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Update on the Botulinum Neurotoxins

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ABSTRACT

The botulinum neurotoxins (BTX) are an exciting group of therapeutic agents with dramatically expanding clinical indications. The US FDA has approved BOTOX[®] (BTX-A, Allergan) and Myobloc[™] (BTX-B, Elan Pharmaceuticals) for the treatment of cervical dystonia. TPP Canada has also approved BOTOX[®] for the treatment of glabellar frown lines. The US FDA is expected to approve this new indication before the end of 2002. These changes will dramatically expand the marketing of BTXs. Concerns about risks and side effects diminish as clinical experience increases with this "most poisonous of poisons".² In particular, the incidence of secondary resistance to the toxin's effect has been dramatically diminished with the reduction of the non-toxic protein in current batches of BOTOX[®].³

Key Words: botulinum toxin, cervical dystonia, glabellar frown lines, hyperhidrosis

Pharmacology

The botulinum toxins are produced by different serotypes of the bacterium, *Clostridium botulinum*. They act to block presynaptic release of acetylcholine,³ which in turn blocks neuromuscular transmission, causing weakening of the treated muscle or even flaccid paralysis. Reversal of the blockade occurs after approximately 3-4 months. The typical clinical response is in the same time range although much longer responses can be seen.

Drug interactions and contraindications⁴

Theoretical interactions with aminoglycoside antibiotics and calcium channel blockers have not proven to be of clinical significance. Of much greater importance is the possibility of exacerbating preexisting neurological disease. A myasthenic crisis was precipitated in a patient who developed unrecognized myasthenia gravis in between regular BTX injections for blepharospasm.⁵ Amyotrophic lateral sclerosis and Eaton-Lambert syndrome can also be worsened by BTX injection.⁴

The safety of BTX injections in pregnant and nursing women has not been established, though there is evidence that BTX does not cross the placenta.^{6,7} Whether it is secreted in breast milk has not been substantiated. However, so little gets into the circulation that the tiny amounts to which a healthy breast-fed infant might be exposed would not pose any likely risk.^{6,7}

Commercially available preparations

BTX-A

BOTOX[®] was the first of the BTXs to be produced and used

clinically, and experience with this toxin is far greater than with any of the other toxins. Early use of the BTXs caused a significant problem with secondary resistance to the toxin's effect resulting from the induction of blocking antibody formation. Gradually, Allergan changed, worldwide, the supply of the toxin to a new, purer product. Secondary resistance has not been reported since this change.²

BOTOX[®] is approved in the US and Canada for the treatment of strabismus, blepharospasm, hemifacial spasm and cervical dystonia (CD) in adults. It was recently approved in Canada for the treatment of glabellar frown lines and approval for this indication in the US is anticipated in 2002. As well, TPP Canada approved this product for the treatment of hyperhidrosis in August 2001, and for the treatment of adult spasticity in November 2001. The European Commission of the European Union passed a positive opinion in October 2001, for the treatment of adult spasticity.

Dysport[®] was introduced in Europe soon after BOTOX[®] was launched in North America. It is also BTX-A, however, the Dysport[®] unit does not appear to be as effective as the BOTOX[®] unit. Studies suggest a 3-5 fold difference in potency,⁸ which is thought to be due to differences in product formulation (see Table 1). Dysport[®] has a similar incidence of secondary resistance in CD patients, to the original batch of BOTOX[®] (3-5%).⁹

BTX-B

Myobloc[™] (Elan Pharmaceuticals) was the first available form of BTX-B (called NeuroBloc[®] outside North America) to be approved for the treatment of CD by the US FDA in December

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Name (Manufacturer)	BTX Type	Dose in CD	Comments
BOTOX® (Allergan)	BTX-A	200units	Reduced immunogenicity
Dysport® (Ipsen)	BTX-A	800units	Not as effective as BOTOX®, with a 3-5 fold difference in potency
Myobloc™ (Elan Pharmaceuticals)	BTX-B	10,000units	Largely clinically untested

Table 1: A review of BTX forms currently available.

2000. In studies published so far, the clinical effectiveness and the duration of response in CD appear to be similar to BOTOX® although the dose is dramatically higher.¹⁰ For effective treatment of CD, at least 10,000 mouse units of Myobloc™ are needed to produce the same effect as 200 mouse units of BOTOX® (see Table 1). This means a tenfold increase in the amount of neurotoxin protein delivered, although Myobloc™ has less inactive neurotoxin protein than BOTOX®.³ Myobloc does not appear to be accompanied by a similar development of clinical resistance to the affect of BTX-B.¹¹ According to information provided by the US FDA, there may be a reduction of treatment benefits with succeeding treatment sessions and/or a lessening of benefit with the uppermost level of dosing examined. Although no definite conclusions may be drawn, data provided by the US FDA suggests that resistance may be possible.¹²

Side effects of Myobloc™ seem to be similar to those of the other BTXs with the exception of dry mouth. Although mild, this occurs in up to 34% of CD patients treated with an effective dose of 10,000 units.¹¹ This is a systemic effect of the neurotoxin and is indicative of a difference between BTX-A and BTX-B. It may be possible to exploit this and other differences and find indications for which Myobloc™ is superior to BOTOX® and vice versa.

