

Skin Therapy Letter[®]

Volume 13 • Number 6 • July-August 2008

Indexed by the US National Library of Medicine and PubMed

EDITOR: DR. STUART MADDIN

EDITOR-IN-CHIEF

Stuart Maddin, MD
University of British Columbia, Vancouver, Canada

ASSOCIATE EDITORS

Hugo Degreef, MD, PhD
Catholic University, Leuven, Belgium

Jason Rivers, MD
University of British Columbia, Vancouver, Canada

EDITORIAL ADVISORY BOARD

Murad Alam, MD
Northwestern University Medical School, Chicago, USA

Kenneth A. Arndt, MD
Beth Israel Hospital
Harvard Medical School, Boston, USA

Wilma Fowler Bergfeld, MD
Cleveland Clinic, Cleveland, USA

Jan D. Bos, MD
University of Amsterdam, Amsterdam, Holland

Alastair Carruthers, MD
University of British Columbia, Vancouver, Canada

Bryce Cowan, MD, PhD
University of British Columbia, Vancouver, Canada

Jeffrey S. Dover, MD
Yale University School of Medicine, New Haven, USA
Dartmouth Medical School, Hanover, USA

Boni E. Elewski, MD
University of Alabama, Birmingham, USA

Barbara A. Gilchrist, MD
Boston University School of Medicine, Boston, USA

Christopher E.M. Griffiths, MD
University of Manchester, Manchester, UK

Aditya K. Gupta, MD, PhD, MBA/MCM
University of Toronto, Toronto, Canada

Mark Lebwohl, MD
Mt. Sinai Medical Center, New York, USA

James J. Leydon, MD
University of Pennsylvania, Philadelphia, USA

Harvey Lui, MD
University of British Columbia, Vancouver, Canada

Howard I. Maibach, MD
University of California Hospital, San Francisco, USA

Jose Mascaro, MD, MS
University of Barcelona, Barcelona, Spain

Larry E. Millikan, MD
Tulane University Medical Center, New Orleans, USA

Jean Paul Ortonne, MD
Centre Hospitalier Universitaire de Nice, Nice, France

Ted Rosen, MD
Baylor College of Medicine, Houston, USA

Alan R. Shalita, MD
SUNY Health Sciences Center, Brooklyn, USA

Wolfram Sterry, MD
Humboldt University, Berlin, Germany

Richard Thomas, MD
University of British Columbia, Vancouver, Canada

Stephen K. Tyring, MD, PhD, MBA
University of Texas Health Science Center, Houston, USA

John Voorhees, MD
University of Michigan, Ann Arbor, USA

Guy Webster, MD
Jefferson Medical College, Philadelphia, USA

Klaus Wolff, MD
University of Vienna, Vienna, Austria

MANAGING EDITOR

Penelope Gray-Allan

Botulinum Toxin Products Overview

A. Carruthers, MD, FRCPC¹;

J. Carruthers, MD, FRCS(C), FRC(Ophth)²

¹Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

²Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

The tremendous success of botulinum toxin type A (BOTOX[®], Allergan Inc.) in the cosmetic arena has acted as a stimulus for the development of other neurotoxins. After more than 2 decades of use, BOTOX[®] has become synonymous with wrinkle reduction and is considered to be the one of the most common non-surgical cosmetic procedures performed worldwide. Because of its vast popularity among patients seeking non-invasive methods to achieve facial rejuvenation, physicians from diverse specialties have integrated botulinum toxin injections into their existing practices. Herein, we present an overview of botulinum toxin products for cosmetic applications that have received regulatory approval or are under development.

Keywords: botulinum toxin type A, botulinum toxin type A-Hall strain, botulinum toxin type B, BTX, wrinkles, aging

In 1982, one of us (JC) first brought the concept and the application of botulinum toxin (BTX) for clinical use in ophthalmology to Health Canada. This submission was approved and experimental use for misaligned eyes began in 1983. The subsequent use for benign essential blepharospasm led to its cosmetic use, which we developed in 1987. Following 25 years of therapeutic applications and over 20 years of cosmetic experience with this neurotoxin in Canada, its uses and development of new products continue to expand.¹

BTX Products Under Development in North America

In addition to the original product, several BTX injectables are in clinical development in North America (Table 1).

BOTOX[®] Cosmetic/Vistabel[®]/Vistabex[®] (Allergan Inc.)

