Ophthalmological Preparations

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The eye is an external organ, and is susceptible to injury, infection, and irritation, as well as to organic and functional disorders. The products and preparations for ophthalmic use therefore comprise a broad category and include medications, diagnostic agents, and medical device formulations.

Over-the-counter and prescription medications are used to treat chronic ailments (e.g., glaucoma, blepharitis, and dry eye), as well as temporary conditions (e.g., infections, allergic reactions, and injuries).

Ocular diagnostic agents are a specialized group of drugs and dyes utilized primarily for ocular examination and the identification of potential disease conditions.

Medical device products are used for the hydration, wetting, cleaning, and disinfection of contact lenses.

1. Anesthetics

Topical anesthetics diminish sensory nerve impulse generation and conduction locally, and are used to anesthetize the ocular surface during short corneal or conjunctival procedures (e.g.,

Ullman's Encyclopedia of Industrial Chemistry 5th Ed
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tonometry, removal of sutures or foreign bodies) [1]–[4]. Proxymetacaine (0.5%), oxybuprocaine (0.4%), or tetracaine (0.25–1.0%) solutions are commonly used [1]; proxymetacaine is particularly useful [4]. These agents provide rapid onset of local anesthesia of relatively short duration (e.g., one or two drops of a 0.5% proxymetacaine solution take effect within 30 s with anesthesia lasting about 15 min). Cocaine exhibits significant corneal epithelial toxicity and is now rarely used; however, it may still be employed for debridement of the corneal epithelium, as in herpetic epithelial keratitis [3], [4]. Topical application of combinations of local anesthetics does not provide additive effects but increases the risk of side effects [2].

Regional anesthetics are employed in ophthalmic surgical procedures. They are administered by injection for infiltration anesthesia or for regional nerve block (facial or retrobulbar) anesthesia [1]–[3]. Onset of action is typically 3–11 min, and anesthesia may last from 30–45 min (procaine) up to 300–600 min (etidocaine) or longer (480–720 min for bupivacaine with epinephrine) [2]. Combination of injectable anesthetics with vasoconstrictors such as epinephrine decreases the rate of systemic absorption and prolongs the duration of anesthesia.

Most of the anesthetics listed in Sections 2.1 and 2.2 are described in detail elsewhere, see → Local Anesthetics.

1.1. Topical Anesthetics

Cocaine hydrochloride [*53-21-4*], $C_{17}H_{21}NO_4 \cdot HCl$, M_r 339.8. Cocaine is not commercially available as a solution for clinical use.

Proxymetacaine hydrochloride [*5875-06-9*], 2-diethylaminoethyl 3-amino-4-propoxybenzoate monohydrochloride, proparacaine hydrochloride, $C_{16}H_{26}N_2O_3 \cdot HCl$, M_r 330.9.

Trade names: Ak-taine (Akorn); Alcaine (Alcon); Kainair (Pharmafair); Keracaine, Kcrakain (Chibret); Ocu-caine (Ocumed); Ophthaine (Squibb); Ophthetic (Allergan).

Tetracaine hydrochloride [*136-47-0*], 2-dimethylaminoethyl 4-butylaminobenzoate monohydrochloride, $C_{15}H_{24}N_2O_2 \cdot HCl$, M_r 300.8.

Trade names: Minims Amethocaine Hydrochloride (Smith & Nephew), Pontocaine (Winthrop).

Oxybuprocaine hydrochloride [*5987-82-6*], 2-diethylaminoethyl 4-amino-3-butoxybenzoate monohydrochloride, benoxinate hydrochloride, $C_{17}H_{28}N_2O_3 \cdot HCl$, M_r 344.9.

Trade names: Alcon Opulets Benoxinate (Alcon); Cebesine (Chauvin-Blanche); Conjuncain (Mann); Minims Benoxinate Hydrochloride, Minims Oxybuprocaine Hydrochloride (Smith & Nephew); Novesin (Dispersa); Novesina (Sandoz); Novesine (Chibret, Wander); Oftalmocaina, Oxibuprokain Minims (Smith & Nephew); Poen Caina, Prescaina (Llorens).

Oxybuprocaine hydrochloride (0.4%) is available in combination with sodium fluorescein (0.25%) under the trade name Fluress (Sola/Barnes-Hind) for applanation tonometry.

1.2. Regional Anesthetics

Bupivacaine hydrochloride [*18010-40-7*] (monohydrate [*14252-80-3*]), 1-butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide monohydrochloride monohydrate, $C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$, M_r 342.9.

Etidocaine hydrochloride [*36637-19-1*], *N*-(2,6-dimethylphenyl)-2-(ethylpropylamino)butanamide monohydrochloride, $C_{17}H_{28}N_2O \cdot HCl$, M_r 312.9.

Hexylcaine hydrochloride [*532-76-3*], 2-cyclohexylamino-1-methylethyl benzoate monohydrochloride, $C_{16}H_{23}NO_2 \cdot HCl$, M_r 297.8.

Lidocaine hydrochloride [*73-78-9*] (anhydrous), monohydrate [*6108-05-0*], 2-diethylaminoaceto-*N*-(2,6-dimethylphenyl)acetamide monohydrochloride monohydrate, $C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$, M_r 288.8.

Mepivacaine hydrochloride [*1722-62-9*], *N*-(2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide hydrochloride, $C_{15}H_{22}N_2O \cdot HCl$, M_r 282.8.

Prilocaine hydrochloride [*1786-81-8*], *N*-(2-methylphenyl)-2-(propylamino)propanamide hydrochloride, $C_{13}H_{20}N_2O \cdot HCl$, M_r 256.8.

Procaine hydrochloride [*51-05-8*], 2-diethylaminoethyl 4-aminobenzoate hydrochloride, $C_{13}H_{20}N_2O_2 \cdot HCl$, M_r 272.8.

Tetracaine hydrochloride (see Section 1.1).

2. Antimicrobial Agents

2.1. Antibacterial Agents

Successful therapy for bacterial infection with antibiotics relies upon five considerations:

1) Appropriate indications for use
2) Isolation and identification of the infective agent
3) Efficacy of the antibiotic for the infective agent
4) Adequate levels of the antibiotic at the site of infection
5) Low toxicity of the antibiotic for the host [5]

Antibiotics act upon bacteria through a variety of mechanisms. The penicillins, cephalosporins, vancomycin, and bacitracin inhibit development of the bacterial cell wall. Tetracycline, erythromycin, clindamycin, chloramphenicol, and the aminoglycosides inhibit protein synthesis.

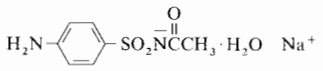
2.1.1. Sulfonamides

See also → Chemotherapeutics, **A 6**, pp. 186–192.

Although the use of sulfonamides for the treatment of major bacterial infections has been largely supplanted by antibiotics, they are still prescribed for the topical treatment of minor ocular infections. They exhibit broad-spectrum bacteriostatic activity against many gram-positive and gram-negative organisms, and are useful against the protozoa *Toxoplasma gondii* and *Plasmodium falciparum*. Some strains of *Pseudomonas, Chlamydia*, and *Actinomyces* are also sensitive to these drugs. A major disadvantage is the frequent occurrence of cross-resistant microorganisms. Many side effects have been reported following the topical administration of sulfonamides. These drugs are contraindicated for the treatment of keratoconjunctivis sicca or penetrating corneal wounds. Sulfacetamide sodium is the most widely used sulfonamide at a concentration of 10%, or in combination with the steroid prednisolone acetate (0.2–0.5%).

The sulfonamides are antimetabolites. Their structural similarities to 4-aminobenzoic acid allow them to act as competitive inhibitors in the folic acid biosynthetic pathway.

Sulfacetamide sodium [*144-80-9*], *N*-[(4-aminophenyl)sulfonyl]acetamide, $C_8H_{11}N_2NaO_3S$, M_r 238, *mp* 182–184 °C, is incorrectly called sulfacetimide. For synthesis, see [6].



Trade names: Ak-Cide, Ak-Sulf (Akorn); Bleph-10, Blephamide Liquifilm/S.O.P. (Allergan); Cetamide Ointment, Cetraprcd Ointment (Alcon); FML-S (Allergan); Isopto Cetmide Solution (Alcon); Metimyd Ophthalmic Solution/Ointment—Sterile (Schering); Ocu-Lone-C Sterile Ophthalmic Ointment/Suspension (Ocumed); Predsulfair Ointment/Suspension (Pharmafair); Sodium Sulamyd Ophthalmic Ointment 10%, Sodium Sulamyd Ophthalmic Suspension 10% (30%) Sterile (Schering); Sulf-10 Dropperettes 10%/Ophthalmic Solution 10% (IOLAB); Sulfair (Pharmafair); Sulphrin (Bausch & Lomb); Sulpred Suspension (Pharmafair); Sulten-10 (Bausch & Lomb); Vasocidin Ointment/Solution, Vasosulf (IOLAB).

Sulfadiazine [*68-35-9*] (sodium [*547-32-0*], silver [*22199-08-2*]), 4-amino-*N*-2-pyrimidinylbenzenesulfonamide, $C_{10}H_{10}N_4O_2S$, M_r 250.3, *mp* 252–256 °C. For synthesis, see [7].

Sulfamerazine sodium [*127-58-2*], 4-amino-*N*-(4-methyl-2-pyrimidinyl)benzenesulfonamide sodium salt, $C_{11}H_{11}N_4NaO_2S$, M_r 286.3. For synthesis, see [7]. Sulfamerazine sodium is a short-acting sulfonamide with action similar to that of sulfamethoxazole. It is usually administered with other sulfonamides.

Sulfamethizole [*144-82-1*], 4-amino-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide, $C_9H_{10}N_4O_2S_2$, M_r 270.3, *mp* 208 °C. For synthesis, see [8].

Sulfisoxazole diolamine [*4299-60-9*], 4-amino-*N*-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide diethanolamine, M_r 372.4. For synthesis, see [9].

Trade names: Ganstrin Ophthalmic Ointment/Solution, Suladrin, Sulfium (Roche).

2.1.2. β-Lactam Antibiotics

2.1.2.1. Penicillins

Penicillins are effective antimicrobials, although they have two drawbacks: (1) microbial resistance is relatively common, and (2) penicillins may be antigenic; anaphylactic shock is therefore a concern when they are administered systemically. See also →Antibiotics, **A 2**, pp. 473–475.

Ampicillin [*69-53-4*], (sodium derivative [*69-52-3*], trihydrate [*7177-48-2*]), $C_{16}H_{19}N_3O_4S$, M_r 349.42, *mp* 202 °C (decomp.). Ampicillin is a semisynthetic derivative of penicillin. For synthesis, see [10]. See also →Antibiotics, **A 2**, p. 508.

Methicillin sodium [*132-92-3*], $C_{17}H_{19}N_2NaO_6S$, M_r 402.42, *mp* 196–197 °C. Methicillin sodium is a semisynthetic antibiotic related to penicillin. For synthesis, see [11]. See also →Antibiotics, **A 2**, p. 507.

2.1.2.2. Cephalosporins

The cephalosporins originated from a mold of the genus *Cephalosporium*. Although cephalosporins do not usually cause an allergic reaction in patients sensitized to penicillin, allergy to cephalosporins can also develop. The cephalosporins are not inactivated by penicillin-resistant bacteria and have a broader spectrum of activity than penicillin. See also →Antibiotics, **A 2**, pp. 474–478.

Carbenicillin [*4697-36-3*] (disodium derivative [*4800-94-6*], indanyl sodium derivative [*26605-69-6*], phenyl sodium derivative [*21649-57-0*]), $C_{17}H_{18}N_2O_6S$, M_r 378.42. For synthesis, see [12]. See also →Antibiotics, **A 2**, p. 506.

Cefazolin [*25953-19-9*] (sodium salt [*27164-46-1*]), $C_{14}H_{14}N_8O_4S_3$, M_r 454.50, *mp* 198–200 °C. For synthesis, see [13]. For structure, see →Antibiotics, **A 2**, p. 477.

Cephalothin [*153-61-7*] (cephalothin sodium [*58-71-9*]), $C_{16}H_{15}N_2NaO_6S_2$, M_r 418, *mp* 160 °C. Cephalothin is a semisynthetic cephalosporin antibiotic. For synthesis, see [14]. For structure, see →Antibiotics, **A 2**, p. 477.