Indications

Cosmetic¹³

The principal area for cosmetic use of BTX is in the upper face. Glabellar frown lines, horizontal forehead lines and lateral orbital lines (crows feet) are commonly treated and respond well. More recently, the ability of BTX to produce a modest brow lift, to correct eyebrow asymmetry, to open the eyes, to soften perioral wrinkles, to lift the corners of the mouth, and to improve neck lines have excited interest in the mid and lower face.

Hyperhidrosis

BTX has been used successfully to treat hyperhidrosis affecting a number of areas. It was initially used in Frey's syndrome, which led to treatment of the palms and axillae. The face and feet are also treated. More recently, the use of BTX to reduce sweating was shown to be effective in improving benign familial pemphigus.¹⁴ This may lead to the use of BTX for other intertriginous dermatoses where sweating is thought to play a role.

Headache and Migraine¹⁵

Early in the cosmetic use of BTX, alleviation of tension headaches was reported, and migraine headaches were also reported to have improved. Subsequent studies have provided conflicting results. Unquestionably, some patients have fewer and less severe migraines after BTX injection, but it has been difficult to establish a scientific basis for this in placebo-controlled, double blind studies. Further work in this important area will establish the

indications, effective injection techniques, and possibly further define the pathogenesis of migraine, which should not respond to BTX injections according to current theories.

Conclusion

The clinical indications of the botulinum neurotoxins continue to expand dramatically. At the same time, our background knowledge is also expanding and a form of the B serotype is now commercially available. Differences have been established between BTX-A and BTX-B including different sites of action, different dosages and different side-effect profiles.¹⁶ Clinical experience with BTX-B is currently so limited that conclusions about these differences are premature.

References

- Lamanna C. The Most Poisonous Poison. *Science* 130:763-72 (1959).
- Brin MF, et al. An interim analysis of the clinical status of patients receiving current BOTOX (lot 2024 or subsequent lots) for the treatment of cervical dystonia. Presented at International Conference 1999: Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins, Orlando, Florida, November 16-18, 1999. Abstract: pg 21.
- Simpson LL, editor. *Botulinum neurotoxin and tetanus toxin*. San Diego:Academic Press (1989).
- Assessment: the clinical usefulness of botulinum toxin – A in treating neurologic disorders. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 40(9):1332-6 (1990 Sep).
- Borodic G. Myasthenic crisis after botulinum toxin. *Lancet* 352(9143):1832 (1998 Dec).
- Polo JM, Martin J, Berciano J. Botulism and pregnancy. *Lancet* 348(9021):195 (1996 Jul).
- Robin L, Herman D, Redett R. Botulism in pregnant women. *N Eng J Med* 335(11):823-4 (1996 Sep).
- Marion MH, Sheehy M, Sangla S, Soulayrol S. Dose standardization of botulinum toxin. *J Neural Neurosurg Psychiatry* 59(1):102-3 (1995 Jul).
- Poewe W, Wissel J. Experience with Botulinum Toxin in cervical dystonia. In: Jankovich J, Hallet M, eds. *Therapy with Botulinum Toxin*. New York:Marcel Dekker (1994) pg. 267-78.
- Brashear A, Lew MF, Dykstra DD et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A responsive cervical dystonia. *Neurology* 53(7), 1439-46 (1999 Oct).
- Myobloc™ package insert. Elan Pharmaceuticals, Dublin, Ireland.
- US FDA. BLA 99-1396. Response Submission to Complete Review Letter. Elan Pharmaceuticals. Botulinum Toxin Type B for Treatment of Cervical Dystonia: Supplemental Clinical Review. (2000 Dec).
- Carruthers A, Carruthers J. Botulinum Toxin Type A: History and Current Cosmetic Use in the Upper Face. *Sem Cutan Med Surg* 20(2):71-84 (2001 Jun).
- Glogau RG. Treatment of Palmar Hyperhidrosis with Botulinum Toxin. *Sem Cutan Med Surg* 20(2):101-8 (2001 Jun).
- Carruthers A, Langtry JA, Carruthers J, Robinson G. Improvement of Tension-Type Headache When Treating Wrinkles with Botulinum Toxin A Injections. *Headache* 39(9):662-5 (1999 Nov/Dec).
- Carruthers A, Carruthers J. Toxins 99, new information about the botulinum neurotoxins. *Dermatol Surg* 26:174-6 (2000 Mar).