This is the original botulinum toxin type A (BTX-A) product, which was initially purified in crystalline form by Shantz and adapted for clinical use by Scott in San Francisco.¹ There was a formulation change in 1997 in order to reduce the amount of immunogenic protein in the material, but there have been no modifications since. In order to gain European regulatory approval, production of a vial containing 50 units was required; it was previously only available as a 100 unit vial. BTX has a broad range of approvals for both therapeutic and cosmetic indications. This neurotoxin currently captures 85% of the worldwide BTX market and the majority of scientific peer reviewed articles on BTXs are about BOTOX[®].¹

	BOTOX®	BOTOX® Cosmetic/ Vistabel®/ Vistabex®	Dysport®/ Reloxin®	Dysport® Cosmetic	Myobloc®/ NeuroBloc®	NT-201/ XEOMIN®	PurTox®
Company	Allergan Inc.	Allergan Inc.	Ipsen Inc./ Medicis Inc.	Ipsen Inc./ Medicis Inc.	Solstice Neurosciences Inc.	Merz Pharmaceuticals	Mentor Corporation
Type	Type A-Hall strain	Type A-Hall strain	Type A	Type A	Type B	Type A-Hall strain	Type A-Hall strain
Approvals	In over 75 countries worldwide, including US and Canada	In over 16 countries, including US, Canada, Italy, France	In over 65 countries; not approved in US or Canada	Germany, other European countries	Some European countries, US, Canada	Germany, other European countries, Mexico, Argentina	None
Active Substance (molecular weight)	Botulinum toxin type A complex (900kD)	Botulinum toxin type A complex (900kD)	Botulinum toxin type A complex (900kD)*	Botulinum toxin type A complex (900kD)*	Botulinum toxin type B complex (700kD)	Botulinum toxin type A, free from complexing proteins (150kD)	Botulinum toxin type A, free from complexing proteins (150kD)
Strength of Action (BTX-A:Product)	1:1	1:1	1:2 - 1:4 (approximate)	1:2 - 1:4 (approximate)	1:50 - 1:100	1:1	1:1.5?
Indications	Blepharospasm; cervical dystonia; glabellar lines; hyperhidrosis	Glabellar lines	Blepharospasm; cervical dystonia	Glabellar lines	Cervical dystonia	Blepharospasm; cervical dystonia; glabellar lines in Argentina	Phase 3 for glabellar lines; Phase 1 for spasmodic torticollis/ cervical dystonia
Mode of Action	SNAP-25	SNAP-25	SNAP-25	SNAP-25	VAMP	SNAP-25	SNAP-25
Pharmaceutical Form	Powder dissolved in solution for injection	Powder dissolved in solution for injection	Powder dissolved in solution for injection	Powder dissolved in solution for injection	Solution	Powder dissolved in solution for injection	?
Units/vial	100	50	500	300 or 500	2,500; 5,000; 10,000	100	?
Volume	10mL maximum	1.25mL or 2.5mL recommended	2.5mL recommended	5mL maximum	0.5mL; 1mL; 2mL	8mL maximum	?
Re-constitution	0.9% NaCl solution	0.9% NaCl solution	0.9% NaCl solution	0.9% NaCl solution	Prepared solution, dilutable	0.9% NaCl solution	0.9% NaCl solution
Storage	2-8°C or < -5°C	2-8°C or < -5°C	2-8°C	2-8°C	2-8°C do not freeze	Up to 25°C	?

Table 1 Summary of botulinum toxin products approved or under development for cosmetic indications

SNAP-25 (synaptosomal associated protein with the molecular mass of 25kD) = An intracellular protein that is essential for synaptic vesicle transmission; it has been identified as the molecular target of BTX-A.

VAMP (synaptobrevin) = A protein involved in synaptic vesicle movement that has been identified as the molecular target of BTX-B.

* The formulation contains complexes of variable size between 500kD-900kD.²

? = Data unavailable or unconfirmed

Dysport®/Reloxin® (Ipsen Inc./ marketed for cosmetic indications in North America by Medicis Inc.)

This formulation of type A neurotoxin is approved in over 65 countries, although, at the time of writing, it has not been approved for cosmetic use in North America or Europe. The difference between Dysport®/Reloxin® and its original counterpart is that BOTOX® is purified by repeated

precipitation and redissolution, whereas Dysport®/Reloxin® is produced by purification using a column separation method. The distinct processes used for purification produce some differences in the surrounding multi-protein complex that is formed around the neurotoxin; however, the clinical significance of this variation is still unclear.³ Another potential difference may reside in the diffusion characteristics

of the injected materials, which may produce varying levels of adhesion and retention. In North America, the vial size of Reloxin® will be 300 units. This formulation is currently under US FDA review for esthetic use. In Europe, a 125 unit vial is anticipated to become available.