2.1.3. Tetracycline Antibiotics

Tetracyclines reversibly block protein synthesis by specifically binding to the bacterial ribosome. Tetracycline and chloramphenicol were the first broad-spectrum antimicrobials discovered. The tetracycline antibiotics listed below are described in detail elsewhere; see →Antibiotics, **A 2**, pp. 484, 485, 516.

Chlortetracycline hydrochloride [*64-72-2*] (chlortetracycline [*57-62-5*]), $C_{22}H_{24}Cl_2N_2O_8$, M_r 493.9. Chlortetracycline is isolated from *Streptomyces aureofaciens* [15].

Trade name: Aureomycin Ophthalmic (IOLAB).

Oxytetracycline [*79-57-2*] (hydrochloride [*2058-46-0*]), $C_{22}H_{24}N_2O_9$, M_r 460.44, is an antibiotic isolated from the fermentation of *Streptomyces rimosus* [16].

Trade name: Terramycin (5 mg/mL) with Polymyxin B Ointment (10000 U/mL) (Roerig).

Tetracycline [*60-54-8*] (hydrochloride [*64-75-5*], phosphate complex [*1336-20-5*]), $C_{22}H_{24}N_2O_8$, M_r 444.43, is an antibiotic produced by *Streptomyces* spp. [17], [18].

Trade names: Achromycin and Achromycin Ophthalmic Ointment 1% (IOLAB).

2.1.4. Aminoglycoside Antibiotics

The aminoglycoside antibiotics exhibit broad-spectrum antimicrobial activity, particularly against gram-negative organisms (→Antibiotics, **A 2**, pp. 485–491). They inhibit protein synthesis and decrease translational efficiency through interaction with the 30 S subunit of bacterial ribosomes. Cross resistance exists among the aminoglycosides.

Aminoglycosides are generally administered topically because systemic adsorption may produce oto- and nephrotoxicity. Aminoglycosides and β-lactam antibiotics are incompatible in the same formulation. Aminoglycosides are not effective under acid conditions, in high salt concentrations, or against intracellular bacteria.

Framycetin sulfate [*4146-30-9*], [*28002-70-2*], the sulfate of neomycin B, $C_{23}H_{46}N_6O_{13} \cdot 3\,H_2SO_4$, M_r 908.9. Neomycin B is isolated from the mixture of neomycins A, B, and C produced by *Streptomyces fradiae*; see also →Antibiotics, **A 2**, p. 520 [19]. Framycetin sulfate has broad-spectrum activity similar to that of neomycin but is more efficacious against *Pseudomonas* spp. Unlike most other aminoglycosides, framycetin sulfate can be administered by subconjunctival injection; however, because of its high degree of systemic absorption, extreme caution must be employed to avoid toxicity.

Trade names: Framygen (Fisons), Soframycin (Roussel), with 0.5% hydrocortisone acetate in Framycort (Fisons), with 0.05% dexamethasone and 0.005% gramicidin in Sofradex (Roussel).

Gentamicin sulfate [*1405-41-0*] (gentamycin [*1403-66-3*]) is a complex mixture of the sulfates of gentamicin C_1, C_{1a}, and C_2. This complex is produced by fermentation of *Micromonospora purpurea* [20]; see also →Antibiotics, **A 2**, p. 519. Gentamicin sulfate is used as a drop, ointment, or buffered preserved solution, generally at a concentration of 0.3%.

Trade names: Alcomicin (Alcon); Cidomycin (Roussel); Garamycin (Kirby-Warrick); Garamycin Ophthalmic Ointment/Solution—Sterile (Schering); Genopyic (Allergan); Gentacidin (CooperVision); Gentafair (Pharmafair); Genticina (Antibioticos); Genoptic Liquifilm Sterile Ophthalmic Solution (Allergan); Genoptic S.O.P. Sterile Ophthalmic Ointment (Allergan); Gentafair Cream and Ointment/Solution (Pharmafair); Gentak Ointment and Solution (Akorn); Genticidin Ointment/Solution (IOLAB); Gentrasul Ointment/Solution (Bausch & Lomb); Minims Centamicin Sulfate (Smith & Nephew); Ocu-Mycin Sterile Ophthalmic Ointment/Solution (Ocumed); Pred-G Liquifilm Sterile Ophthalmic Suspension (Allergan); Pred-G S.O.P. Sterile Ophthalmic Ointment (Allergan).

Micronomicin sulfate (micronomicin [*52093-21-7*]), $(C_{20}H_{41}N_5O_7)_2 \cdot 5\,H_2SO_4$, M_r 1417.5, *mp* 260 °C. This gentamicin C complex antibiotic is produced by *Micromonospora sagamiensis* var. *nonreducans* [21].

Trade names: Sagamicin (Kyowa), Santemycin (Santen).

Neomycin [*1404-04-2*] is an antibiotic complex made up of neomycins A, B, and C from *Streptomyces fradiae* [22]–[24]. See also →Antibiotics, **A 2**, p. 520.

Trade names: Ak-Spore (H.C.) Ointment/Solution, Ak-Trol Ointment & Suspension (Akorn); Cortisporin Ophthalmic Ointment/Suspension (Burroughs Wellcome); Dexacidin Ointment/Suspension (IOLAB); Dexasporin Ointment/Suspension (Pharmafair); Infectrol Ointment/Suspension (Bausch & Lomb); Maxitrol Ophthalmic Ointment/Suspension (Alcon); NeoDecadron Sterile Ophthalmic Ointment (Merck Sharp & Dohme); Neo Dexair Ophthalmic Solution (Pharmafair); Neosporin Ophthalmic Ointment/Solution (Burroughs Wellcome); Neotricin Ointment/Solution (Bausch & Lomb); Ocu-Cort Sterile Ophthalmic Ointment, Ocu-Spor-B Sterile Ophthalmic Ointment, Ocu-Spor-G Sterile Ophthalmic Solution (Ocumed); Ocutricin HC Ointment/Suspension, Ocutricin Ointment/Solution (Pharmafair); Ocu-Trol Sterile Ophthalmic Ointment/Suspension (Ocumed); Poly-Pred Liquifilm (Allergan).

Sisomicin [*32385-11-8*] (sulfate [*53179-09-2*]), $C_{19}H_{37}N_5O_7$, M_r 447.6, monohydrate from ethanol, *mp* 198–201 °C. Sisomicin is an antibiotic produced by *Micromonospora inyoesis* [25]. It is usually administered systemically and not commonly used as an ophthalmic antibiotic. See also →Antibiotics, **A 2**, p. 522.

Streptomycin sulfate [*3810-74-0*] (streptomycin [*57-92-1*]), $C_{42}H_{84}N_{14}O_{36}S_3$, M_r 1457.40. Streptomycin is produced by *Streptomyces griseus* [26]; see also →Antibiotics, **A 2**, p. 521. Corneal penetration of streptomycin is poor but can be greatly enhanced by iontophoresis.

Tobramycin [*32986-56-4*] (sulfate [*79645-27-5*]), $C_{18}H_{37}N_5O_9$, M_r 467.5. Tobramycin is produced by *Streptomyces tenebrarius* [27]. See also →Antibiotics, **A 2**, p. 318. Tobramycin has a broad spectrum of activity similar to that of gentamicin. Cross resistance of tobramycin and gentamicin has been observed. Tobramycin is four times more effective against *Pseudomonas aeruginosa*, and less effective against *Serratia*, than gentamicin. Unlike other aminoglycosides, tobramycin is ineffective against mycobacteria.

Trade names: TobraDex Ophthalmic Suspension and Ointment, TobraLex, Tobral, Tobramaxin, Tobrex (Alcon); Tobra-Gobens (Normon); Tobra-Laf (Andalucia).

2.1.5. Polypeptide Antibiotics

Bacitracin [*1405-87-4*], bacitracin A (major component): $C_{66}H_{103}N_{17}O_{16}S$, M_r 1422.71. Commercial bacitracin is a mixture of at least nine bacitracins produced by *Bacillus subtilis* and *B. licheniformis* [28], [29]; see →Antibiotics, **A 2**, p. 528. It is available singly only as an ointment (500 mg/g) and in combination with other antimicrobials (see Table 1).

Trade names: Ak-Poly-Bac Ointment, Ak-Spore (H.C.) Ointment (Akorn); Bacitracin Ophthalmic Ointment Sterile (Pharmafair); Cortisporin Ophthalmic Ointment Sterile, Neosporin Ophthalmic Ointment Sterile (Burroughs Wellcome); Neotricin Ointment/Solution (Bausch & Lomb); Ocumycin (HC) Ointment (Pharmafair); Polysporin Ophthalmic Ointment Sterile (Burroughs Wellcome).

Colistimethate sodium [*8068-28-8*], $C_{58}H_{105}N_{16}Na_5O_{28}S_5$, M_r 1749.8. Colistimethate sodium is an injectable form of colistin, a cyclopolypeptide produced by *Bacillus colistinus* [30]. See also →Antibiotics, **A 2**, p. 528.

Trade name: Coly-Mycin M (Parke-Davis).

Polymyxin B sulfate [*1405-20-5*] is a mixture of polymyxins B_1 and B_2 produced by *Bacillus polymyxa* [31], [32]. See also →Antibiotics, **A 2**,

Table 1. Combination antibiotic solutions and ointments*

Product	Polymyxin B sulfate, units/g	Neomycin, mg/g	Bacitracin, units/g	Oxytetracycline, mg/g	Gramicidin, mg/mL	Company
Neotal Ophthalmic Ointment	5000	5	400			Hauck
Terramycin with Polymyxin B Ointment	10000			5		Roerig
Ak-Poly-Bac Ointment	10000		500			Akorn
Polysporin Ointment	10000		500			Burroughs Wellcome
Neomycin Sulfate–Polymyxin B Sulfate–Gramicidin Solution	10000*	1.75**			0.025	Rugby
Ak-Spore Solution	10000*	1.75**			0.025	Akorn
Neocidin Solution	10000*	1.75**			0.025	Major
Neosporin Ophthalmic Solution	10000*	1.75**			0.025	Burroughs Wellcome
Neotricin Opthalmic Solution	10000*	1.75**			0.025	Bausch & Lomb
Statrol Ointment	10000	3.5				Alcon
Ak-Spore Ointment	10000	3.5	400			Akorn
Neosporin Ophthalmic Ointment	10000	3.5	400			Burroughs Wellcome
Neotricin Ointment	10000	3.5	400			Bausch & Lomb
Mycitracin Ophthalmic Ointment	10000	3.5	500			Upjohn
Statrol Solution	16250*	3.5**				Alcon

* Units/mL. ** mg/mL.

p. 527. Polymyxins are cyclic polypeptides that are similar to detergents in having basic groups with a fatty acid side chain. They exert their antimicrobial effect by solubilizing the cell membrane. Polymyxin B sulfate is available as a sterile powder for reconstitution or in combination with other antimicrobials (see Table 1).

Trade names: Ak-Poly-Bac Ointment, Ak-Spore (H.C.) Ointment/Suspension, Ak-Trol Ointment & Suspension (Akorn); Cortisporin Ophthalmic Ointment/Suspension (Burroughs Wellcome); Dexacidin Ointment/Suspension (IOLAB); Dexasporin Ointment/Suspension (Pharmafair); Infectrol Ointment/Suspension (Bausch & Lomb); Maxitrol Ophthalmic Ointment/Suspension (Alcon); Neosporin Opthalmic Ointment/Ophthalmic Solution Sterile (Burroughs Wellcome); Neotricin Ointment/Solution (Bausch & Lomb); Ocu-Cort Sterile Ophthalmic Ointment (Ocumed); Ocumycin Ointment (Pharmafair); Ocu-Spor-B Sterile Ophthalmic Ointment, Ocu-Spor-G Sterile Ophthalmic Solution (Ocumed); Ocutricin HC Ointment/Suspension, Ocutricin Ointment/Solution (Pharmafair); Ocu-Trol Sterile Ophthalmic Ointment/Suspension (Ocumed); Opthocort (Parke-Davis); Polymyxin B Sulfate Sterile Ophthalmic (Pfizer); Poly-Pred Liquifilm (Allergan); Polysporin Ophthalmic Ointment Sterile (Burroughs Wellcome).