Moisturizers: What They Are And How They Work

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ABSTRACT

Moisturizers are widely used in various dermatologic and cosmetic skin therapies. Different classes of moisturizers are based on their mechanism of action, including occlusives, humectants, emollients and protein rejuvenators. Commercially available moisturizers often utilize components of each of these classes to provide their beneficial effect. Dry skin (xerosis) is the major indication of use. Others include atopic dermatitis, irritant contact dermatitis, ichthyosis, and dermatoheliosis. Although generally efficacious, moisturizers can cause a number of unwanted side effects, including occlusive folliculitis, irritation, allergic contact dermatitis and contact urticaria.

Key Words: moisturizers, mechanism of action, side effects, dry skin

"Dry skin" is an extremely common problem. Our society and its advertising suggest that we have a simple solution - just apply a moisturizer. The marketplace has a great number of products to moisturize the skin and billions of dollars are spent yearly on these products.

What Are Moisturizers?

Interestingly, standard textbooks of dermatology devote very little space or discussion to this subject, and no standard definition exists yet dermatologists use and recommend moisturizers many times daily. They are bland oleaginous substances that are applied to the skin by rubbing. They are used to replace natural skin oils, to cover tiny fissures in the skin, and to provide a soothing protective film. They may, thus, slow evaporation of the skin's moisture, thereby maintaining hydration, and improving the appearance and tactile properties of dry and aging skin.

How Do Moisturizers Work?

Traditionally, moisturization was believed to inhibit transepidermal water loss (TEWL) by occlusion. Water originates in the deeper epidermal layers and moves upward to hydrate cells in the stratum corneum, eventually being lost to evaporation.

Occlusive moisturization, then, prevents the dehydration of the stratum corneum.

Much more is now known about the epidermis, and in particular, the stratum corneum. The "bricks and mortar" model suggests that its role is as an active membrane. Loss of intercellular lipids, i.e., the ceramides, cholesterol and fatty acids that form the bilayers, damages the water-barrier function. The stratum corneum then calls into action repair mechanisms.¹

The Natural Moisturizing Factor (NMF), a natural mixture of amino acids, lactates, urea and electrolytes, which help the stratum corneum retain water is also now known.² Dry skin is noted when the moisture content is less than 10%, and there is loss of continuity of the stratum corneum.

Scientifically, the moisturizing treatment involves a 4-step process:

1. Repairing the skin barrier
2. Increasing water content
3. Reducing TEWL
4. Restoring the lipid barriers' ability to attract, hold and redistribute water.

Class Action	Mechanism of Ingredients	Example	Indication	Side Effects
I. Occlusive	Physically block TEWL	Petrolatum Lanolin Mineral Oil Silicones Zinc Oxide	Xerosis – Atopic Dermatitis Prevention of Irritant Contact Dermatitis	Messy, Cosmetically Unacceptable, Folliculitis, (Mineral Oil) Comedogenic Contact Dermatitis,(Lanolin)
II. Humectants	Attract water to stratum corneum (transepidermal)	Glycerin Sorbital Urea Alpha hydroxy acids Sugars	Xerosis Ichthyosis Skin Rejuvenation?	Irritation (Urea, Lactic Acid)
III. Emollients	Smooth Skin by filling spaces between skin flakes, with droplets of oil	Cholesterol Squalene Fatty Acids	Decrease skin roughness	Not always effective
IV. Protein Rejuvenators	Claim rejuvenate skin by replenishing essential proteins in skin	Collagen Keratin Elastin	Skin Rejuvenation?	Unlikely to work Protein too large to cross epidermis Contact reactions

Table 1: There are currently several groupings of moisturizing substances that are based on their theoretical mechanism of action.

Occlusives

Occlusives are substances that physically block TEWL in the stratum corneum. Petrolatum in a minimum concentration of 5% is the most effective occlusive followed by lanolin, mineral oil, and silicones such as dimethicone. Petrolatum is widely used as a classic moisturizer. Lanolin, a complex structure of esters, diesters, and hydroxyesters of high molecular weight, lanolin alcohols, and lanolin acids, is also widely used and quite effective.^{1,3,4}

Humectants

Humectants attract water when applied to the skin and theoretically improve hydration of the stratum corneum. However, the water that is drawn to the skin is trans-epidermal water, not atmospheric water. Continued evaporation from the skin can actually exacerbate dryness. Humectants include glycerin, sorbitol, urea, alpha

hydroxy acids (i.e., lactic acid) and other sugars. NMF is made up of a mix of low molecular weight soluble hygroscopic substances including lactic acid, pyrrolidone-carboxylic acid and amino acids. This naturally mixing compound is thought to be a major player, keeping the horny layer hydrated and flexible.² Manufacturers' attempts to include the above humectants into moisturizers do not always produce a beneficial effect. High concentrations of propylene glycol and urea can be irritating. Pure mixtures of amino acids are useless as moisturizers. Pure solutions of glycerin are ineffective and propylene glycol by itself is irritating.¹ In addition to their humectant properties, urea and lactic acid are keratolytic. Urea is a humectant in lower concentrations (10%), but in higher concentrations (20-30%) it is mildly keratolytic by disrupting hydrogen bonds or epidermal proteins. Alphahydroxy acids, such as lactic acid or glycolic acid, appear to increase cohesion of the stratum corneum cells, thereby reducing roughness and scaling.