PurTox® (Mentor Corporation)

Complexing proteins are therapeutically superfluous and present a high foreign protein load, which may in turn increase the potential for eliciting an immune response. PurTox® is an uncomplexed type A neurotoxin (i.e., the neurotoxin molecule is stripped of its complexing proteins) that is licensed to Mentor Corporation. It is currently in Phase 3 testing for glabellar frown lines, as well as in various stages of development for therapeutic indications. The neurotoxin units of PurTox® appear to be slightly less effective than that of BOTOX®, and they are subjected to different purification processes.

NT-201/ XEOMIN® (Merz Pharmaceuticals)

This uncomplexed BTX-A is produced by Merz Pharmaceuticals and has received approval for the treatment of blepharospasm and cervical dystonia in some European countries, as well as in Mexico and Argentina. Currently, regulatory approval for the esthetic indication of treating glabellar frown lines has been obtained in Argentina only. In terms of potency, NT-201 appears to exhibit a 1:1 dose ratio when compared with BOTOX®, and it has a smaller molecule relative to the other BTX products discussed. In studies that compared NT-201/XEOMIN® with BOTOX® for therapeutic indications, no significant differences were detected in both safety and efficacy.^{4,5} Jost, et al. proposed that the absence of complexing proteins in NT-201 does not hinder its performance.⁴ Instead, uncomplexed forms of BTX-A may result in purer formulations that can potentially reduce sensitization and antibody formation, as well as improve clinical efficacy; this has been a concern with past formulations containing complexing proteins.

Myobloc®/NeuroBloc® (Solstice Neurosciences Inc./ Eisai Co., Ltd.)

Myobloc®/NeuroBloc® is the only available botulinum toxin type B (BTX-B) product, and cervical dystonia is currently its sole approved indication. This BTX-B neurotoxin was originally developed by Elan Pharmaceuticals, but it is now produced by Solstice Neurosciences Inc.; Eisai Co., Ltd. holds the commercial rights to the product in Japan, Russia, European Union nations, as well as other countries. Myobloc®/NeuroBloc® is approved in Canada, US and Europe for cervical dystonia, and is available as a liquid with an acidic pH level of 5.5 to 5.6. Due to the elevated acidity, patients may find injections to be very painful. In addition, the units are substantially less effective when compared with BTX-A units. For example, in cervical dystonia, the ratio is estimated to be approximately 50:1, whereas for glabellar frown lines, the ratio is 100:1. When used for the temporary

correction of glabellar frown lines, the clinical duration did not appear to be as long-lasting as BOTOX®.^{6,7} However, Myobloc® does appear to exhibit a more rapid onset of action and a greater area of diffusion.⁸ Associated adverse effects, such as dry mouth and dysphagia, are generally mild-to-moderate, transient, and more common at higher doses.

Other BTX Products Under Global Development

CBTX-A (Lanzhou Institute of Biological Products)

This is the only BTX-A product that is approved in the People's Republic of China; as well, it is marketed in Brazil as Prosigne®. The major difference between this preparation and the other BTX-A products is that a bovine gelatin protein is added to the vial in order to prevent the BTX from sticking to the wall of the vial, syringe, etc. Human serum albumin is almost always used, but in the case of CBTX-A, the gelatin utilized is of bovine derivation, which has the potential to induce allergic reactions, or possibly bovine spongiform encephalopathy, a neurological disease commonly known as "mad cow disease".

CNBTX-A (Nanfeng Medical Science and Technology Development Co., Ltd.)

Although product orders may be placed via the internet, CNBTX-A is neither licensed nor approved in any country. The potency of CNBTX-A was recently investigated and found to contain significantly higher levels of botulinum neurotoxin than listed on the product's label, which could constitute a severe health risk for patients.⁹ We are not aware of any additional details about this preparation.

Neuronox® (Medy-Tox Inc.)

This BTX-A preparation is produced by Medy-Tox in South Korea. It is widely used in Korea and South East Asia, and it appears to be effective. We are not aware of any additional details except that the worldwide licensing of its cosmetic use has been acquired by Q-Med Inc. (Sweden).