2.1.6. Miscellaneous Antimicrobial Agents

Chloramphenicol [*56-75-7*], $C_{11}H_{12}Cl_2N_2O_5$, M_r 323.1, *mp* 150.5–151.5 °C, is a broad-spectrum antibiotic produced by *Streptomyces venezuelae* [33]–[35]. Chloramphenicol reversibly blocks the bacterial ribosome, inhibiting protein synthesis. See also →Antibiotics, **A 2**, p. 535.

Trade names: Ak-Chlor Sterile Ophthalmic Ointment/Solution (Akorn); Chlorofair Ointment/Solution (Pharmafair); Chloromycetin Ophthalmic Ointment/Solution/Powder, Hydrocortisone Ophthalmic Solution (Parke-Davis); Chloroptic S.O.P., Chloroptic Sterile Ophthalmic Solution (Allergan); Ocu-Chlor Sterile Opthalmic Ointment/Solution (Ocumed); Opthochlor Ophthalmic Solution (Parke-Davis).

Clindamycin [*18323-44-9*] (palmitate hydrochloride [*25507-04-4*], hydrochloride monohydrate [*58207-19-5*]), $C_{18}H_{33}ClN_2O_5S$, M_r 424.98, is a semisynthetic antibiotic prepared from lincomycin [36]. See also →Antibiotics, **A 2**, p. 534.

Trade name: Cleocin Phosphate (Upjohn).

Erythromycin [*114-07-8*], $C_{37}H_{67}NO_{13}$, M_r 733.9, *mp* 135–140 °C, resolidifies with second *mp* 190–193 °C. Erythromycin is produced by *Streptomyces erythreus* [37] and is a mixture of erythromycin A, B, and C, with A predominant. It is the most widely used of the macrolide anti-

biotics and exerts its effect at the level of protein synthesis by reversibly inhibiting the bacterial ribosome. See also →Antibiotics, **A 2**, pp. 494, 523.

Trade names: Ak-Mycin Ointment (Akorn), Erythromycin Ophthalmic Ointment (Pharmafair), Ilotycin (Dista).

Lincomycin [*154-21-2*], $C_{18}H_{34}N_2O_6S$, M_r 406.6, is an antibiotic produced by *Streptomyces lincolnensis* var. *lincolnensis* [38], [39]. Lincomycin reversibly inhibits the bacterial ribosome. See also →Antibiotics, **A 2**, p. 534.

Trade name: Lincocin (Upjohn).

Ofloxacin [*82419-36-1*], $C_{18}H_{20}FN_3O_4$, M_r 361.4, *mp* 250–257 °C, is a broad-spectrum, fluorinated quinoline antibacterial. See also →Chemotherapeutics, **A 6**, p. 184. For synthesis, see [40]. It is currently in clinical trials by Allergan.

Silver nitrate [*7761-88-8*], $AgNO_3$, M_r 169.9, *mp* 212 °C, is used to treat the eyes of newborns. Caution should be used with repeated applications because cauterization of the cornea and blindness may result. Silver nitrate is incompatible with sulfacetamide preparations.

Trade name: Silver Nitrate (Lilly).

Vancomycin [*1404-90-6*] (hydrochloride [*1404-93-9*]), $C_{66}H_{75}Cl_2N_9O_{24}$, M_r 1449.2. Vancomycin is an amphoteric glycopeptide produced by *Streptomyces orientalis* [41]. It inhibits cell wall synthesis. See also →Antibiotics, **A 2**, p. 530.

Trade names: Vancocin (Lilly), Vancoled (Lederle), Vancor (Adria).

2.2. Antifungal Agents

For general information see →Antimycotics.

Ocular fungal infection is a rare disease but is increasing in occurrence [42]–[44]. Commensal fungi commonly present in the eye include *Aspergillus, Penicillium, Candida, Fusarium*, and *Rhodotorula*. These may become opportunistic pathogens if the eye's defenses are compromised by physical trauma or an underlying disease such as diabetes.

Although natamycin is the only antifungal agent currently available commercially in the United States as a topical ophthalmic formulation, other antifungal drugs (including polyenes and imidazoles) have been used topically in dilute solution or suspension [45].

The *polyene antimycotics* (amphotericin B, nystatin, natamycin) are insoluble in water and unstable in oxygen, light, water, heat, and at extreme pH. Their biological specificity for yeast relies on preferential binding to yeast membranes via ergosterol over their affinity for cholesterol, the primary sterol in mammalian cell membranes. Cell death is induced by increasing the permeability of the fungal membrane, allowing depletion of intracellular components.

The *imidazoles* (miconazole and ketoconazoles) have a broad antifungal and antimicrobial spectrum, with significantly less toxicity than the polyenes. Antifungal effects may result from the inhibition of estergol synthesis, leading to cell membrane permeability. Miconazole physically disrupts the membrane, leading to cell lysis. High concentrations of miconazole also increase intracellular concentrations of hydrogen peroxide, presumably through inhibition of cytochrome C peroxidase.

Flucytosine is a widely used *pyrimidine antimycotic*.

Amphotericin B [*1397-89-3*], $C_{47}H_{73}NO_{17}$, M_r 924.1, is a polyene antibiotic produced by *Streptomyces nodosus* [46]. Amphotericin can be administered parenterally for systemic mycosis. Topical administeration of 0.1 and 0.25% has been effective for the treatment of keratomycoses. See also →Antimycotics, **A 3**, p. 78.

Trade name: Fungizone (Squibb).

Nystatin [*1400-61-9*] is a polyene antifungal antibiotic complex containing three active components (A_1, A_2, and A_3) produced by several *Streptomyces* spp. [47]. See also → Antimycotics, **A 3**, p. 78. Nystatin is effective in topical application for ocular infection.

Trade names: Mycostatin (Squibb), Nilstat (Lederle), Nystex (Savage), O-V Statin (Squibb).

Natamycin [*7681-93-8*], $C_{33}H_{47}NO_{13}$, M_r 665.75, *mp* 280–300 °C (decomp.), is a polyene antibiotic produced by *Streptomyces natalensis* and *S. chattanoogensis* [48]. See also →Antimycotics, **A 3**, p. 79. Natamycin is the least toxic, least irritating, and most stable polyene. It is only useful, however, for the treatment of super-

ficial keratomycosis because it penetrates tissue poorly.

Trade name: Natacyn (Alcon).

Miconazole [*22916-47-8*] (nitrate [*22832-87-7*]), $C_{18}H_{14}Cl_4N_2O$, M_r 416.12. See also →Antimycotics, **A3**, p. 82. For synthesis, see [49].

Trade names: Micatin, Monistat-Derm (Ortho).

Ketoconazole [*65277-42-1*], $C_{26}H_{28}Cl_2N_4O_4$, M_r 531.44, *mp* 146 °C, is an orally active, broad-spectrum antimycotic. See also →Antimycotics, **A3**, pp. 83–84. For synthesis, see [50].

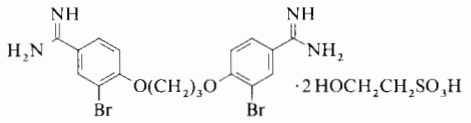
Trade name: Nizoral (Janssen).

Flucytosine [*2022-85-7*], 5-fluorocytosine, $C_4H_4FN_3O$, M_r 129.1, *mp* 295–297 °C (decomp.). For synthesis, see [51]. Flucytosine, a fluorinated pyrimidine, is metabolized to either 5-fluorouracil, an inhibitor of RNA synthesis, or 5-fluoro-2′-deoxyuridylic acid, a potent inhibitor of DNA synthesis. Flucytosine has a limited spectrum of activity but is effective in topical application against external infections. It exhibits poor ocular penetration but can be administered orally. See also →Antimycotics, **A3**, pp. 84–85.

Trade name: Ancobon (Hoffmann–La Roche).

2.3. Antiprotozoal Agents

Broline [*496-00-4*], 4,4′-(trimethylenedioxy)-bis(3-bromobenzamidine), $C_{21}H_{30}Br_2N_4O_{10}S_2$, M_r 722.4, *mp* 226 °C, is used to treat *Acanthamoeba* keratitis infections [52]. For synthesis, see [53].



Trade names: Brolene Eye Drops (Bausch & Lomb); Broline Ointment, Brulidene (May & Baker).

Sulfadiazine [*68-35-9*] (silver salt [*22199-08-2*]), 4-amino-*N*-2-pyrimidinylbenzenesulfonamide, $C_{10}H_{10}N_4O_2S$, M_r 250.3, *mp* 252–256 °C. For synthesis, see [7]. See also →Chemotherapeutics, **A6**, p. 190. This compound is used to treat toxoplasmic retinochoroiditis in triple sulfonamide mixtures with sulfamerazine and sulfamethazine.

Trade names: Coco-Diazine (Lilly), Eskadiazine (SKF).

Antibiotic–Corticosteroid Preparations. A variety of ophthalmic antibiotic–corticosteroid combination preparations are available for treating protozoal infections. Ophthalmic applications of corticosteroids and corticosteroid–antibiotic combination preparations are discussed in Section 3.1.

2.4. Antiviral Agents

Currently marketed antivirals are available only as topical applications for the treatment of infection with the herpes simplex virus (HSV). These agents inhibit viral replication at the level of DNA synthesis. The prophylactic use of antivirals may reduce the frequency of viral latency [54]. The use of high dosages does not rid the host of latent virus but may reduce the frequency of recurrences during therapy [55].

Acyclovir [*59277-89-3*], $C_8H_{11}N_5O_3$, M_r 225.2, *mp* 256.5–257 °C, is an orally active acyclic nucleoside used against HSV. It is also used as a 3% ointment in HSV infections of the epithelium. For synthesis, see [56]. See also →Chemotherapeutics, **A6**, p. 216.

Trade name: Zovirax (Burroughs Wellcome).

Idoxuridine [*54-42-2*], 2′-deoxy-5-iodouridine, $C_9H_{11}IN_2O_5$, M_r 354.1. Idoxuridine is a functional analogue of the nucleoside thymidine; see →Chemotherapeutics, **A6**, p. 217. Incorporation into DNA results in death of the viral particle through DNA base-pair mismatches and mutation. The toxicity of the substance is attributable to its incorporation into the host cell DNA. This agent is best used topically on a superficial lesion and is available as a 0.1% solution or a 0.5% ointment. For synthesis, see [57].

Trade names: Herpex (Allergan); Stoxil Ointment, Stoxil Solution (SKF).

Trifluridine [*70-00-8*], 2′-deoxy-5-(trifluoromethyl)uridine, $C_{10}H_{11}F_3N_2O_5$, M_r 296.2, *mp* 186–189 °C. Trifluridine is a thymidine analogue but unlike idoxuridine is rapidly metabolized and thus less toxic. Trifluridine is effective against HSV [58] and, in addition, is compatible with corticosteroids [59]. See also →Chemotherapeutics, **A6**, p. 217. Trifluridine is generally available as a 1% solution or a 3% ointment. For synthesis, see [60].

Trade names: TFT-Ophtiole (Mann), TFT Eye Ointment (Mann), Viroptic (Burroughs Wellcome).

Vidarabine (anhydrous [*5536-17-4*], monohydrate [*243566-66-9*]), $C_{10}H_{13}N_5O_4 \cdot H_2O$, M_r 285.3, *mp* 257–257.5 °C, is an adenosine analogue produced by *Streptomyces antibioticus*. Its mechanism of action is similar to that of idoxuridine. The number and severity of adverse reactions of the two drugs are not significantly different, although vidarabine has been used to treat cases unresponsive to idoxuridine [61]. Vidarabine is available as a 3% ointment. See also → Chemotherapeutics, **A 6**, pp. 217–218.

Trade name: Vira-A (Parke-Davis).

3. Anti-inflammatory Agents

A variety of agents are available for the treatment of ocular inflammatory conditions, including corticosteroids, nonsteroidal anti-inflammatory agents that block mediator synthesis or release, and, more rarely, immunosuppressive agents. For general information, see →Anti-inflammatory–Antirheumatic Drugs.

3.1. Corticosteroids

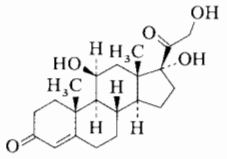
For general information, see → Hormones, **A 13**, pp. 134–154.

Corticosteroids are widely used for the treatment of ocular inflammation [62]–[64]. Prednisolone, hydrocortisone, dexamethasone, medrysone, and fluorometholone are available in topical ocular preparations (suspension, ointment, or solution). In certain cases, topical application may be supplemented or replaced by systemic or periocular administration (e.g., severe anterior uveitis and inflammation of the posterior segment, optic nerve, or orbit) [62], [63].