Class		Product Name	Active Ingredients
I		A & D Ointment (Schering-Plough)	Vitamin A 1 500 IU/g; Vitamin D 213 IU/g
		Alpha Keri Bath Oil (Bristol-Myers Squibb)	3% Mineral oil 91.7%
		Aveeno Oilated Bath Powder (S.C. Johnson)	Mineral oil 95%; Oatmeal -colloidal 43.3%
		Barrier Cream (National Care Products)	Dimethicone 20%
		Barriers (Roberts)	Dimethylpolysiloxene 20%
		Complex 15 Hand Cream (Schering)	Dimethicone 1.5%
		Keri Lotion (Bristol-Myers Squibb)	Lanolin 0.8%; Mineral oil 15.9%
		Moisturel Cream (Westwood Squibb)	Dimethicone 1%; Petrolatum 30%
		Nutraderm Cream (Galderma)	Light mineral oil
		Prevex Cream (TCD)	Petrolatum 67%
		Scott Silicone Skin Cream (Scott Chemical)	Dimethylpolysiloxane 20%
	Zinc Ointment 15% (Various manufacturers)	Zinc oxide 15%	
II		Epi-Lyt (Stiefel)	Lactic acid 5%; Glycerin 25%
		Hydrax Forte (Axxess Pharma)	Pthyluronate; PVP-Eicosene Copolymer
		Lac-Hydrin (Westwood-Squibb)	Ammonium lactate 12%
		Lacticare (Stiefel)	Lactic acid 5%
		NeoStrata AHA Sensitive Cream (Canderm Pharma)	Glycolic acid 4%
		Reversa AHA Cream (Dermtek)	Glycolic acid 8%
		Ti-U-Lac Lotion (Draxis)	Urea 10%
		Ultra Mide 25 (Baker Cummins)	Urea 10%
		Uremol 10% Cream (TCD)	Urea 10%
		Wibi (Galderma)	Glycerin 23%
III		Aquaderm Cream (Baker Cummins)	Hypoallergenic cream
		Aquatin Cream (Whitehall-Robins)	Hypoallergenic cream
		Cetaphil Moisturizing Lotion & Cream (Galderma)	Non-medicated emollient
		Dormer 211 Cream (Dormer)	Hyaluronic acid complex; Lecithin
		Glaxal Base (Roberts)	Non-medicated hypoallergenic; Base
		Schering Base (Schering)	Non-medicated emollient cream
Combination	I, II, III	Lubriderm Advanced Moisture Therapy (Warner-Lambert Consumer Healthcare)	Glycerin; Mineral oil; Vitamin A; Vitamin E
	I, II	Penederm Cream (Penederm)	Lactic acid 7.5%; Petrolatum liquid 1%
	I, III	Spectro Gluvs 19 (SpectroPharm)	Perfluoropolymethyl-Methylizopropyl ether Cerebroside hyaluronate complex
	I, II, III	Vaseline Intensive Care Lotion Aloe & Naturals (Lever Ponds)	Aloe; Dimethicone; Eucalyptus; Glycerin; Lavender; Lacithin; Sunflower seed oil; Vitamin E acetate

Table 2: A summary of some moisturizing products and their active ingredients.

Emollients

Emollients smooth skin by filling spaces between skin flakes with droplets of oil, and are not usually occlusive unless applied heavily. When combined with an emulsifier, they may help hold oil and water in the stratum corneum. Vitamin E is a common additive, which appears to have no effect, except as an emollient. Likewise, other vitamins, e.g., A and D, are also added with questionable effect. Examples of emollients include mineral oil, lanolin, fatty acids, cholesterol, squalene, and structural lipids.

Long chain saturated fatty acids and fatty alcohols are commonly used in topical pharmaceuticals and cosmetic formulations. They exert their benefits through effects on the skin barrier and on permeability. Examples include stearic, linoleic, linolenic, oleic, and lauric, which can be found in palm oil, coconut oil, and wool fat. Fatty acids and fatty alcohols can change the properties of intracellular lipids or the stratum corneum. Medium chain saturated hydrocarbons or longer chain unsaturated hydrocarbons are the most effective.⁵ Essential fatty acids (i.e., linoleic and alpha-linolenic acids) influence skin physiology and pathology via their effects on skin barrier functions, eicosanoid production, membrane fluidity, and cell signaling.