Conclusion

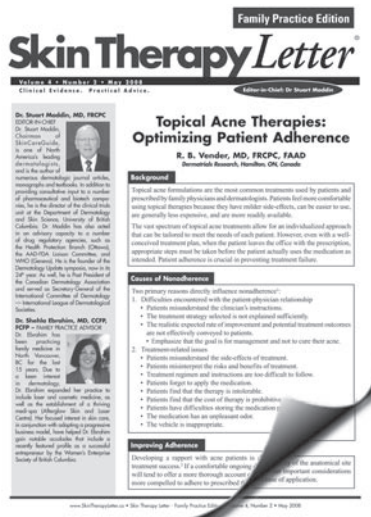
The use of botulinum toxin is continuing to increase rapidly, with a worldwide growth in sales that is forecasted to be in excess of 20% annually for the near future. A milestone was reached in 2006 when BOTOX® became a billion dollar drug for Allergan Inc.; the company continues to retain 85% of the worldwide neurotoxin market. However, competing products will receive regulatory approval for esthetic indications in the near future. Reloxin® will likely be approved in the US towards the end of 2008 or early 2009, and NT-201 and PurTox® are expected to follow suit in a couple of years. Other neurotoxins not discussed in this overview will undoubtedly appear, especially as the applications of BTX continue to expand. At the present time, the most dramatic area of development of BTX is occurring in the field of urology, but it is highly likely that further innovative uses for this exceptional molecule will also emerge.

References

1. Carruthers J, Carruthers A. The evolution of botulinum neurotoxin type A for cosmetic applications. *J Cosmet Laser Ther* 9(3):186-92 (2007 Sep).
2. Wenzel R, Jones D, Borrego JA. Comparing two botulinum toxin type A formulations using manufacturers' product summaries. *J Clin Pharm Ther* 32(4):387-402 (2007 Aug).
3. Spencer JM. Botulinum toxin B: the new option in cosmetic injection. *J Drugs Dermatol* 1(1):17-22 (2002 Jul).
4. Jost WH, Blumel J, Grafe S. Botulinum neurotoxin type A free of complexing proteins (XEOMIN) in focal dystonia. *Drugs* 67(5):669-83 (2007).
5. Roggenkamper P, Jost WH, Bihari K, et al. Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm. *J Neural Transm* 113(3):303-12 (2006 Mar).
6. Jacob CI. Botulinum neurotoxin type B--a rapid wrinkle reducer. *Semin Cutan Med Surg* 22(2):131-5 (2003 Jun).
7. Spencer JM, Gordon M, Goldberg DJ. Botulinum B treatment of the glabellar and frontalis regions: a dose response analysis. *J Cosmet Laser Ther* 4(1):19-23 (2002 Mar).
8. Flynn TC, Clark RE. Botulinum toxin type b (MYOBLOC) versus botulinum type a (BOTOX) frontalis study; rate of onset and radius of diffusion. *Dermatol Surg* 29(5):519-22 (2003 May).
9. Hunt T, Clarke K. Potency of the botulinum toxin product CNBTX-A significantly exceeds labeled units in standard potency test. *J Am Acad Dermatol* 58(3):517-8 (2008 Mar).

Skin Therapy Letter[®]

Special Editions



Skin Therapy Letter[®]

Family Practice Edition

Read it on: www.SkinTherapyLetter.ca

Skin Therapy Letter[®]

Pharmacist Edition

Read it on: www.SkinPharmacies.ca

Go online to read these new dermatology publications
for family physicians and pharmacists

- Peer Reviewed
- Practical Advice
- Current Treatment Information

Update on Sunscreens

R. Bissonnette, MD, FRCPC

Innovaderm Research, Montreal, QC, Canada

ABSTRACT

Sunscreens have been around for more than 70 years. Designed originally to protect against sunburn, recognition of the various harmful effects of ultraviolet (UV) radiation has broadened the use of sunscreens. The addition of effective UVA sunscreen agents has enabled claims beyond protection against sunburn to include prevention of idiopathic photodermatitis, actinic keratoses, skin cancer, and photoaging. This article will review some of the recent advances in photoprotection, including the development of sunscreen formulations offering higher and broader protection against solar radiation.

Key Words: sunscreens, photoprotection, ultraviolet A, ultraviolet B, UVA, UVB, sun protection factor, SPF

Protection Against Ultraviolet A (UVA) Radiation

Rating UVA Protection

The almost universal use of the sun protection factor (SPF) has lured many consumers into thinking that a higher SPF means a better sunscreen. Because SPF is mostly an indicator of UVB protection, it is difficult for consumers and physicians to compare the UVA protection afforded by sunscreens.¹ For many years, some countries have been using UVA labeling systems that can provide guidance on both UVA and UVB protection that is offered by sunscreens. Other countries, like the US and Canada, have been slower to introduce guidelines for UVA protection labeling.