The use of corticosteroids is not without potential ocular and systemic side effects (e.g., elevated intraocular pressure, posterior subcapsular cataracts, and inhibition of epithelial wound healing [60], [62], [65]–[67]). Because corticosteroids have immunosuppressive properties, resistance to infection is lowered. Accordingly, a number of ophthalmic preparations containing combinations of corticosteroids and antimicrobial agents are available for anti-inflammatory/anti-infective therapy (Tables 2 and 3).

Hydrocortisone [*50-23-7*], 17-hydroxycorticosterone, cortisol, $C_{21}H_{30}O_5$, M_r 362.5. See also → Hormones, **A 13**, pp. 137–141.

Hydrocortisone (1%) is available in antimicrobial–anti-inflammatory ointment or suspension combination products (Tables 2 and 3).

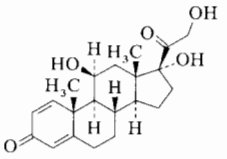


Trade names: Ak-Spore ointment (Akorn; hydrocortisone, neomycin sulfate and polymyxin B sulfate); Cortisporin ointment (Burroughs Wellcome: hydrocortisone, polymyxin B sulfate, neomycin sulfate, and bacitracin zinc); Cortisporin suspension (Burroughs Wellcome: hydrocortisone, neomycin sulfate, and polymyxin B sulfate); Ocu-Cort ointment (Ocumed: hydrocortisone, polymyxin B sulfate, neomycin sulfate, and bacitracin zinc); Ocutricin HC ointment (Pharmafair: hydrocortisone, bacitracin zinc, polymyxin B sulfate, and neomycin sulfate); Ocutricin HC suspension (Pharmafair: hydrocortisone, neomycin sulfate, and polymyxin B sulfate).

Hydrocortisone acetate [*50-03-3*], hydrocortisone 21-acetate, cortisol acetate, $C_{23}H_{32}O_6$, M_r 404.5.

Trade names: Hydrocortone (Merck Sharp & Dohme), Optef (Upjohn); also see Tables 2 and 3.

Prednisolone [*50-24-8*], 1,2-dehydrohydrocortisone, $C_{21}H_{28}O_5$, M_r 360.5. See also → Hormones, **A 13**, pp. 143–144.



Prednisolone acetate [*52-21-1*], prednisolone 21-acetate, $C_{23}H_{30}O_6$, M_r 402.5.

Trade names: Ak-Tate (Akorn); Econopred, Econopred Plus (Alcon); Ocu-pred A (Ocumed); Pred Forte, Pred Mild (Allergan); see also Tables 2 and 3.

Prednisolone sodium phosphate [*125-02-0*], prednisolone 21-(disodium orthophosphate), $C_{21}H_{27}Na_2O_8P$, M_r 484.4, is water soluble and is available as solutions.

Trade names: Ak-Pred—0.125% and 1% (Akorn); I-Pred and I-Pred 1% (Americal); Inflamase Forte 1%, Inflamase Mild (IOLAB); Ocu-Pred, Ocu-Pred Forte (Ocumed); Predair, Predair Forte (Pharmafair); see also Tables 2 and 3.

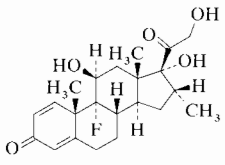
Table 2. Steroid and antibiotic drops

Product	Steroid	Antibiotic	Company
Chlormycetin Hydrocortisone Powder	0.5% hydrocortisone acetate	0.25% chloramphenicol	Parke-Davis
Neo-Cortef Suspension	0.5% hydrocortisone acetate	neomycin sulfate equivalent to 0.35% base	Upjohn
Bacticort Suspension	1% hydrocortisone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/mL	Rugby
Triple-Gen Suspension	1% hydrocortisone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/mL	Goldline
Cortisporin Suspension	1% hydrocortisone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/mL	Burroughs Wellcome
Terra-Cortil Suspension	1.5% hydrocortisone acetate	0.5% oxytetracycline	Roerig
Ak-Neo-Cort Suspension	1.5% hydrocortisone acetate	neomycin sulfate equivalent to 0.35% base	Akorn
Cor-Oticin Suspension	1.5% hydrocortisone acetate	neomycin sulfate equivalent to 0.35% base	Americal
Ortho Drops Suspension	1.5% hydrocortisone acetate	neomycin sulfate equivalent to 0.35% base	Vortech
Poly-Pred Suspension	0.5% prednisolone acetate	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/mL	Allergan
Pred-G Suspension	1% prednisolone acetate	gentamycin sulfate equivalent to 0.3% gentamycin base	Allergan
NeoDecadron Solution	0.1% dexamethasone phosphate	neomycin sulfate equivalent to 0.35% base	MSD
TobraDex Suspension	0.1% dexamethasone	0.3% tobramycin	Alcon
Dexasporin Suspension	0.1% dexamethasone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/mL	Pharmafair, Rugby, and others
Ak-Trol Suspension	0.1% dexamethasone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/mL	Akorn
Dexacindin Suspension	0.1% dexamethasone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/mL	IOLAB
Maxitrol Suspension	0.1% dexamethasone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/mL	Alcon

Table 3. Steroid and antibiotic ointments

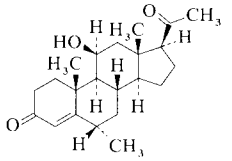
Product	Steroid	Antibiotic	Company
Orthocort	0.5% hydrocortisone acetate	1% chloramphenicol and 10000 units polymyxin B/g	Parke-Davis
Cortisporin	1% hydrocortisone	neomycin sulfate equivalent to 0.35% base, 400 units bacitracin zinc, and 10000 units polymyxin B sulfate/g	Burroughs Wellcome
Coracin	1% hydrocortisone acetate	0.5% neomycin sulfate, 400 units bacitracin zinc and 10000 units polymyxin B sulfate/g	Coracin
NeoDecadron	0.05% dexamethasone phosphate	neomycin sulfate equivalent to 0.35% neomycin base	MSD
AK-Trol	0.1% dexamethasone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/g	Akorn
Dexacidin	0.1% dexamethasone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/g	IOLAB
Dexasporin	0.1% dexamethasone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/g	Pharmafair, Rugby, and others
Maxitrol	0.1% dexamethasone	neomycin sulfate equivalent to 0.35% base and 10000 units polymyxin B sulfate/g	Alcon

Dexamethasone [*50-02-2*], 9α-fluoro-16α-methylprednisolone, $C_{22}H_{29}FO_5$, M_r 392.5. See also → Hormones, **A 13**, pp. 147–149.



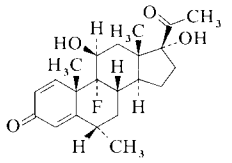
Trade names: Ak-Dex, Ak-Trol (Akorn); Baldex (Bausch & Lomb); Dexacidin (IOLAB); Decadron Phosphate (Merck Sharp & Dohme); Dexair (Pharmafair); Dexasporin (Pharmafair); Infectrol (Bausch & Lomb); Maxidex, Maxitrol (Alcon); I-Methasone (Americal); Ocu-Trol (Ocumed); Tobradex (Alcon); see also Tables 2 and 3.

Medrysone [*2668-66-8*], 11β-hydroxy-6α-methylprogesterone, $C_{22}H_{32}O_3$, M_r 344.5.



Trade names: HMS Liquifilm, Ipoflogin (Allergan); Medrifar (Farmila); Medriusar (Difa); Ophtocortin (Winzer); Sedesterol (Poen); Spectramedryn (Allergan); Visudrisone (LOA).

Fluorometholone [*426-13-1*], $C_{22}H_{29}FO_4$, M_r 376.5, is used ophthalmically as a 0.1 or 0.25% suspension or as a 0.1% ointment. See also → Hormones, **A 13**, pp. 146–147.



Trade names: Flucon, Isopto-Flucon (Alcon); FML Liquifilm, FML Forte Liquifilm, FML S.O.P. (Allergan); Fluor-Op (IOLAB).

3.2. Miscellaneous Anti-inflammatory Agents

Disodium cromoglycate [*15826-37-6*], DSCG, cromolyn sodium, sodium cromoglycate, $C_{23}H_{14}Na_2O_{11}$, M_r 5123, appears to achieve its antiallergic and anti-inflammatory effects by stabilizing mast cells and inhibiting antigen-induced mast cell degranulation and the associated release of a variety of inflammatory mediators [62], [68]. See also →Antiallergic Agents, **A 2**, pp. 429–430. Topical ophthalmic DSCG (Opticrom, Fisons) is available for prophylactic treatment of allergic disorders such as vernal or allergic keratoconjunctivitis. Maintaining DSCG therapy throughout the allergy season may be more advantageous than sporadic treatment of flare-ups [68]. Therapy with DSCG may permit the reduction or elimination of topical corticosteroid treatment [62].

Trade names: Opticrom (Fisons), Vividrin (Mann).

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclooxygenase, which is responsible for the first step in the synthesis of prostaglandins from arachidonic acid. The prostaglandins mediate certain steps of the inflammatory process. The role of arachidonic acid metabolites in ocular inflammation and pressure elevation continues to emerge [62]. Oral administration of NSAIDs has been approached as an alternative to corticosteroid anti-inflammatory therapy [62], [65]. Oral administration of classical cyclooxygenase inhibitors (e.g., acetylsalicyclic acid and indomethacin) has met with mixed success in the treatment of ocular inflammation, partially due to systemic intolerance (e.g., gastrointestinal side effects). A number of more recently developed NSAIDs such as diflusinal (Dolobid) and naproxen (Naprosyn) may be better tolerated orally.

Flurbiprofen [*5104-49-4*], 2-fluoro-α-methyl-(1,1′-biphenyl)-4-acetic acid, $C_{15}H_{13}FO_2$, M_r 244.3. The sodium salt dihydrate of flurbiprofen is available as an ophthalmic solution (0.03%) for topical application (Ocufen Liquifilm, Allergan) for inhibition of intraoperative miosis.

Tetracycline (see Section 2.1.3) is used to treat ocular rosacea [69].

Immunosuppressive agents, including alkylating agents such as cyclophosphamide, the folic acid antimetabolite methotrexate, and the antibiotic cyclosporin A, are systemically cytotoxic and dangerous drugs. Although their use in ocular therapy is rare, some of them have been used to treat intractable and progressively destructive ocular conditions [65].

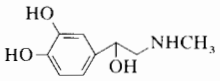
4. Antiglaucomatous Agents

Glaucoma is a leading cause of blindness and may be defined as a loss of visual function and optic nerve damage associated with an elevated intraocular pressure (IOP). Ocular hypertension alone is not predictive of glaucoma or visual impairment [70]. In a healthy eye, the IOP (ca. 2–2.6 kPa, 15–20 mm Hg) [71] is maintained by a balance of aqueous humor formation and outflow. Glaucoma therapy often involves a reduction in IOP by increasing outflow or decreasing production. A variety of therapeutic agents have ocular hypotensive effects [68]–[74] and include adrenergic agents, miotics, carbonic anhydrase inhibitors, and hyperosmotic agents. The applications and adverse effects of ocular hypotensives are discussed in [70]–[80].

Glaucoma associated with congenital ocular abnormalities is treated surgically or with a combination of surgical and medical therapy. Glaucomas may be classified as primary (direct disturbance of the aqueous circulation) or secondary (arising from other disease states). They are also classified as open angle or narrow angle, depending on the anterior chamber angle (the anatomy of the structures within the angle of the eye as visualized by gonioscopy). These classifications are important in determining whether surgery or drug therapy should be employed and which ocular hypotensive drug therapies may be appropriate.

4.1. Sympathomimetic Drugs

Epinephrine [*51-43-4*], adrenaline, $C_9H_{13}NO_3$, M_r 183.2, is used widely in primary open-angle glaucoma but is contraindicated in narrow-angle glaucoma [70], [71] because of its mydriatic effects (dictation of the pupil). Topically applied epinephrine has mydriatic, vasoconstricting, and ocular hypotensive effects. Although its mechanism of action is not fully understood, it may lower the IOP by reducing aqueous humor production and also increasing outflow [70]–[74]. Epinephrine is often used in combination with other ocular hypotensives (e.g., pilocarpine).



