalcohol. Cork closures should not be used.

Toxic Effects : When taken by mouth, cetrimide and other quarternary ammonium compounds cause nausea and vomiting. They have depolarising muscle relaxant properties and toxic symptoms include dyspnea and cyanosis due to paralysis of the respiratory muscles, possibly, leading to asphyxia. Depression of the central nervous system with convulsion, hypotension, and coma may also occur. At the concentrations used on the skin, solutions of cetrimide and other quarternary compounds do not generally cause irritation, but some patients become hypersensitivity to cetrimide after repeated applications, this is shown by excessive dryness of the skin.

Treatment of Toxic Effects : Empty the stomach by aspiration and lavage, a dilute soap solution may be used. Respiration should be assisted until spontaneous breathing is fully restored. The circulation should be maintained with infusions of plasma or suitable electrolyte solutions, or with a pressor drugs. Convulsions may be treated with the cautious use of a short-acting barbiturate such as thiopentone sodium.

Precautions : Cetrimide should not be applied repeatedly to the skin and wet dressings should not be left in contact as hypersensitivity may occur.

Uses : Cetrimide is a quarternary ammonium disinfectant with properties and uses typical of cationic surfactants. These surfactants dissociate in aqueous solution into a relatively large and complex cation, which is responsible for the surface activity, and a smaller inactive anion. In addition to the emulsifying and detergent properties usually associated with surfactants, the cationic compounds have bactericidal activity against both Gram-positive and Gram-negative organisms but higher concentrations are necessary to kill the latter type; they are, however, relativety ineffective against bacterial spores, acid-fast bacteria, viruses, and fungi.

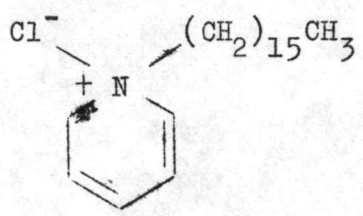
Doses : For application to the skin, solutions containing 0.1 to 1 % are used. A 0.5 % solution in alcohol (70 %) is used for pre-operative skin disinfection after all traces of soap have been removed from the skin. A 1 to 3 % solutions are used as shampoos to remove the scales in seborrhoea.

Cetylpyridinium Chloride (22,29)

Synonyms : Cetamium, Dobendan, Ceepryn chloride, 1-Hexadecylpyridinium chloride monohydrate.

Descriptions : A white powder with a slight characteristic odor, melting point 77-80°C.

Formula : The monohydrate of the quarternary salt of pyridine and cetyl chloride



$C_{21}H_{38}ClN \cdot H_2O = 358.0$

Solubilities : Soluble 1 in 20 of water; very soluble in alcohol and chloroform; slightly soluble in ether. A % solution in water has a pH of 5 to 5.4.

Incompatibilities : Incompatible with soaps and other anionic surfactants.

Toxic Effects and Treatment. As for cetrimide.

Uses : Cetylpyridinium chloride is a cationic disinfectant with properties and uses similar to those of other cationic surfactants as described under cetrimide.

Dose : A 0.1 % aqueous solution is applied to minor wounds and burns. A 1 % aqueous solution is used for pre-operative skin disinfection. For mucous membranes or large areas of exposed tissue a 0.01 to 0.02 % solution is employed.

Table 1 Releasing time and concentration of Hexamidine from 0.1 % W/W of different ointment bases at 37°C

Time (Min)	Concentrations (µg)			
	White Oint	Hydrophilic Petro.	Hydrophilic Oint	PEG Oint.
15	16.5	16.5	16.5	34.5
30	17.6	35.6	35.6	53.3
45	17.6	36.8	53.3	70.9
60	17.6	36.8	70.9	96.0
75	17.6	36.8	79.5	126.1
90	17.6	36.8	90.5	144.5
105	17.6	36.8	107.7	172.6
120	17.6	36.8	119.3	214.9

Table 2 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment with 1 % of various cationic surfactants at 37°C.

Time (Min)	Concentrations (µg)			
	PEG alone	1% Cetrimide	1 % C.P.C	1 % BZCl
15	34.5	40.5	34.5	34.5
30	53.5	61.2	53.3	53.3
45	70.9	89.4	70.9	88.9
60	96.0	107.7	100.5	107.7
75	126.1	177.8	126.4	177.8
90	144.5	215.4	144.5	221.4
105	172.6	252.1	180.1	263.0
120	214.9	305.4	215.4	324.1

Table 3 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment with 3 % of various cationic surfactants at 37°C

Time (Min)	Concentrations (µg)			
	PEG.alone	3% Cetrimide	3 % C.P.C	3 % BZCl.
15	34.5	51.0	40.5	75.0
30	53.5	61.9	61.2	90.5
45	70.9	99.9	71.4	107.7
60	96.0	126.4	106.5	143.3
75	126.1	179.0	159.8	180.1
90	144.5	228.9	181.2	233.4
105	172.6	260.5	215.4	287.8
120	214.9	323.9	231.1	358.7