Modifications to Sunscreen Labeling

The US FDA recently proposed inclusion of a 4 star grading system in conjunction with a descriptor (i.e., low, medium, high, and highest) to rate UVA protection.² This star rating system will depend on results of both *in vitro* and *in vivo* UVA testing. According to the agency, UVA ratings would be based on 2 tests: one would measure the sunscreen's ability to reduce UVA penetration and the second would measure the product's ability to prevent tanning. The test that yields the lowest level of UVA protection would determine the number of stars that the sunscreen would receive. This will help consumers and physicians identify the level of UVA protection provided by the different sunscreens. Other modifications include making minor changes to UVB testing procedures to improve accuracy, increasing the maximum sunburn protection factor from SPF 30+ to SPF 50+, and sanctioning the use of new combinations of active ingredients.²

Avobenzone and Photostability

Protection against UVA radiation was revolutionized by the introduction of butyl methoxydibenzoylmethane (avobenzone) in the late 1980s and early 1990s. This was the first organic sunscreen agent that provided some protection for mid- to long-range UVA rays. However, the degradation of some UVA filters, such as avobenzone, by

sunlight, prompted the need to stabilize the formulation in order to prevent the loss of efficacy. Upon absorption of UV radiation, the avobenzone molecule can transform into a molecule that no longer absorbs UVA radiation. In formulations where avobenzone is not photostable, UVA protection decreases with the time spent under the sun. This has been shown to occur after as little as 60-90 minutes of sun exposure.³

A number of different companies have developed systems to stabilize avobenzone in the final formulations. For example, a combination of avobenzone and 2-ethylhexyl ester (octocrylene) has been shown to achieve a photostable product.⁴ The addition of diethylhexyl 2,6-naphthalate also makes avobenzone photostable.⁵ The combination of diethylhexyl 2,6-naphthalate, avobenzone and oxybenzone is known under the commercial name of Helioplex™ and it is present in UltraSheer® and Age Shield® sunscreens (Neutrogena®/Johnson & Johnson). The addition of Tinosorb S® (Ciba Specialty Chemicals) has also been shown to photostabilize avobenzone.⁶ Confirmation of avobenzone's photostability in a given formulation is difficult unless the sunscreen's chemical stability has been studied and the results are published in a peer reviewed journal. In the absence of such studies, physicians can get indirect evidence of the photostability of a given formulation from UVA protection factor determination with methods such as persistent pigment darkening (PPD). PPD evaluates pigmentation present at 2 hours after the end of exposure to different UVA fluences. Because UVA exposures for these methods are rather lengthy, a sunscreen formulation with unstable avobenzone will have a lower protection factor than a similar formulation with stabilized avobenzone.

Recently Introduced Organic UVA Sunscreen Agents

A number of UVA sunscreen agents have been introduced in the past few years. Unfortunately, their availability varies widely from country to country. For example, in the US and Canada, sunscreen agents are considered to be drugs. Sunscreen manufacturers must therefore submit a new drug

application when they want to incorporate a new agent into a formulation. This explains why ecamsule (terephthalylidene dicamphor sulphonic acid [Mexoryl SX™, L'Oréal]) was only recently introduced in the US in 2006, whereas, this agent has been available in most other regions of the globe for more than 10 years. Mexoryl SX™ is a photostable chemical sunscreen agent that offers mid-range UVA protection.⁷ When combined with avobenzone, UVA protection is enhanced. Sunscreen products that contain Mexoryl SX™, and are available in the US, include Anthelios SX™ Daily Moisturizing Cream (SPF 15), Anthelios™ 15 Sunscreen Cream (SPF 15) and Anthelios SX™ 40 Sunscreen Cream (SPF 40, to be introduced in 2008).

Dometrizole trisiloxane (Mexoryl XL™) is another recently introduced organic sunscreen agent offering mid-range UVA protection. The addition of Mexoryl XL™ to Mexoryl SX™ has been shown to increase UVA protection in a synergistic manner, which may be attributable to its 2 phase component. Mexoryl XL™ was introduced in Canada in 2006. It has not yet been approved in the US, but has been available worldwide for many years in different sunscreens made by L'Oréal. In Canada, Mexoryl XL™ can be found in sunscreens sold under different brands including Anthelios™, Ombrelle™, Vichy™ and Biotherm™ (L'Oréal).

Bemotrizinol and bisoctrizole (Tinosorb S® and Tinosorb M® respectively, Ciba Specialty Chemicals) are organic compounds that also provide broad-spectrum UV protection. Tinosorb S® has been shown to increase photostability of avobenzone.⁶ Tinosorb S® and Tinosorb M® are mid-range photostable sunscreen agents that have been used in Europe for many years, but they are not yet approved in the US. These UV filters have recently been introduced in Canada and are formulated in Minesol® SPF 60 products (RoC®/Johnson & Johnson).