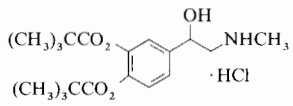
Trade names: Simplene (Smith & Nephew), 1 and 2% solutions (Pharmafair); U.S.P. Ophthalmic Solution: a solution of epinephrine prepared with hydrochloric acid.

Epinephrine hydrochloride [*55-31-2*], Epifrin (0.25, 0.5, 1, or 2%; Allergan), Glaucon (1 or 2%; Alcon).

Epinephrine bitartrate [*51-42-3*], adrenaline bitartrate, $C_9H_{13}NO_3 \cdot C_4H_6O_6$, M_r 333.3, Epitrate (Wyeth-Ayerst). Epinephrine bitartrate is also available in combination with pilocarpine hydrochloride (E-Pilo-1–6, IOLAB)

Epinephryl borate [*5579-16-8*]: Eppy/N (0.5, 1.0, and 2%, Sola/Barnes Hind).

Dipivefrin hydrochloride [*52365-63-6*], dipivalylepinephrine hydrochloride, dipivalyladrenaline hydrochloride, $C_{19}H_{29}O_5N \cdot HCl$, M_r 387.9. For synthesis, see [81]. Dipivefrin hydrochloride is a dipivalyl prodrug that is converted to epinephrine by esterase action. It has enhanced corneal penetration and hypotensive potency relative to epinephrine [71], [73]. Dipivefrin 0.1% is about as potent as 2% epinephrine.



Trade names: d Epifrin (Allergan), Glaucothil (Thilo), Glaudrops (Cusi), Propine (Allergan).

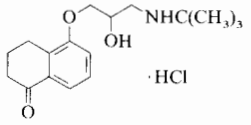
4.2. β-Adrenergic Blocking Agents

Although systemic blockers of the β-adrenoceptors are not approved for ocular hypotensive indications, some reduce IOP in addition to having cardiovascular activity against arrhythmias, angina, and hypertension. The β-blockers lower the IOP by decreasing aqueous humor production [72]–[74]. Although topical preparations are generally well tolerated, systemic (CNS, cardiovascular, and respiratory) side effects have been observed [72]–[74], [76]–[78].

Timolol maleate [*26921-17-5*] (timolol [*26839-75-8*]), (*S*)-1-[(1,1-dimethylethyl)amino]-3-[(4-morpholinyl-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate, $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$, M_r 432.5, is available as 0.25 and 0.5% solutions. For synthesis, see [82]. See also → Blood Pressure Lowering Agents, **A 4**, p. 240. Timolol can provide an additive effect when used concurrently with other ocular hypotensive agents such as miotic agents or carbonic anhydrase inhibitors, although the effects with epinephrine are more controversial [72]–[74].

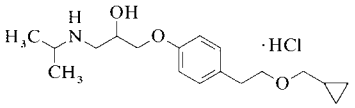
Trade names: Timoptic, Timoptol (Merck Sharp & Dohme).

Levobunolol hydrochloride [*27912-14-7*] (levobunolol [*47141-42-4*]), (–)-bunolol hydrochloride, (–)-5-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride, $C_{17}H_{25}NO_3 \cdot HCl$, M_r 327.9. For synthesis, see [83].



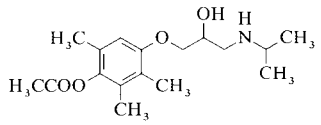
Trade name: Betagan (0.5%, Allergan).

Betaxolol hydrochloride [*63659-19-8*] (betaxolol [*63659-18-7*]), 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-isopropylamino-2-propanol hydrochloride, $C_{18}H_{29}NO_3 \cdot HCl$, M_r 343.9. For synthesis, see [84].



Trade name: Betoptic (0.5% Alcon).

Metipranolol [*22664-55-7*], 4-(2-hydroxy-3-isopropylaminopropoxy)-2,3,6-trimethylphenyl acetate, $C_{17}H_{27}NO_4$, M_r 309.4. For synthesis, see [85], [86].



Trade names: Betamann, Beta-Ophtiole (Mann); Glauline, Minims Metipranolol (Smith & Nephew); Optipranolol (Bausch & Lomb); Normoglaucon (Mann).

4.3. Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors decrease the IOP by blocking bicarbonate formation in the ciliary process required for aqueous humor production [74], [79]. These agents are administered systemically and are useful in treating glaucoma cases that do not respond to topical therapy [72], [74]. Virtually all (90–99%) of the carbonic anhydrase activity must be blocked before the IOP is lowered [72], [79], and oral doses are usually administered several times a day. The sulfonamide carbonic anhydrase inhibitors are diuretics that are readily absorbed from the gastrointestinal tract. Effective oral doses of these agents for glaucoma therapy depend on their pharmacokinetic properties [72], [74], [79]. Systemic side effects [72], [74], [76], [79] may limit the use of oral carbonic anhydrase inhibitors, especially in the elderly. Unfortunately, no topically effective preparations of these agents are available, possibly due to poor corneal penetration. Orally administered carbonic anhydrase inhibitors may provide additive effects when used in combination with topically applied antiglaucoma agents (e.g., pilocarpine and timolol) [74], [79].

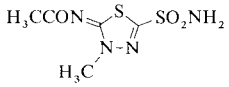
Acetazolamide [*59-66-5*], 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide, $C_4H_6N_4O_3S_2$, M_r 222.2. See also → Diuretics, **A9**, p. 30.

Trade names: Acetamide (Nessa); Diamox, Diamox Sequels (Lederle); Diuriwas (IFI); Edemox (Wasserman); Glaupax (Erco, Dispersa); Theraplix (Cycanamide, Cyanamide-Novalis).

Dichlorphenamide [*120-97-8*], 4,5-dichloro-1,3-benzenedisulfonamide, $C_6H_6Cl_2N_2O_4S_2$, M_r 305.2. For synthesis, see [87].

Trade names: Antidrasi (ISF, Merck Sharp & Dohme); Daranide (Merck Sharp & Dohme); Fenamide (Farmigea); Glauconide (Llorens); Glaumid (SIFI); Hipotensor Oftalmico, Oralcon, Oratrol (Alcon).

Methazolamide [*554-57-4*], *N*-[5-(aminosulfonyl)-3-methyl-1,3,4-thiadiazol-2(3*H*)-ylidene]-acetamide, $C_5H_8N_4O_3S_2$, M_r 236.3. For synthesis, see [88].



Trade names: Neptazane, Theraplix (Lederle).

4.4. Hyperosmotic Agents

Orally (glycerol, isosorbide, urea) or intravenously (mannitol) administered hyperosmotic agents produce a rapid reduction of IOP as a result of migration of water from the eye to ocular blood vessels [72], [75]. These drugs may have significant side effects [72], [75], [76]. They are used primarily to treat acute IOP elevation and in ocular surgical procedures [72].

Glycerol [*56-81-5*], propane-1,2,3-triol, $C_3H_8O_3$, M_r 92.1.

Trade names: Ophthalgan (Wyeth-Ayerst), Osmoglyn (Alcon).

Isosorbide [*652-67-5*], 1,4:3,6-dianhydrosorbitol, $C_6H_{10}O_4$, M_r 146.1.

Trade name: Ismolic (Alcon).

Mannitol [*69-65-8*], cordycepic acid, mannite, $C_6H_{14}O_6$, M_r 182.2.

Trade name: Mannitol Injection (Astra).

Urea [*57-13-6*], carbamide, ureum, CH_4N_2O, M_r 60.1.

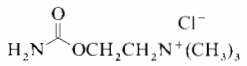
Trade name: Ureaphil (Abbott).

4.5. Miotics (Parasympathomimetic Agents)

Miotics are agents that cause constriction of the pupil. Two classes of miotics, cholinergics and anticholinesterases (parasympathomimetic agents), have therapeutic roles in glaucoma. Acetylcholine itself is not generally useful because of its short biological half-life and topical ineffectiveness, although it can induce miosis when applied directly to the iris during surgery [73]. Cholinergic agonists (pilocarpine, carbachol) act directly on cholinergic effector cells to mimic the effects of acetylcholine; anticholinesterases (physostigmine, demecarium bromide, echothiophate iodide, isoflurophate) prolong the action of endogenous acetylcholine by blocking its hydrolysis by cholinesterases. In the eye, miotics appear to reduce IOP through activation of muscarinic acetylcholine receptors, which contract the ciliary muscle and enhance flow through the trabecular meshwork. Muscarinic activation also constricts the pupillary sphincter and produces miosis, which is sometimes an undesirable side effect of antiglaucoma therapy. Other ocular and systemic side effects may be associated with the use of miotics for antiglaucoma therapy [72], [73], [76], [77], [80].

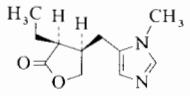
4.5.1. Cholinergic Agonists

Carbachol [*51-83-2*], *O*-carbamoylcholine chloride, $C_6H_{15}ClN_2O_2$, M_r 182.7. Carbachol is inherently more potent and longer acting than pilocarpine but has poorer corneal penetration and more severe ocular side effects. Enhancement of corneal penetration may be achieved with 0.03% benzalkonium chloride (BAK) in the formulation, or with lower levels of BAK along with methyl cellulose or hydroxypropyl methyl cellulose to prolong contact with the ocular surface [73]. Carbachol is used when the response to pilocarpine is inadequate or when a pilocarpine allergy develops [73], [76].



Trade names: Isopto Carbachol (Alcon), also available as a 0.01% solution; Miostat (Alcon) for intraocular injection for miosis during surgery.

Pilocarpine [*92-13-7*], (3*S*,4*R*)-3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]-furan-2(3*H*)-one, $C_{11}H_{16}N_2O_2$, M_r 208.3. Pilocarpine is one of the most useful drugs for management of glaucomas, including primary open-angle and acute angle-closure glaucomas [72], [73]. Principal ocular side effects of pilocarpine solutions (0.25–10%) include miosis, ciliary spasm, and visual blurring [72], [73], [76]. A sustained-release drug delivery system (Ocusert) for pilocarpine base is also available [72], [73], [76].



Trade names: Ocusert Pilo-20 and Ocusert Pilo-40 Ocular Therapeutic System (20 or 40-μg pilocarpine delivery per hour for one week, Alza).

Pilocarpine hydrochloride [*54-71-7*], $C_{11}H_{16}N_2O_2 \cdot HCl$, M_r 244.7.

Trade names: Akarpine (Akorn); I-Pilocarpine (Americal); Isopto Carpine (Alcon); Ocu-Carpine (Ocumed); Pilocar (IOLAB); Pilokair (Pharmafair); Pilopine (Alcon), and in various combinations with epinephrine bitartrate: E-Pilo-1–6 (IOLAB).

Pilocarpine nitrate [*148-72-1*], $C_{11}H_{16}N_2O_2 \cdot HNO_3$, M_r 271.3.

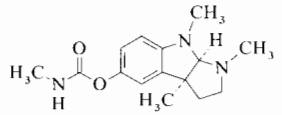
Trade name: Pilagan Liquifilm (Allergan).

4.5.2. Anticholinesterases

Anticholinesterases may be divided into two classes. The short-acting "reversible" inhibitors (e.g., physostigmine and demecarium) transfer a carbamoyl group to the enzyme, which is removed within a few hours to regenerate the enzyme. The long-acting irreversible inhibitors (e.g., echothiophate and isoflurophate) phosphorylate the enzyme, and cholinesterase activity is restored only through synthesis of new enzyme.

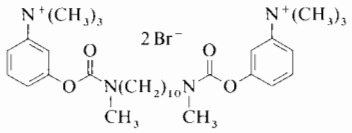
The anticholinesterases are contraindicated for angle-closure glaucoma [72], and their ocular use may produce a variety of systemic and ocular side effects [72], [73], [76]. Anticholinesterases are used primarily when other antiglaucoma medications have failed and are the least commonly used antiglaucoma agents [72].

Physostigmine [*57-47-6*], eserine, $C_{15}H_{21}N_3O_2$, M_r 275.4.



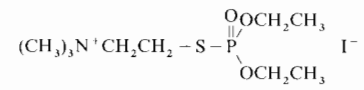
Trade names: Eserine sulfate (0.25%) Sterile Ophthalmic Ointment (IOLAB).

Demecarium bromide [*56-94-0*], $C_{32}H_{52}Br_2N_4O_4$, M_r 716.6.



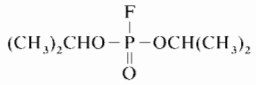
Trade names: Humorsol (Merck Sharp & Dohme), Tosmilen (Chem Linz, Sinclair).