Structural lipids, i.e., intracellular lipids comprising multilamellae, which are located between stratum cornea cells, are also felt to play a considerable role in the water-holding potential of the stratum corneum. Ceramide is a major component of the inner cellular lipids and plays a major role in generating multilamellae architecture. Natural ceramides themselves, or their synthesis, are at present too expensive to make commercially available. Several pseudo ceramides have been synthesized and clinically shown to be effective in preventing and improving dry skin.¹

Moisturizers containing collagen and other proteins, i.e., keratin and elastin, claim to rejuvenate the skin by replenishing its essential proteins. This is unlikely to occur since these protein molecules are too large to penetrate the dermis. Protein additives may provide temporary relief of dry skin by filling irregularities in the stratum corneum. Like emollients, when they dry they shrink slightly, leaving a protein film that appears to smooth the skin and stretch out some of the fine wrinkles.

Indications Of Use

Indications for emollients include dry skin, i.e., xerosis or as a result of metabolic conditions, such as renal insufficiency and diabetes; atopic dermatitis; ichthyosis vulgaris; irritant contact

dermatitis and prevention⁶; nummular dermatitis; psoriasis; skin protection, i.e., frequent hand washing; and dermatoheliosis.

What Is The Ideal Moisturizer?

Patients who are confused by media hype often ask this question. The ideal moisturizer should be:⁷⁻¹⁰

- An effective moisturizer – hydrating the stratum corneum reduces and prevents TEWL
- An emollient – makes skin smooth and supple and reduces TEWL
- An aid in restoring the lipid barrier, i.e., duplicating and enhancing the skin's natural moisture retention mechanisms
- Cosmetically elegant and acceptable
- Moisturizing to sensitive skin – i.e., hypoallergenic, non-sensitizing, fragrance free, non-comedogenic
- Offered at an affordable price
- Long-lasting
- Absorbed rapidly providing immediate hydration.

Conclusion

As the population ages, the number of people suffering from dry skin will increase. A fundamental understanding of the physiochemical effects of moisturizers on the basic functions of the skin barrier will allow the further development of physiologically effective products for the prevention and treatment of dry skin and its related skin conditions.

References

1. Loden M, Maibach H. *Dry Skin and Moisturizers Chemistry and Function*. New York: CRC Press 1999.
2. Harding, C. Bartolone, J. Rawlings A. Effects of Natural Moisturizing Factor. In: Loden M, Maibach H, eds. *Dry Skin and Moisturizers; Chemistry and Function*. New York: CRC Press 1999.
3. Tanner F, Beurbe G. Mineral oil and petrolatum – reliable moisturizers. *Cosmetic Toiletries* 93:81 (1978).
4. Ghadially R, Halkier-Sorenson L, Elias P. Effects of petrolatum on stratum corneum structure and function. *J Am Acad Dermatol* 26(3 Pt. 2):387-96 (1992 Mar).
5. Jackson EM. Moisturizers: what's in them and how do they work. *Amer J Contact Dermatitis* 3:162-168 (1992).
6. Zhai H, Maibach HI. Moisturizers in preventing irritant contact dermatitis: an overview. *Contact Dermatitis* 38(5):241-4 (1998).
7. Jackson EM. Moisturizers: adjunct therapy and advising patients. *Amer J Contact Dermatitis* 7(4):247-50 (1996 Dec).
8. Wehr RF, Krochmal L. Considerations in selection a moisturizer. *Cutis* 39(6):512-5, 1987.
9. Dry skin, winter itch. *Health News*. University of Toronto Faculty of Medicine 9(6) (1991 December).
10. Gossel, T. Dry Skin. *US Pharmacist* 15(1):20-25 (1990).

Adverse Side Effects	Moisturizer Components
Occlusive Folliculitis	Petrolatum; Mineral oil
Sweat Retention	Miliara rubra, i.e., petrolatum and lanolin
Irritation	Urea; Lactic acid; Propylene glycol; Solvents
Allergic Contact Dermatitis	Fragrances; Preservatives, i.e, parabens, formaldehyde, Quaternium 15 and Imidazolidinyl urea; Lanolin; Additives, i.e., vitamin E and aloe vera
Photo Contact Dermatitis	Fragrances; UV filters
Contact Urticaria	Preservatives, i.e., sorbic acid; Fragrances, i.e., Balsam of Peru

Table 3: Adverse effects caused by moisturizers.

Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Anti-Acne Agent</i>	Tazarotene 0.1% <i>Tazorac</i> [®] Allergan	The US FDA gave marketing approval for this receptor-selective retinoid in October 2001, for the treatment of acne vulgaris.
<i>Neurotoxin</i>	Botulinum Toxin <i>BOTOX</i> [®] Allergan	The European Commission of the European Union passed a positive opinion on this neurotoxin in October 2001, for treating focal spasticity of the wrists and hands of adult post-stroke patients after reviewing data from a 126 patient phase III trial. In November 2001, TPP – Canada approved this product for managing post-stroke focal spasticity in adults.
<i>Atopic Dermatitis Agent</i>	Tacrolimus Ointment <i>Protopic</i> [®] Fujisawa	The European Union's Committee for Proprietary Medicinal Products recommended approval of this ointment in October 2001, for the treatment of patients with moderate to severe atopic dermatitis who do not respond to or cannot tolerate conventional treatment.
<i>Mouth and Throat Product</i>	Amlexanox 5% paste <i>Aptheal</i> [®] Strakan Ltd.	The UK Medicines Control Agency (UK MCA) gave marketing approval in October 2001, for the treatment of aphthous ulcers.
<i>HIV/AIDS</i>	Tenofovir Disoproxil Fumarate <i>Viread</i> [™] Gilead Sciences	The US FDA approved this antiretroviral agent in October 2001, for the treatment of HIV infection when taken in combination with other antiretroviral agents.
<i>HIV/AIDS</i>	HIV Drug Resistance Test <i>Trugene</i> [™] <i>HIV-1 Genotyping Test</i> Visible Genetics	The US FDA approved this HIV drug resistance test in October 2001, for HIV and AIDS patients. This test can identify which HIV medications have become ineffective because of the virus' mutation in individual patients. An estimated 60% of HIV/AIDS patients are resistant to at least one of the 15 anti-AIDS drugs.

Drug News

<i>Dear Health Care Professional</i>	Centocor released a "Dear Healthcare Professional" letter addressing new safety information for Remicare [®] (infliximab). In a Phase II study of 150 patients with moderate to severe CHF, higher incidences of mortality and hospitalization for worsening CHF were seen in the Remicade [®] treated patients, especially those treated with the higher 10mg/kg dose. The company recommends that therapy not be initiated in CHF patients and that treatment discontinuation be considered in patients with stable concomitant CHF, Remicade [®] is an unlabelled drug used for treating psoriasis.
<i>Antibacterial Agent</i>	Cubist Pharmaceuticals announced in October 2001, that data from Phase III clinical trials showed in all study populations, the clinical success rates ranged from 74-85% for Cidecin (daptomycin for injection) vs. 73 – 84% for the comparator (i.e., vancomycin or semi-synthetic penicillin) in the treatment of complicated skin and soft tissue infections caused by Gram-positive bacteria. These results form the basis for an NDA they are filing with the US FDA, which Cubist anticipates will be completed by mid-2002.



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Articles are indexed by drug names, trade-names, and disease terms.

Drug name **Issue #: Page #**

Isotretinoin 5: 3,4 (bold entries refer to major references)