Protection Against Visible Light

The effect of visible light on the skin has received very little attention, compared with UV radiation. The role of visible light, viewed as both physiologic and pathologic phenomena, and its effects on the skin are probably less important than the role of UV radiation. However, visible light sensitivity is an important phenomenon in diseases such as porphyria, solar urticaria, and other idiopathic photodermatoses, such as polymorphous light eruption. Patients who undergo photodynamic therapy treatments also become sensitive to visible light for a few days because of the accompanying topical medications, such as aminolevulinic acid and methylaminolevulinate, or for a few weeks due to systemic agents like porfimer sodium. A recent study by Mahmoud, et al. suggested that visible light exposure can increase pigmentation in patients with skin phototype IV to VI.⁸ Protection against visible light might be important for darker skinned patients who have pigmentary disorders such as post-inflammatory hyperpigmentation and

melasma. Further research on the effects of visible light is definitely needed.

Organic sunscreen agents usually offer no protection against visible light, as their absorption spectrum is limited to UVB and UVA wavebands. Inorganic sunscreen agents, such as iron oxide, titanium dioxide, and zinc oxide can offer some visible light protection. However, the spectral protection of these agents varies according to their particle size. Larger particles of titanium dioxide and zinc oxide can protect in the visible range. Earlier formulations containing physical blocking agents tended to leave a white/pasty film on the skin, but with the advent of smaller-sized particles, modern physical sunscreens have made improvements in their effect on cosmetic appearance. Iron oxide is another physical UV blocking agent; however, it has the unique advantage of being closer to the natural skin color of phototype II and III individuals. The difference in visible light protection afforded by high SPF sunscreens with inorganic sunscreen agents was illustrated in a recent study that compared 2 inorganic sunscreens containing titanium dioxide, zinc oxide, and iron oxide for their ability to protect against blue light sensitivity induced by aminolevulinic acid application.⁹ The sunscreen containing 3.2% iron oxide (Avène Compact, Pierre Fabre Dermo-Cosmétique) offered a protection factor of 22:1 (i.e., the ratio of the lower blue light fluence that induced erythema on sunscreen protected skin to the lower blue light fluence that induced erythema on skin that was unprotected). Whereas the sunscreen with a lower concentration of 0.3% iron oxide offered only a protection factor of 2:1.

Systemic Absorption of Sunscreening Agents

Until recently, systemic exposure to sunscreen agents had also received relatively little attention in the medical literature. Agents such as benzophenones and octyl-methoxycinnamate can be detected in plasma and urine after topical application of sunscreen products.¹⁰ Unfortunately, most of these studies were conducted with non-commercial sunscreen formulations or were performed at significantly higher doses than what the average consumer uses. Additional research is definitely needed to explore the absorption of active agents contained in commercial sunscreens used under normal conditions. Furthermore, studies assessing the risks (or benefits) of systemic absorption of various sunscreen agents in adults, children, and pregnant women are also warranted.

Sunlight, Vitamin D and Sunscreens

Over the past few years there has been considerable media coverage about the influence of vitamin D and sun exposure on various diseases, including different types of cancer. The incidence of and mortality from many cancers have been reported to be reduced with decreasing latitude.¹¹ Holick hypothesized that this reduction is related to higher vitamin D production from increased sun exposure.¹¹ Vitamin D synthesis is a UVB phenomenon and sunscreens are usually very effective in protecting against UVB. Few prospective studies on the role of vitamin D and sun exposure in cancer

prevention have been published. Additional studies are necessary to address issues such as the optimal amount of vitamin D needed to have beneficial effects and the role of oral vitamin D intake versus vitamin D synthesis following sun exposure.

Sun avoidance and the adequate use of high SPF and high UVA protection sunscreens on all exposed skin areas may still be appropriate for a kidney transplant patient who already has had multiple invasive squamous cell carcinomas. However, the situation is different for a healthy phototype IV indoor worker living in Canada who has no personal or familial history of skin cancer and takes part in no outdoor activities. Based on the current retrospective and prospective studies, physicians should individualize the sun protection advice that they give to their patients and discuss whether additional benefits can be derived from oral vitamin D supplementation. The Canadian Cancer Society issued a statement in 2007 recommending that Canadian adults should consider taking 1000 IU of vitamin D daily. This was based on evidence suggesting that vitamin D could reduce the risks of breast, colorectal, and prostate cancers.

Conclusion

Many sunscreens now offer very good broad-spectrum protection in both the UVA and UVB ranges. In many countries, changes in labeling guidelines will make it easier for consumers and physicians to evaluate the level of UVA protection afforded by sunscreens. However, further research is needed in many areas including the role of visible light, the risks of systemic absorption of sunscreen agents, and the role of vitamin D and sun exposure in preventing cancers and other diseases.