Echothiophate iodide [*513-10-0*] (echothiophate [*6736-03-4*]), mercaptoethyltrimethylammonium iodide *O*,*O*-diethyl phosphorothioate, $C_9H_{23}INO_3PS$, M_r 383.2.



Trade names: Echofilina, Iodeto de fosfolina, Phospholine (Sodip); Phospholine Iodide (Wyeth-Ayerst, Promedica, Chinoin); Phospholinjodid (Winzer).

Isoflurophate [*55-91-4*], diisopropyl fluorophosphate, $C_6H_{14}FO_3P$, M_r 184.1.



Trade names: Diflupyl (Labaz), DFP-Oel (Winzer), Floropryl (Merck Sharp & Dohme).

5. Mydriatics and Cycloplegics

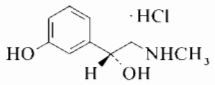
Mydriatic and cycloplegic agents are used routinely in ophthalmic practice for dilating the pupil to facilitate examination of the retina [89]–[98]. In addition to dilation, cycloplegics cause paralysis of accommodation for near vision and are used primarily as an aid in refraction and in the treatment of uveitis [97]. They are also used as postoperative agents in cataract and retinal detachment surgery.

Mydriatics and cycloplegics are divided into sympathomimetics and parasympatholytics. They can be used alone or in combination. Sympathomimetic agents imitate (direct acting) or potentiate (indirect acting) the action of norepinephrine at sympathetic nerve terminals and produce mydriasis by stimulating the iris dilator muscle fibers. Parasympatholytic agents block the action of acetylcholine at the neuromuscular junction and produce pupil dilation with loss of accommodation by immobilizing the iris sphincter and ciliary muscle.

Although serious side effects from mydriatics and cycloplegics are rare, individual response to these drugs varies [98]. They should be used with caution in patients with closed-angle glaucoma or in patients with a narrow angle between the iris and the cornea because they may increase the IOP and precipitate an acute attack [98].

5.1. Sympathomimetics

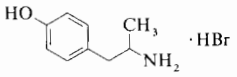
Phenylephrine hydrochloride [*61-76-7*], (*S*)-1-(3-hydroxyphenyl)-2-methylaminoethanol hydrochloride, $C_9H_{13}NO_2 \cdot HCl$, M_r 203.7. Phenylephrine hydrochloride is used topically (2.5 and 10% solutions) to dilate the pupil both for ophthalmoscopy in the treatment of uveitis and for cataract surgery [97]. Maximum dilation occurs within 45–60 min and recovery in about 6 h. A 1% solution can be used in the diagnosis of Horner's syndrome [97].



Trade names: Ak-Dilate, Ak-Vernacon (Akorn); Blephamide (Allergan); I Phrine (Americal); Isonefrine (Allergan); Isopto Frin (Alcon); Minims Phenylephrine Hydrochloride (Smith & Nephew); Mydfrin (Alcon); Neosynephrine (Winthrop); Opstin (Allergan); Phenylephrine Hydrochloride (IOLAB); Prefin (Allergan); Vasosulf (Cooper Vision); Vistosan (Allergan); Zincfrin (Alcon).

Hydroxyamphetamine hydrobromide [*306-21-8*], (±)-4-(2-aminopropyl)phenol hydrobromide, $C_9H_{13}NO \cdot HBr$, M_r 232.1. For synthesis, see [99]. Hydroxyamphetamine hydrobromide is an indirect-acting sympathomimetic agent. It is used in a 1% solution as a mydriatic (effect com-

parable to 2.5% phenylephrine) and in the diagnosis of Horner's syndrome [98]. Hydroxyamphetamine hydrobromide may be used in patients allergic to phenylephrine.



Trade name: Paredrine (SKF).

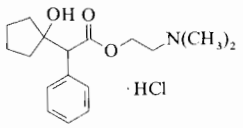
Cocaine [*53-21-4*], $C_{17}H_{21}NO_4 \cdot HCl$, M_r 339.8, is an indirect-acting sympathomimetic agent. In addition to its mydriatic action, it is also a local anesthetic and vasoconstrictor. Cocaine is not available commercially as a solution for clinical use.

5.2. Parasympatholytics

Atropine sulfate [*5908-99-6*] (monohydrate [*55-48-1*]), $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$, M_r 694.8. See also →Alkaloids, **A 1**, pp. 360–362; →Antiasthmatic Agents, **A 2**, p. 464. Atropine is the most effective cycloplegic agent and has the longest duration of action. It is used to maintain a dilated pupil after intraocular surgery. Pupil dilation occurs within 30–40 min and lasts up to 2 weeks.

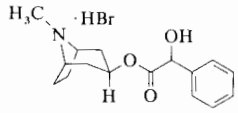
Trade names: Alcon Opulets Atropine 1% (Alcon); Atropine-Care Ophthalmic (Akorn); Atropine Minims (Smith & Nephew); Atropine Sulfate Ophthalmic (Alcon, Allergan, Moore, Rugby, Schein, Steris, Balon, Fougera, Lilly); Atropine Sulfate S.O.P. (Allergan); Atropisol (IOLAB); Ciclopiegyl (Winzer); Isopto Atropine (Alcon); I-Tropine (Americal); Minims Atropine Sulfate (Smith & Nephew); SMP Atropine (Cooper Vision).

Cyclopentolate hydrochloride [*5870-29-1*], $C_{17}H_{25}NO_3 \cdot HCl$, M_r 327.9. For synthesis, see [100]. Cyclopentolate hydrochloride has a rapid onset (30–60 min) but shorter duration of action (< 24 h) than atropine [97].



Trade names: Alcon Opulets Cyclopentolate (Alcon); Ak-Pentolate (Akorn); Ciclolux (Allergan); Ciclopegic, Colircusi ciclopejico, Colirio Oculos Cicloplegic (Llorens), Cyclopen, Cyclopentol Colircusi, Cyclomydril, Cyclogyl (Alcon); Cyclopentolat Minims, Cyplegin, Mydplegin, Minims Cyclopentalate Hydrochloride (Smith & Nephew); Mydrilate (Boehringer, Ingelheim); Skiacol (Pos); Zyklolat (Mann).

Homatropine hydrobromide [*51-56-9*], $C_{16}H_{21}NO \cdot HBr$, M_r 356.3. Homatropine hydrobromide is weaker and less toxic than atropine. The onset of action occurs in about 15–20 min and lasts ca. 3 h. Complete recovery time is about 36–48 h. Homatropine is used for refraction, in the treatment of inflammatory conditions of the uveal tract, and as a pre- and postoperative agent. It is also used as an optical aid for axial lens opacities [97].

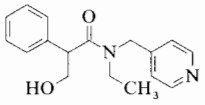


Trade names: Ak-Homatropine (Akorn), Allergan Homatropine (Allergan), Ancatropine Infant Drops (Anca), Homatrine (Americal), Homatropine HBr Ophthalmic (IOLAB), Isopto Homatropine (Alcon), Minims Homatropine Hydrobromide (Smith & Nephew).

Scopolamine hydrobromide [*114-49-8*], (trihydrate [*6533-68-2*]), $C_{17}H_{21}NO_4 \cdot HBr \cdot 3\,H_2O$, M_r 438.3. See also →Alkaloids, **A 1**, p. 361. Scopolamine hydrobromide is an effective cycloplegic and is used in the treatment of uveitis, in refraction of children, postoperatively, and in patients sensitive to atropine. Mydriasis and cycloplegia occur within 20–60 min and last 3–7 d. The duration of action is much shorter in eyes with inflammation.

Trade names: Contac (Allergan), Isopto Hyoscine (Alcon), Minims Hyoscine Hydrobromide (Smith & Nephew), Murocoll-2 (Bausch & Lomb).

Tropicamide [*1508-75-4*], *N*-ethyl-*N*-(4-pyridylmethyl)tropamide, $C_{17}H_{20}N_2O_2$, M_r 284.4. For synthesis, see [101]. Tropicamide is used as a shorter-acting substitute for atropine or scopolamine when prolonged mydriasis and cycloplegia are not required. It is an effective mydriatic with weak cycloplegic activity and is, therefore, useful for ophthalmoscopy and some preoperative and postoperative states. Onset of mydriasis takes place within 15–20 min and lasts ca. 7 h [98]. Mydriasis may be counteracted by local application of pilocarpine. Maximum cycloplegia occurs within 20–25 min; the duration of this peak effect is 15–20 min and has passed in 6–8 h.

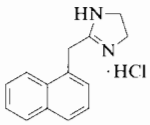


Trade names: I-Picamide (Americal), Minims Tropicamide (Smith & Nephew), Mydriacyl (Alcon), Mydrian (Dispersa), Mydriaticum (Merck Sharp & Dohme), Phenyltrope (Akorn), Tropicacyl (Akorn), Tropikamid Minims (Smith & Nephew), Tropimil (Farmigea), Visumidriatic (Merck Sharp & Dohme).

6. Vasoactive (Adrenergic) Agents

In addition to their mydriatic effect, adrenergic agents constrict the vascular system of the conjunctiva within minutes (α-adrenergic effect) and are used to treat congestion and relieve minor allergy irritation and itching of the conjunctiva. Commercially available ophthalmic vasoconstrictive agents usually contain ephedrine, naphazoline, oxymetazoline, phenylephrine, or tetrahydrozoline. Side effects are not typically observed because of the relatively low concentrations used but rebound congestion can occur with extended use [97].

Naphazoline hydrochloride [*550-99-2*], 2-(1-naphthylmethyl)-2-imidazoline hydrochloride, $C_{14}H_{14}N_2 \cdot HCl$, M_r 246.7. For synthesis, see [102]. One or two drops of naphazoline solution (0.012–0.1%) are administered in the eye every 3–4 h.



Trade names: Ak-Con (Akorn); Albalon (Allergan); Allerest Eye Drops (Pharmacraft); Allergy Drops (Bausch & Lomb); Clear Eyes (Ross); Clera (Person and Covey); Comfort Eye Drops, Degest 2 (Barnes-Hind); Imidazyl (Allergan); Naphcon (Alcon); I-Naphline (Americal); Opcon (Bausch & Lomb); Optazine (Lederle); Otrivin, Privin, Privina, Privine (Ciba); Vasocon Regular (IOLAB).

Naphazoline formulations that also contain an antihistamine are also available: Ak-Con-A (Akorn); Opcon-A (Bausch & Lomb); Naphcon-A, Vasocon-A (IOLAB); Vasoclear (IOLAB); Vistalbalon, Albalon A Liquifilm (Allergan); Zincfrin-A also contains zinc sulfate (Alcon).

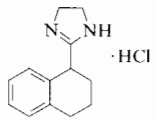
Oxymetazoline hydrochloride [*2315-02-8*], 2-(4-*tert*-butyl-3-hydroxy-2,6-dimethylbenzyl)-2-imidazoline hydrochloride, $C_{16}H_{24}N_2O \cdot HCl$, M_r 296.8.

Trade names: Ocuclear Eye Drops (Schering), Visine L.R. Eye Drops (Pfizer).

Phenylephrine hydrochloride [*61-76-7*], (*S*)-1-(3-hydroxyphenyl)-2-methylaminoethanol hydrochloride, $C_9H_{13}NO_2 \cdot HCl$, M_r 203.7. Phenylephrine is used at a concentration of 0.12%. This relatively low concentration causes vasoconstriction with little or no pupillary dilation. One or two drops are instilled in the eye(s) three or four times daily to relieve burning and itching in mild cases of noninfectious conjunctivitis.

Trade names: Ak-Dilate, Ak-Vernacon, Ak-Nephrin, (Akorn); Isonefrine (Allergan); Isopto Frin, Isopto Phenylephrine (Alcon); Metaoxedrin Minims, Minims Phenylephrine Hydrochloride (Smith & Nephew); Mydfrin (Alcon); Ocu-Phrin (Ocumed); Optistin, Prefrin, Prefrin Liquifilm, Prefrin-A, Prefrin-Z (Allergan); Vasosulf (CooperVision); Relief (Allergan); Zincfrin (Alcon).

Tetrahydrozoline hydrochloride [*522-48-5*], 2-(1,2,3,4-tetrahydro-1-naphthyl)-2-imidazoline hydrochloride, $C_{13}H_{16}N_2 \cdot HCl$, M_r 236.7. For synthesis, see [103]. Tetrahydrozoline hydrochloride solutions (0.05%) are used to decrease swelling of the mucosa in conjunctivitis. One or two drops are instilled in the eye up to four times daily. The onset of vasoconstriction becomes apparent within minutes.