5-Fluorouracil 0.5% Cream	9:1-4	Biochemotherapy	4:3-4	Diane-35 [®]	2:1-4;5:1-3
5-FU Microsponge	3:6;5:5	Biologically Active Dressing	6:6	Diane-50 [®]	2:1-4;5:1-3
Abreva [®]	5:5	Biphosphanates	1:4	Diclofenac Sodium	3:6;5:5
Accutane [®]	2:1-5;5:7;10:6	Bleomycin	1:6;5:6	Diltiazem	1:4
Acemannan Hydrogel [®]	5:6	Botulinum Toxin Type A	4:6;8:6; 13:1-2,6	Docosanol	1:6;2:6;5:4;6:6;6
Acetylsalicylic Acid	1:4	Botulinum Toxin Type B	4:6;5:5;6:6; 13:1-2	Dofetilide	9:6
Acitretin	3:1-2,5	Bronzing Gels	3:3-4	Dovonex [®]	5:4
Acne	2:1-4;5:1-3	Bronzing Powders	3:3-4	Doxepin	8:4
Actinac [®]	5:4	Bupropion	8:4	Doxycycline	11:6;12:6
Actinic Keratosis	9:1-4;10:1-2,5	Butenafine HCl	10:6;12:6	D-penicillamine	1:4
Adapin [®]	8:4	Butoconazole Nitrate	2:6;5:6	Drospirenone	11:6
Aerius [™]	12:6	Calcipotriol	5:4	Dysport [®]	13:1-2
Agalsidase	5:6;11:6;12:6	Cancidas [®]	6:6	Effexor [®]	8:4
Agenerase [®]	3:6;5:5	Capsaicin	7:6	Eflornithine	7:1-2,5
Alcohol	3:1-2,5	Carac [®]	9:1-4	Elavil [®]	8:3
Aldara [®]	6:1-4	Casporfungin Acetate	6:6	EMLA [®]	5:6
Alefacept	8:6	CellCept [®]	10:6	Enbrel [®]	12:6
Alitretinoin	1:6;5:5	Ciclopirox Olamine 1%	5:4	Ephedra	11:6
Alopecia Areata	6:5	Ciclopirox 8% Nail Lacquer	1:1,2,5;	Estradiol Transdermal Systems	2:6;5:6;7:6
Allegra [®]	1:6;5:6	Cidecin [®]	7:6;13:6	Estradiol Vaginal Ring	5:6
Allovecin 7	1:6	Ciprofloxacin	12:6	Estradot [®]	7:6
Ambisome [®]	5:4	Claritin [®]	4:6;5:4;6:6;9:6	Estring [®]	5:6
AMEVIVE [®]	8:6	Clindamycin/Benzoyl Peroxide	5:4;6:6;12:6	Estrostep [®]	12:6
Amitriptyline	8:4	Clindamycin phosphate	5:4	Etanercept	12:6
Aminolevulinic Acid	10:1-2,5,6;	Clindasol [®]	5:4	Ethinodiol Acetate	5:1-3
Amlexanox	4:6;5:4;13:6	Clindets [®] Pledgets	5:4	Ethinyl Estradiol	5:1-3;11:6;12:6
Amlodipine	1:4	Clindoxyl [®]	5:4	Etretinate	3:1-2,5
Amphotericin B Liposome	5:4	Clobetasol Propionate	1:6;5:6	Fabrazyme [®]	5:6;11:6
Amprenavir	3:6;5:5	Clomipramine	8:4	Famciclovir	5:6; 12:1-2,5
AndroGel [®]	5:5	Clotrimazole	5:6;10:6	Famvir [®]	5:6; 12:1-2,5
Anthrax	12:6	CO ₂ laser	1:4	Fexofenadine HCl	1:6;5:6
Antidepressants	8:3-5;	Colchicine	1:4	Finevin [®]	9:6
Apligraf	1:6;5:6;8:6	Colloidal silver	7:6	Flamazine [®]	5:4
Aptheal [®]	13:6	Composite Cultured Skin [®]	6:6	Flumethasone Pivalate	5:5
Aphthera [®]	4:6;5:4	Corticosteroids	11:3-5;12:3	Fluvoxamine	8:4
Arsenic Trioxide	7:6	Coumadin	1:4	Fluoxetine	8:4
Aslera [®]	3:6	Cyclophosphamide	5:6	Folinic acid	3:1-2,5
ASM 981	5:6	Cyclosporin	2:6;3:1-2,5;4:1-2,5;5:5;12:4	Gen-Terbinafine [®]	5:4
Aspirin	3:1-2,5	Cyproterone Acetate	5:1-3	Gengraf [®]	5:5
Atopic Dermatitis	4:1-2,5	Dapsone	8:6;9:6	Gestodene	5:1-3
Atrison [®]	8:6;9:6	Daptomycin	7:6;13:6	Ginkgo	11:6
Avelox [®]	8:6; 11:1-2	Denavir [®]	5:6	Ginseng	11:6
Azaleic Acid Cream 20%	9:6	Dendritic cellular immune response vaccine	4:3-4	Graftskin [®]	1:6;5:6;8:6
Benzaclin Topical Gel [®]	6:6;12:6	Dermatop [®]	5:5	Gynazole [®]	2:6;5:6
Betamethasone Dipropionate	10:6	Desloratidine	4:6;5:6;6:6;9:6;12:6	Halofuginone	5:5
Betamethasone Valerate	12:6	Desogestrel	5:1-3	HCT-1026	8:6
Bexarotene	1:6;5:5			Headache, Migraine	13:1-2