References

1. Bissonnette R, Allas S, Moyal D, et al. Comparison of UVA protection afforded by high sun protection factor sunscreens. *J Am Acad Dermatol* 43(6):1036-8 (2000 Dec).

2. Department of Health and Human Services, Food and Drug Administration. Federal Register, 21 CFR Parts 347 and 353 Sunscreen Drug Products for Over-the-Counter Human Use; Proposed Amendment of Final Monograph; Proposed Rule. Vol. 72, No. 165 (2007 August 27). Available from: <http://www.fda.gov/cder/drug/infopage/sunscreen/default.htm>. Last accessed July 24, 2008.
3. Gonzalez H, Tarras-Wahlberg N, Stromdahl B, et al. Photostability of commercial sunscreens upon sun exposure and irradiation by ultraviolet lamps. *BMC Dermatol* 7:1 (2007).
4. Gaspar LR, Maia Campos PM. Evaluation of the photostability of different UV filter combinations in a sunscreen. *Int J Pharm* 307(2):123-8 (2006 Jan 13).
5. Cole C, Chu M, Finkey MB, et al. Comparison of photoprotection efficacy and photostability of broad spectrum sunscreens. Presented at: The 64th Annual Meeting of the American Academy of Dermatology; San Francisco, CA; March 3-7, 2006. Poster #P2617.
6. Chatelain E, Gabard B. Photostabilization of butyl methoxydibenzoylmethane (Avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S), a new UV broadband filter. *Photochem Photobiol* 74(3):401-6 (2001 Sep).
7. Moyal D. Prevention of ultraviolet-induced skin pigmentation. *Photodermatol Photoimmunol Photomed* 2004;20(5):243-7 (2004 Oct).
8. Mahmoud BH, Hexsel C, Lim H, et al. Impact of long wavelength UVA and visible light on melanocompetent skin. Presented at: The 66th Annual Meeting of the American Academy of Dermatology; San Antonio, TX; February 1-5, 2008. Poster #P2420.
9. Bissonnette R, Nigen S, Bolduc C, et al. Protection afforded by sunscreens containing inorganic sunscreens agents against blue light sensitivity induced by aminolevulinic acid. *Dermatol Surg*. In press 2008.
10. Janjua NR, Kongshoj B, Andersson AM, et al. Sunscreens in human plasma and urine after repeated whole-body topical application. *J Eur Acad Dermatol Venereol* 22(4):456-61 (2008 Apr).
11. Holick MF. Vitamin D deficiency. *N Engl J Med* 357(3):266-81 (2007 Jul 19).

www.SkinTherapyLetter.ca – A Physician's site for:

- **A-Details™: Online Drug Presentations**
- **SkinTherapyLetter® Articles**
- **Meeting Abstracts and Proceedings**
- **To get more information, Canadian medical professionals and consumers can access all of our sites from www.SkinCareGuide.ca or go directly to:**

AcneGuide.ca	BotoxFacts.ca	ColdSores.ca	DermatologyCare.ca
EczemaGuide.ca	FungalGuide.ca	HerpesGuide.ca	Lice.ca
MildCleanser.ca	MohsSurgery.ca	PsoriasisGuide.ca	PsoriaticArthritisGuide.ca
RosaceaGuide.ca	SkinCancerGuide.ca	Sweating.ca	UnwantedFacialHair.ca

- **Medical professional sites:**

SkinPharmacies.ca	SkinTherapyLetter.ca	Dermatologists.ca
-------------------	----------------------	-------------------

We welcome your comments and suggestions. Please e-mail us at physicians@skincareguide.com

Class	Name/Company	Approval Dates/Comments
<i>Acne</i>	Adapalene <i>Differin® Gel 0.1%</i> Galderma KK/ Shionogi	Japan's Ministry of Health, Labour and Welfare approved this first-in-class topical retinoid in July 2008 for the treatment of acne vulgaris.
<i>Actinic Keratosis</i>	Methyl Aminolevulinate Hydrochloride Cream <i>Metvixia™ + Aktelite® CL128</i> Photocure ASA/ Galderma	The US FDA approved the combined use of this topical light sensitizing agent used in photodynamic therapy in June 2008 for the treatment of actinic keratosis. This novel therapy involves the local application of Metvixia™ in combination with Aktelite® CL128, which is an LED based narrow band (630 nm) red light technology device.
<i>Dermal Filler</i>	Cross-linked Collagen <i>EVOLENCE®</i> OrthoNeutrogena/ ColBar LifeScience Ltd.	The US FDA accepted a Biologics License Application in May 2008 to market this neuromuscular blocking agent for aesthetic indications. Marketing is anticipated to commence in the US during the second quarter of 2009.