Trade names: Berberin Ophtiole (Mann); Collyrium (Wyeth); Optigene 3 (Pfeiffer); Mallazine Drops (Hauck); Murine (Abbott); Murine Plus (Ross); Soothe Eye Drops (Alcon); Visine A.C., Visine Eye Drops (Leeming); Visine Plus (G.P. Laboratories).

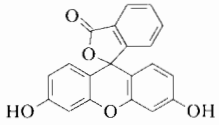
7. Diagnostic Agents

Diagnostic agents are used to examine the eye for signs of systemic disease and to diagnose ocular abnormalities. Dyes used for this purpose include fluorescein, rose bengal, indocyanine green [*3599-32-4*], trypan blue [*72-57-1*], alcian blue [*12040-44-7*], methylene blue [*61-73-4*], and fluorexon. Of these, only fluorescein, rose bengal, and fluorexon are commercially available [104], [105]. Several drugs are also used as ophthalmic diagnostic agents, including edrophonium chloride, methacholine, and pilocarpine.

Fluorescein C.I. 45350 [*2321-07-5*] (fluorescein sodium [*518-47-8*]), $C_{20}H_{12}O_5$, M_r 332.3, *mp* 314–316 °C (decomp.). The synthesis, properties, and histological uses of fluorescein have been reviewed [106], [107]. Fluorescein sodium is used typically as a 1 or 2% solution or as impregnated filter paper strips for detecting foreign bodies and examination of the corneal surface. During corneal surgery, topical administration of fluorescein can be used to detect leakage from the anterior chamber. In cataract surgery, leaks are detected as bright green rivulets [104], [105].

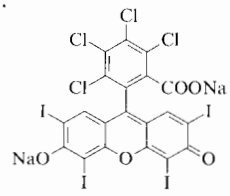
Fluorescein is used for the fitting and management of hard contact lenses. In the presence of fluorescein the tear layer fluoresces green under a cobalt blue light and contrasts with a blue fluorescence or the absence of fluorescence where the lens comes in contact with the cornea. Fluorescein is not useful for fitting soft contact lenses because it penetrates the lens matrix, providing insufficient contrast between the lens and the tissue [104], [105].

Fluorescein is also used intravenously in concentrations of 5–25% for examination of the ophthalmic vasculature and the presence of ocular lesions.



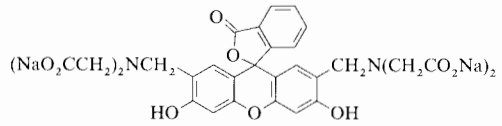
Trade names: Ak-Fluor (Akorn), Fluorescite (Alcon), Fluorets (Akorn), Fluor-I-Strip (Wyeth-Ayerst), Ful-Glo (Barnes-Hind), Funduscein (CooperVision); with proparacaine hydrochloride: Fluoracaine (Akorn).

Rose bengal, C.I. 45440 [*11121-48-5*], (disodium salt [*15632-69-9*]), $C_{20}H_2Cl_4I_4Na_2O_5$, M_r 1017.6. The dipotassium or disodium salt of rose bengal dissolves in water, giving a bluish red color [106]. Unlike fluorescein, rose bengal stains degenerated corneal and conjunctival epithelial tissue red. The stain intensity correlates with the state of degeneration, with dead cells staining intensely [108]. The dye is useful in highlighting abnormal epithelial cells in "dry eye" conditions. It is also a useful adjunct in determining the area of epibulbar squamous neoplasms [109].



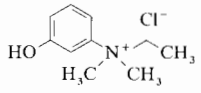
Trade names: EV Rose Bengal (Eagle Vision), Rose Bengal (Akorn).

Fluorexon [*1461-15-0*], $C_{30}H_{26}N_2O_{13}$, M_r 618.54; tetrasodium salt $C_{30}H_{22}N_2Na_4O_{13}$, M_r 710.5. Unlike fluorescein, fluorexon is slow to penetrate the matrix of soft contact lens materials and may be used as an adjunct for fitting soft contact lenses. (However, it is not recommended for lenses with >60% water content [110].)



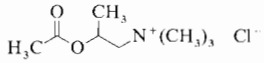
Trade name: Fluoresoft (Holles).

Edrophonium chloride [*116-38-1*], ethyl-(2-hydoxyphenyl)dimethylammonium chloride, $C_{10}H_{16}ClNO$, M_r 201.7, *mp* 162–163 °C (decomp.). For synthesis, see [111]. Edrophonium chloride (an anticholinesterase) may be injected intravenously to determine whether the cause of ptosis (drooping of the upper eyelid) is myasthenia gravis (a neuromuscular disease).



Trade name: Enion (Anaquest), Tensilon (Roche).

Methacholine chloride [*62-51-1*], acetyl-β-methylcholine chloride, $C_8H_{18}ClNO_2$, M_r 195.7, *mp* 172–173 °C. A 2.5% methacholine (a cholinergic drug) solution is applied topically to the conjunctival sac to diagnose Adie's pupil (a disruption of cholinergic innervation to the iris). Normal pupils do not respond significantly to methacholine, whereas the Adie's pupil responds with intense miosis.



Trade name: Provocholine (Hoffmann-La Roche).

Pilocarpine, see Section 4.5.1. A 0.1–0.125% solution of pilocarpine can be used to diagnose Adie's pupil. A 0.5–1% solution can be used in the differential diagnosis of the fixed, dilated pupil. The dilated pupil responds to the drug if the dilation is of neurologic origin, where it does not

respond if the etiology is anticholinergic in nature [104], [112].

8. Dry Eye Medications

"Dry eye" denotes a number of conditions including insufficient lacrimation, mucin deficiency, lipid abnormality, impaired blinking, or primary ocular disorder [113]. The seriousness of dry eye ranges from mild "dry and scratchy" eyes to serious degeneration and keratinization of corneal tissue, which may lead to blindness. The latter condition is often found in developing countries in areas of malnutrition (deficiency of protein and vitamin A). However, in highly developed nations, a milder form of dry eye occurs, which is characterized by chronic eye irritation and decreased visual acuity [114]. Symptoms are normally subclinical but become symptomatic in a dry, windy, or dusty atmosphere, in air conditioning; or when contact lenses are worn.

If dietary deficiency is the underlying cause of the dry eye syndrome, a proper diet should be implemented. *trans*-Retinoic acid ointment may be applied topically to counter vitamin A deficiency [115]. In dry eye conditions induced by infection, treatment with an antimicrobial agent should be initiated.

The most common treatment of nonspecific, incipient dry eye is with tear substitutes [113]. Commercial dry eye preparations typically contain at least one *demulcent*, which lubricates and wets the eye, and a *preservative* to prevent microbial contamination of the product. Nonpreserved preparations are also available in single-dose containers. Some demulcents serve as thickening agents (e.g., substituted cellulose ethers) based on the concept that highly viscous tear substitutes should have a longer retention time in the eye. Because contact lens wearers generally experience improved comfort from the lubricant and wetting properties of demulcents, many lens preparations include one or more of these agents (see Section 9.1).

Other components of dry eye medications include *emollients* (such as petrolatum, mineral oil, and lanolin), which lubricate and protect the eye from drying, and *lipids*, which are intended to supplement a deficient superficial lipid layer of tear fluid. Both emollients and lipids may, however, interfere with visual acuity.

The most common demulcents are listed below.

Carboxymethyl cellulose sodium [*9004-32-4*], exists as white granules, with water solubility dependent on the degree of substitution. It is available in various viscosities.

Trade names: Bro-Lac (Riker), Celluvisc (Allergan).

Dextran [*9004-54-0*], a polysaccharide with a backbone of D-glucose units is produced from bacteria cultured with a sucrose substrate.

Trade names: With hydroxymethyl cellulose: Muro Tears TM (Muro), Tears Naturale R (Alcon); with hydroxypropyl methyl cellulose and dextran 70: Moisture Drops (Bausch & Lomb).

Gelatin is a mixture of water-soluble proteins obtained after collagen-containing animal tissues (e.g., skin, tendons, ligaments, bones) have been boiled with water.

Trade names: Lacril R (Allergan).

Gycerol [*56-81-5*], propane-1,2,3-triol, $C_3H_8O_3$, M_r 92.1.

Trade names: Dry Eye Therapy (Bausch & Lomb); with dextran 70 and hydroxypropyl methyl cellulose: Moisture Drops (Bausch & Lomb).

Ophthalmic Preparation: Glycerin Ophthalmic Solution, U.S.P.

Hydroxyethyl cellulose [*9004-62-0*], nearly odorless, yellowish-white, white, or grayish-white, hygroscopic granules or powder.

Trade names: Adsorbo Tears (Alcon); Lyteers (Barnes-Hind); with polyvinyl alcohol: Comfort Tears, Neo Tears (Barnes-Hind); with lipid: TearGard (Bioproducts).

Contact lens products: Soft Mate ps (Barnes-Hind), Clerz (CooperVision)

Hydroxypropyl cellulose [*9004-64-2*] is an off-white powder that softens at 130 °C, produces aqueous solutions with a wide range of viscosities, and precipitates from solution at 40–45 °C.

Trade name: Lacrisert (Merck Sharp & Dohme), a sterile (prescription only) ophthalmic insert that slowly releases hydroxypropyl cellulose.

Hydroxypropyl methyl cellulose [*9004-65-3*] is a powder that slowly dissolves in cold water (insoluble in hot water) to give solutions with a wide range of viscosities.

Trade names: Isopto Alkaline, Isopto Plain, Isopto Tears (Alcon); Tearisol (CooperVision); Ultratears (Alcon); with gelatin and polysorbate 80: Lacril (Allergan);

with dextran: Tears Naturale (Alcon); with dextran 70 and glycerol: Moisture Drops (Bausch & Lomb).

Lens care products: With poly(vinyl alcohol): Liquifilm.

Methyl cellulose [*9004-67-5*], consists of white granules that are soluble in cold water (insoluble in hot water), with solubility and viscosity dependent on the degree of substitution.

Trade names: Methopto Forte (Bioproducts), Methulose (Warner-Lambert), Milroy Artificial Tears (Milroy), Murocel Ophthalmic Solution (Muro), Visculose (Warner-Lambert).

Polyethylene glycol [*25322-68-3*], is a clear liquid or white solid that dissolves in water to form transparent solutions of various viscosities.

Trade names: With poly(vinyl alcohol): HypoTears (CooperVision).

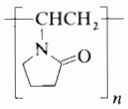
Contact lens products: With polyoxyl 40 stearate: Blink-N-Clean (Allergan).

Poly(vinyl alcohol) [*9002-89-5*] is a white to cream colored powder that softens at ca. 200 °C; it is available in a variety of viscosities and solubilities in water.

Trade names: Liquifilm, Pre-Sert (Allergan); with poly(ethylene glycol): HypoTears (CooperVision); with hydroxyethyl cellulose: NeoTears (Barnes-Hind); with polyvinylpyrrolidone: Refresh, Tears Plus (Allergan).

Contact lens products: Lens-Wet, Pre-Sert, Total, Wet-N-Soak (Allergan), Hy-Flow (Cooper-Vision); with hydroxypropyl methyl cellulose: Liquifil (Allergan), Barnes-Hind Wetting Solution, Visalens Wetting Solution; with povidone and hydroxyethyl cellulose: Barnes-Hind Wetting and Soaking Solution (Barnes-Hind); with poly(ethylene glycol) and hydroxyethyl cellulose: Lensine 5 (CooperVision).

Povidone [*9003-39-8*], polyvinylpyrrolidone, a pale yellow solid, M_r 10000–700000, gives colloidal solutions in water.



Trade names: With other demulcents: AdsorboTear (Alcon); Refresh, Tears Plus (Allergan).

Contact lens products: Soft Care (Barnes-Hind).

Propylene glycol [*57-55-6*], 1,2-propane-diol, $C_3H_8O_2$, M_r 76.09, *mp* −59 °C.

Contact lens products: Allergan Hydrocare (Allergan).