Table 4 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment with 5 % of various cationic surfactants at 37°C

Time (Min)	Concentrations (µg)			
	PEG alone	5% Cetrimide	5 % C.P.C.	5 % BZCl
15	34.5	58.5	45.0	129
30	53.5	95.4	64.5	145.1
45	70.9	135.1	86.6	213.1
60	96.0	145.1	125.5	252.1
75	126.1	196.6	165.5	323.4
90	144.5	251.0	181.5	412.0
105	172.6	270.9	215.4	452.1
120	214.9	357.5	252.1	539.9

Table 5 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment with 7 % of various cationic surfactants at 37°C

Time (Min)	Concentrations (μg)			
	PEG. alone	7% Cetrimide	7 % C.P.C.	7 % BZCl
15	34.5	85.5	51.0	171.0
30	53.5	118.2	70.9	215.4
45	70.9	144.0	87.0	286.6
60	96.0	162.1	134.5	409.7
75	126.1	214.2	179.6	462.6
90	144.5	252.1	215.4	506.1
105	172.6	288.9	252.1	628.8
120	214.9	444.2	288.9	722.3

Table 6 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment with 10 % of various cationic surfactants at 37°C

Time (Min)	Concentrations (µg)			
	PEG.alone	10 %Cetrimide	10 % C.P.C.	10 % BZCl
15	34.5	102.0	54.0	289.5
30	53.5	143.3	81.6	326.8
45	70.9	162.1	93.7	361.0
60	96.0	181.2	155.9	448.7
75	126.1	233.4	214.0	505.4
90	144.5	287.8	268.6	577.8
105	172.6	358.7	324.5	718.9
120	214.9	499.7	430.0	863.0

Table 7 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment with 12 % of various cationic surfactants at 37°C

Time (Min)	Concentrations (µg)			
	12 % Cetrimide	12 % Cetyl-pyridinium Cl	12 % BZCl	PEG alone
15	171.0	67.5	340.5	34.5
30	284.4	141.0	414.2	53.5
45	342.2	223.6	503.1	70.9
60	396.6	276.8	594.3	96.0
75	434.5	317.5	685.5	126.1
90	469.8	360.5	809.7	144.5
105	524.5	414.2	868.6	172.6
120	544.5	468.6	957.5	214.9
135	596.6	506.5	1014.2	251.0
150	651.0	543.3	1052.1	288.2
165	723.4	596.6	1105.4	327.3
180	761.0	624.0	1210.8	390.1
195	814.2	738.1	1268.6	455.5
210	937.6	931.1	1341.0	525.5
225	1047.6	922.3	1447.6	590.0
240	1156.4	979.0	1539.9	682.4

Table 8 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment various concentration of Benzalkonium chloride 1:1000 solution at 37°C

Time (Min)	Concentrations (μg)				
	1 %	3 %	5 %	7 %	10 %
15	34.5	75.0	129.0	171.0	289.5
30	53.3	90.5	145.1	215.4	326.8
45	88.9	107.7	213.1	286.6	361.0
60	107.7	143.3	252.1	409.7	448.7
75	177.8	180.1	323.4	462.6	505.4
90	221.4	233.4	412.0	506.1	577.8
105	263.0	287.8	452.1	628.8	718.9
120	324.1	358.7	539.9	722.3	863.0

Table 9 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment with various concentration of Cetrimide 1:1000 solution at 37°C

Time (Min)	Concentrations (µg)				
	1 %	3 %	5 %	7 %	10 %
15	40.5	51.0	58.5	85.5	102
30	61.2	61.9	95.4	118.2	143.3
45	89.4	99.9	135.1	144	162.1
60	107.7	126.4	145.1	162.1	181.2
75	177.8	179	196.6	214.2	233.4
90	215.4	228.9	251	252.1	287.8
105	252.1	260.5	270.9	288.9	358.7
120	305.4	323.9	357.5	444.2	499.7

Table 10 Releasing time and concentration of Hexamidine from 0.1 % W/W PEG ointment with various concentration of Cetylpyridinium chloride 1:1000 solution at 37°C

Time (Min)	Concentrations (µg)				
	1 %	3 %	5 %	7 %	10 %
15	34.5	40.5	45.0	51.0	54.0
30	53.3	61.2	64.5	70.9	81.6
45	70.9	71.4	86.6	87.0	93.7
60	100.5	106.5	125.5	134.5	155.9
75	126.4	159.8	165.5	179.6	214.0
90	144.5	181.2	181.5	215.4	268.6
105	215.4	231.1	252.1	288.9	324.5
120	215.4	231.1	252.1	288.9	430.0

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