Hemangiomas	11:3-5	Novo-Terbinafine®	5:4	Solar keratosis	9:1-4;10:1-2,5
Herpes Simplex and Zoster	12:1-2,5	NSAIDS	3:1-2,5	Solex®	5:5
Histamine Dihydrochloride	1:6	Oasis Wound Dressing®	5:6	Sporanox®	9:6
HIV Drug Resistance Test	13:6	Olux® Foam	1:6;5:6	St. John's Wort	11:6
Hormone Replacement Therapy	10:3-5	Onychomycosis	1:1,2,5	Strontium Salts	5:6
Hydroxyuria	3:6;5:6	Ornithine Decarboxylase	7:1-2,5	Sulfonamides	3:1-2,5
Hyperhidrosis	13:1-2	Ortho Tricyclen®	2:1-4;5:1-3	Sunscreens	8:1-2
Imipramine	8:3	Paclitaxel	5:6	Surgical Excision	11:5
Imiquimod	6:1-4	Palmoplantar Pustular Psoriasis	12:3-5	Surgical Extirpation	1:4
Infliximab	10:6;13:6	Panectyl®	5:4	Surmontil®	8:4
Interferon-α	3:6;5:5;11:3-5	Panretin®	1:6;5:5	Sympathectomy	1:4
Interleukin-2	4:3-4	Paroxetine	8:3	Systemic Sclerosis	1:3-5
Intralesional Laser Therapy	11:5	Paxene®	5:6	Tacrolimus	2:6;3:5; 4:1-2,5,6 ;5:5;13:6
Isotretinoin	2:1-5 ;5:7;10:6	Paxil®	8:3	Tar and Anthralins	12:3
Itraconazole	9:6	Penciclovir	5:6	Targretin®	1:6;5:5
Ketoconazole	5:4	Penlac®	1:1,2,5	Tazorac®	13:6
Lamictal®	3:6	Phenytoin	3:1-2,5	Tazarotene	13:6
Lamisil®	3:6;5:4;9:6	Photodynamic Therapy	6:5; 10:1-2,5,6 ;	Tenofovir Disoproxil Fumerate	13:6
Lamotrigine	3:6	PMS-FLUMETHASONE- CLIOQUINOL®	5:5	Terbinafine	3:6;5:4;9:6
Leprosy	9:6	Poison Ivy/Oak	7:3-5	Terbinafine – 250®	5:4
Levaquin®	2:6;5:4	Prasterone	3:6	Testosterone Gel	5:5
Levocetirizine	5:6	Prednicarbate	5:5	Tetracycline	12:4
Levofloxacin	2:6;5:4	Probenecid	3:1-2,5	Tikosyn®	9:6
Levonorgestrel	5:1-3	Prograf®	4:6	Tinted Moisturizers	3:3-4
Levulan® Kerastick™	8:6; 10:1-2,5,6	Protopic®	2:6; 4:1-2,5 ;13:6	Tofranil®	8:4
Lidocaine/Procaine	5:6	Prozac®	8:4;	Tretinoin	2:6;5:6;11:6
Linezolid	5:4;10:6	Psoriasis	3:1-2,5	Trexall®	7:6
Loratidine	5:4	Psychiatric Disorders	8:3-5 ;	Trimeprazine Tartrate	5:4
Loprox®	5:4	Pulsed Dyed Laser	11:3-5	Trimipramine	8:4
Luvox®	8:4	PUVA	3:1-2,5;12:3-4	Trisenox®	7:6
Luxiq®	12:6	Rapamune®	11:6	Trizivir®	4:6;5:5
Lynestrenol	5:1-3	Raynaud's Phenomenon	1:3-5	Trugene™ HIV-1 Genotyping Test	13:6
Maxamine	1:6	Recombinant Human Iduronidase (IDUA)	8:6	Valacyclovir HCl	11:6
Melanoma vaccine	4:3-4	Rectogesic®	1:6	Valcyte®	9:6
Melanoma	4:3-4	Remicade™	10:6;13:6	Valganciclovir	9:6
Mentax®	10:6;12:6	Renova®	2:6;5:6	Valtrex®	11:6
Mequinol 2%/Tretinoin 0.1%	6:6	Replagal™	12:6	Vaniqa®	7:1-2,5
Methotrexate	1:4;3:1-2,5;7:6	Retin-A® Micro® Microsphere	11:6	Varicella Zoster Immune Globulin	5:6
Metronidazole	5:5;8:1-2	Retinoids	12:3	VariZIG®	5:6
Microsurgical Arteriolytic	1:4	Rid Mousse®	5:6	Veldona®	3:6;5:5
Minocycline	2:1-4	Rosacea	8:1-2 ;	Venlafaxine	8:4
Minoxidil	6:6	ROSASOL®	5:5; 8:1-2	Viracept®	4:6
Moisturizers	13:3-5	SangCya®	2:6	Viread™	13:6
Moxifloxacin HCl	8:6; 11:1-2	Santyl® Ointment	9:6	Vivelle®	2:6;5:6
M-Vax®	1:6	Scleroderma	1:3-5	Vulvovaginal Itching	10:3-5
Mycophenolate Mofetil	10:6	Self-Tanning Creams	3:3-4	Warts, Genital/Perianal	6:1-4
Myobloc®	4:6;5:5;13:1-2	Sertraline	8:4	Wellbutrin®	8:4
Nefazadone	8:4	Serzone®	8:4	Xtrac® Excimer Laser System	6:6
Nelfinavir	4:6	Silver Sulfadiazine	5:4	Xyzal/Xusa®	5:6
Neoclarityn®	12:6	Sinequan®	8:4	Yasmin®	11:6
Neomycin	3:1-2,5	Sirolimus	11:6	Zolofit®	8:3
Nifedipine	1:4	Skin Infections, Bacterial	11:1-2	Zyvox®	5:4;10:6
Nitroglycerin	1:4,6	Solage®	6:6		
Norgestrel	5:1-3	Solaraze®	3:6;5:5		
Norgestimate	4:1-3				
Norethindrone	5:1-3;12:6				