9. Miscellaneous Ophthalmic and Contact Lens Preparations

Contact lenses are broadly classified as "hard" or "soft". *Hard lenses* are typically composed of poly(methyl methacrylate) (PMMA); they are inflexible and hydrophobic, and retain their shape when removed from the eye. *Soft ("hydrophilic") lenses* are flexible, hydrophilic (typically with a water content of 30–79 %), and conform to the contour of the supporting surface. They are composed of any one of a wide variety of cross-linked polymers that form a hydrophilic gel network (e.g., polymacon, a copolymer of 2-hydroxyethyl methacrylate with 2-hydroxyethyl-2-methyl-2-propenoate) [116]–[118]. In addition, *"semirigid" or gas-permeable lenses* are available. These lenses are commonly made from PMMA and silicone, and are a hybrid of soft and hard lenses.

The advantages and disadvantages of each type of lens are reviewed elsewhere [116]–[118]. The wide range of polymers used for contact lens materials results in a broad spectrum of physicochemical interactions between the lenses, tear fluid, eye tissue, and contact lens products. For example, 20–30 μg of tear-fluid protein is typically deposited on a polymacon soft lens, whereas >500 μg of protein may be deposited on an etafilcon A soft lens during the same period of wear [119]. (Etafilcon A is a copolymer of 2-hydroxyethyl methacrylate, sodium methacrylate, and the trimethacrylate ester of 2-ethyl-2-hydroxymethyl-1,3-propanediol). Moreover, the compositions of the tear-fluid proteins deposited on each lens type differ: the negatively charged etafilcon A lens attracts more positively charged lysozyme than the nonionic polymacon material.

The effectiveness and cytotoxicity of the agents used for contact lens disinfection, cleaning, lubrication, wetting, etc., vary markedly with the properties of the lens material. Many factors may affect product efficacy, safety, and utility. Heat disinfection is unsatisfactory for some hydrophilic lens materials because it reduces lens life and makes deposits more difficult to remove after thermal disinfection. Chemical *disinfectants and preservatives* are described in Section 9.1. Hydrogen peroxide (3 %) is a good antimicrobial agent, but its use requires a neutralization step and has patient compliance problems. Thimerosal is also a good antimicrobial agent, but a substantial proportion of the popu-

lation has become sensitized to it. Benzyl alcohol is an effective preservative but tends to irritate the eye [120]. Chlorobutanol is only a fair preservative because it has a slow kill rate, is unstable in solutions above pH 6, and is adsorbed by containers. Ethylenediaminetetraacetic acid is not an effective antimicrobial agent when used alone; it disrupts the integrity of bacterial cell walls and is used in combination with other preservatives.

Boric acid (often used as a buffering agent in ophthalmic and contact lens care solutions) and sorbic acid are preservatives with relatively low cytotoxicity, but they are not useful as lens disinfectants. Quaternary amines such as benzalkonium chloride are good disinfectants and preservatives but accumulate on negatively charged hydrophilic lenses with a high water content, causing cytotoxic responses [121]–[126]. Polyquad is the only quaternary amine currently in use for soft lens disinfection.

Biguanides are both potent disinfectants and good preservatives. Unfortunately, chlorhexidine has been associated with sensitivity reactions. In contrast, poly(hexamethylenebiguanide) (PHMB) has a very low frequency of adverse patient response and is safe for use with soft lens materials. Lenses disinfected with PHMB solution (0.5 ppm) can be placed directly on the eye, without the saline rinse required by most other disinfectants.

Considerable variation exists among individuals in both tear chemistry and tear deposits on contact lenses [127]–[132].

Most *lens cleaning agents* are used daily or weekly (see Section 9.3). Daily cleaners (e.g., macrogol esters and ethers, sodium lauryl sulfate, and block copolymers) remove proteinaceous and lipoidal lens deposits by their surfactant action. However, daily cleaners do not completely remove protein deposits, and proteins tend to accumulate with time, serving as a possible site for microbial growth and causing eye irritation and lens clouding. Weekly cleaners are used to remove accumulated protein deposits. They are generally formulations of proteolytic enzymes (e.g., pancreatin, papain, or subtilisin-A), which cleave the protein into smaller fragments that are more readily rinsed off the lens surface.

In addition to disinfectants, preservatives, and cleaning agents, contact lens preparations may contain *lubricants*, *wetting agents*, or *viscosity adjusters* to improve lens comfort. Formulations containing such materials are listed in Chapter 8 (contact lens products). Contact lens solutions also contain *buffers* (e.g., borate, citrate, and phosphate) and *osmolality adjusting agents* (usually sodium chloride).

9.1. Disinfectants and Preservatives

9.1.1. Biguanides

See → Disinfectants, **A 8**, p. 559.

Chlorhexidine gluconate [*18472-51-0*], chlorhexidine digluconate, $C_{22}H_{30}Cl_2N_{10} \cdot 2\,C_6H_{12}O_7$, M_r 897.8.

Contact lens products: Bausch & Lomb Sterile Disinfecting Solution (Bausch & Lomb); Flexcare, Flexsol (Alcon); Soft-Mate (Barnes-Hind).

Poly(hexamethylenebiguanide) hydrochloride [*27083-27-8*], polyaminopropyl biguanide hydrochloride $[C_8H_{17}N_5]_n \cdot HCl$. For synthesis, see [120].

Contact lens products: ReNu Multi-Purpose Solution; ReNu Saline Solution (Bausch & Lomb).

9.1.2. Mercurial Preservatives

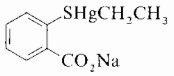
Phenylmercury(II) acetate [*62-38-4*], $C_8H_8HgO_2$, M_r 336.8, *mp* 149 °C.

Trade name: Blinx (Barnes-Hind).

Phenylmercury(II) nitrate [*8003-05-2*], $C_{12}H_{11}Hg_2NO_4$, M_r 634.4, *mp* 187–190 °C (decomp.).

Contact lens preparation: Clean-N-Soak (Allergan).

Thimerosal [*54-64-8*], $C_9H_9HgNaO_2S$, M_r 404.84.



Trade names: Absorbonac, Absorbotear (Alcon); Collyrium (Wyeth); Eye Cool, 20/20 Eye Drops (Milroy); Liquifilm Forte, Prefin Z Liquifilm (Allergan); M/Rinse (Milroy); Neo Tears (Barnes-Hind); Soothe (Alcon).

Contact lens products: Adapettes (Alcon); Cleaning & Disinfecting (Allergan); Clerz (Cooper Vision); Dual-Clean (Sherman); Flex-Care, Flexsol (Alcon); Gel-Clea (Barnes-Hind); LC-65, Lens-Wet (Allergan); Pena-Vel II (Serman Labs.); Soaclens (Alcon); Soft Care, Soft Mate (Barnes-Hind); Stay Brite (Sherman); Sterile Disinfecting Solution, Sterile Lens Lubricant (Bausch & Lomb).

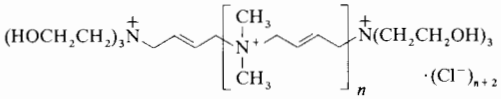
9.1.3. Quaternary Ammonium Compounds

See → Disinfectants, **A 8**, p. 559.
See → Microbiocides, **A 16**, p. 566.

Benzalkonium chloride [*8001-54-5*] is a mixture of alkyldimethylbenzylammonium chlorides.

Trade names and contact lens products are too numerous to list.

Benzethonium chloride [*121-54-0*], $C_{27}H_{42}ClNO_2$, M_r 448.1, *mp* 164–166 °C.

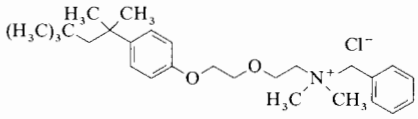


Cetylpyridinium chloride [*123-03-5*], 1-hexadecylpyridinium chloride monohydrate, $C_{21}H_{38}ClN \cdot H_2O$, M_r 358.0, *mp* 77–83 °C.

Cetyltrimethylammonium bromide [*505-86-2*], cetrimide, is chiefly trimethyltetradecylammonium bromide together with dodecyl- and hexadecyltrimethylammonium bromides.

Trade names: Pilomann, Dexamytrex Ophtiole (Mann).

Polyquad [*75345-27-6*], poly[(dimethyliminio)-2-butene-1,4-diyl chloride], polyquaternium-1, polyquat.



Contact lens products: Opti-Free (Alcon).

9.1.4. Miscellaneous Disinfectants and Preservatives

Benzyl alcohol [*100-51-6*], C_7H_8O, M_r 108.1, *mp* −15.2 °C. See also → Benzyl Alcohol.

Boric acid [*10043-35-3*], orthoboric acid, BH_3O_3, M_r 61.84, *mp* ca. 171 °C.

Commercial products: Boric acid is used in a variety of ophthalmic and contact lens care products.

Chlorobutanol [*57-15-8*], 1,1,1-trichloro-2-methyl-2-propanol, $C_4H_7Cl_3O$, M_r 177.5, *mp* 97 °C.

Trade names: Gentamytrex Ophtiole (Mann); Lacril, Liquifilm Tears, Tears Plus (Allergan).

Ethylenediaminetetracetic acid [*60-00-4*], EDTA, $C_{10}H_{16}N_2O_8$, M_r 292.2, *mp* >300 °C. See also → Ethylenediaminetetraacetic Acid and Related Chelating Agents.

Commercial products: EDTA has widespread use in a variety of ophthalmic and contact lens care products.

Hydrogen peroxide [*7722-84-1*], H_2O_2, M_r 34.0. See also → Hydrogen Peroxide.

Contact lens products: OxySept (Allergan); Consept (Barnes-Hind); Quik-Sept (Bausch & Lomb); AOSept (Ciba); MiraSept (CooperVision); Murine Pure Sept (Ross).

Sorbic acid [*110-44-1*], 2,4-hexadienoic acid, M_r 112.12, *mp* 134.5 °C.

Ophthalmic and contact lens products: Sorbic acid is used widely as a preservative in contact lens care products.

9.2. Contact Lens Cleaners and Rewetting Agents

Most lens cleaning agents are used daily or weekly (see Section 9.1). Daily cleaners remove proteinaceous and lipoidal deposits by their surfactant action. Weekly cleaners are used to remove accumulated protein deposits.

9.2.1. Surfactant Cleaners

Octylphenoxypolyethoxy ethanol [*9002-93-1*], poly(ethylene glycol) 4-isooctylphenyl ether, $C_{34}H_{62}O_{12}$, average M_r 647.

Contact lens products: Barnes-Hind Wetting & Soaking, Soft-Mate (Barnes-Hind).

Polyoxyl 40 stearate [*9004-99-3*], poly(ethylene glycol) monostearate.

Contact lens product: Blink-N-Clean (Allergan).

Poly(ethylene glycol) [*25322-68-3*], typical lens product M_r range 190–420; hygroscopic, viscous liquid.

Contact lens products: Blink-N-Clean (Allergan), ReNu Effervescent Enzymatic Contact Lens Cleaner (Bausch & Lomb).

Tyloxapol [*25301-02-4*], 4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and ethylene oxide, tyloxypal.

Trade name: Enuclene (Alcon).

Sodium lauryl sulfate [*151-21-3*], sodium dodecyl sulfate, $C_{12}H_{25}NaO_4S$, M_r 288.4

Contact lens products: Lens Plus Daily Cleaner, Resolve/GP Daily Cleaner (Allergan).

Poloxamer 407 [*9003-11-6*], ethylene–propylene block copolymer, average M_r 4000 with 70 wt% polyethylene.

Contact lens products: Ciba Vision Lens Drops, MiraFlow Extra-Strength Cleaner (Ciba).

Poloxamine, [*110617-70-4*], Tetronic, copolymer of ethylene oxide, propylene oxide, and tetrakis ether of ethylenediamine with propanol.

Contact lens products: ReNu Multi-Purpose Solution (Bausch & Lomb).

9.2.2. Enzymatic Cleaners

See → Enzymes, **A 9**, pp. 395–397.

Pancreatin [*8049-47-6*] is obtained from hog pancreas and has protease, amylase, and lipase activity.

Contact lens products: Optizyme (Alcon).

Papain [*9001-73-4*] is derived from papaya.

Contact lens products: Allergan Enzymatic, Extenzyme (Allergan).

Subtilisin A [*9014-01-1*] is extracted from *Bacillus licheniformis*.

Contact lens products: ReNu Effervescent Enzymatic Contact Lens Cleaner, ReNu Thermal Enzymatic Contact Lens Cleaner (Bausch & Lomb); Ultrazyme (Allergan).

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