Drug News

<i>FDA Early Communication</i>	<p>Despite ongoing safety concerns surrounding the use of tumor necrosis factor (TNF) inhibitors, especially etanercept (Enbrel®, Amgen/Wyeth), a US FDA advisory panel voted in favor of approving the drug for use in children with moderate-to-severe psoriasis in June 2008. Current approved indications include children and adults with rheumatoid arthritis (RA) and adults with psoriasis. However, the favorable vote follows an FDA announcement in the same month that it intends to mandate stricter warnings on labels to draw attention to the risk of death in children and of moderate-to-severe infections in adults. These measures have been proposed following approximately 30 reports of cancer in children and young adults between 1998 and 2008. The agency's Adverse Event Reporting System collects and monitors reports of serious malignancies, infections and neurological problems in children treated with TNF blockers, as well as other immunosuppressive drugs. The FDA is investigating the entire class of TNF antagonists for potential links to childhood cancers, especially lymphoma, in pediatric patients with juvenile RA and Crohn's disease. Approved drugs under this class of agents include adalimumab (Humira®, Abbott Laboratories), etanercept (Enbrel®, Amgen/Wyeth), infliximab (Remicade®, Johnson & Johnson) and certolizumab pegol (Cimzia®, UCB). Additional information may be found at: http://www.fda.gov/cder/drug/early_comm/TNF_blockers.htm</p>
<i>Actinic Keratoses</i>	<p>Although many treatment options exist for actinic keratoses (AKs), those considered to be patient-preferred remain undefined. Tierney, et al.* explored patient perceptions and preferences in the management of AKs, including the comparison of photodynamic therapy (PDT) with other therapies. In 2005-2006, 45 patients in the Henry Ford Health System who received PDT for AKs were mailed a self-administered questionnaire. Several indicators for each treatment were surveyed, including recovery time, cosmetic appearance, patient cost, effectiveness, patient satisfaction, treatment option preference, and perceived burden of treatment. Study findings from 39 respondents revealed that a patient's reported recovery time was significantly more likely to be 1 week or less for PDT when compared with cryotherapy (p=0.02) and surgical excision (p=0.02). Borderline significance was found for the improved cosmetic outcome in PDT vs. surgical excision (p=0.058), and for patient satisfaction with PDT compared with 5-fluorouracil (p=0.058). Patients significantly preferred PDT to 5-fluorouracil (p<0.001) or imiquimod (p=0.031). Even though the efficacy of lesion clearance with PDT for AKs has been well established in the literature, this is the first study to evaluate patient perception of the effectiveness, side-effect profile, and benefits of PDT in comparison with other standard treatment approaches for AKs. PDT was found to have equivalent or improved recovery times, cosmetic outcomes, patient satisfaction, and preference as a treatment for AKs by patients when compared with other options.</p> <p>* Tierney EP, et al. <i>J Cosmet Laser Ther</i> 10(2):81-6 (2008 Jun).</p>

Small Skin Therapy Letter® (ISSN 1201-5989) Copyright 2008 by SkinCareGuide.com. Skin Therapy Letter® is published 10 times annually by SkinCareGuide.com Ltd, 1107 - 750 West Pender, Vancouver, British Columbia, Canada, V6C 2T8. Managing Editor: Penelope Gray-Allan: meditor@skincareguide.com. All rights reserved. Reproduction in whole or in part by any process is strictly forbidden without prior consent of the publisher in writing. While every effort is made to see that no inaccurate or misleading data, opinion, or statement appears in the Skin Therapy Letter®, the Publishers and Editorial Board wish to make it clear that the data and opinions appearing in the articles herein are the responsibility of the contributor. Accordingly, the Publishers, the Editorial Committee and their respective employees, officers, and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion, or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described herein, should only be followed in conjunction with the drug manufacturer's own published literature. Printed on acid-free paper effective with Volume 1, Issue 1, 1995.

Subscription Information. Annual subscription: Canadian \$94 individual; \$171 institutional (plus GST); US \$66 individual; \$121 institutional. Outside North America: US\$88 individual; \$143 institutional. We sell reprints in bulk (100 copies or more of the same article). For individual reprints, we sell photocopies of the articles. The cost is \$20 to fax and \$15 to mail. Prepayment is required. Student rates available upon request. Sales inquiries: business@skincareguide.com