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Imiquimod 5% Cream for the Treatment of Actinic Keratoses

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ABSTRACT

Actinic keratoses (AKs) are premalignant inflammatory skin lesions with the potential to transform into squamous cell carcinoma (SCC). There are several treatment options available for patients presenting with multiple AKs. Imiquimod is believed to stimulate and enhance host immune responses locally against skin tumors and viral infections. Five clinical studies to date have demonstrated its safety and efficacy in the treatment of actinic keratoses. Long-term follow-up studies examining recurrence rates are limited.

Key Words: actinic keratosis, squamous cell carcinoma, immune response modifier

Imiquimod (Aldara[™], 3M) is an immune response modifier that acts via stimulation of toll-like receptor 7 (TLR-7) on plasmacytoid and myeloid dendritic cells.¹ TLR-7 is part of a family of 11 TLRs that are important in the innate immune system's recognition of various microbial antigens. Stimulation of TLR-7 most notably results in dissociation of nuclear factor κ B (NF κ B) away from its inhibitor, thereby freeing it to diffuse into the nucleus and transcribe genes for various cytokines including tumor necrosis factor α (TNF α), interferon γ (IFN γ), interferon α (IFN α), and interleukin-12 (IL-12), among others (see Figure 1). These cytokines upregulate cell mediated Th1 responses that have antitumor and antiviral effects and downregulate Th2 (humoral) responses. Imiquimod may also directly affect cell death through various pathways including via IFN γ modulation of the p53 apoptotic pathway.

Although initially licensed for the treatment of genital warts, imiquimod 5% cream has demonstrated therapeutic efficacy in a variety of dermatologic conditions and has recently been given approval by both the US FDA and Health Canada for the treatment of multiple AKs.

Actinic Keratoses

AKs are relatively common premalignant inflammatory skin lesions. The risk of malignant transformation of an average AK into a SCC in 1 year is 0.0075%.² However, over a 10-year period, a person with an average of 8 AKs has a 6%–10% chance of developing an SCC.³ Treatment modalities employed include cryotherapy, topical fluorouracil (5-FU), photodynamic therapy (PDT), topical 3% diclofenac in 2.5% hyaluronic acid, retinoids, curettage, surgical excision, laser, and chemical peels/resurfacing procedures.

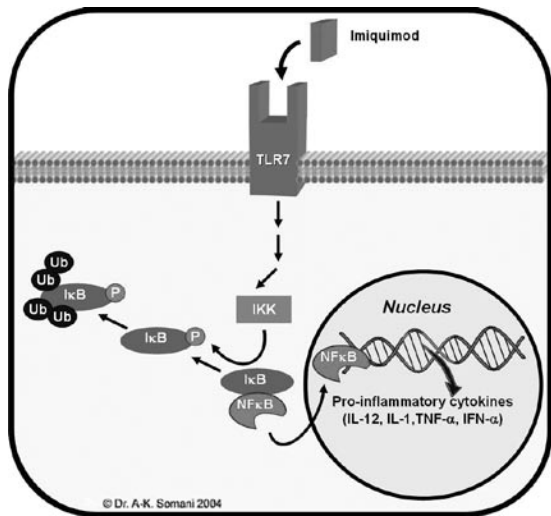


Figure 1: Imiquimod stimulation of TLR-7 results in activation of IKK, which phosphorylates IκB. Unphosphorylated IκB keeps NFκB inactive. Phosphorylated IκB is ubiquitinated and degraded, freeing NFκB to move into the nucleus. NFκB acts as a transcription factor for genes encoding various cytokines.

IKK = inhibitor IκB kinase; IκB = inhibitor of NFκB; NFκB = nuclear factor κB

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Clinical Trials

In a randomized, double-blind, vehicle-controlled study, imiquimod 5% cream or vehicle was applied to AKs three times weekly for a maximum of 12 weeks.⁴ Three to 10 lesions from the scalp, forehead, dorsal forearm, neck, or dorsal hand, in an area not exceeding 20cm², could be selected. At 2 weeks post-treatment, 21/25 (84%) patients were clinically cleared and 2/25 (8%) were partially cleared. No response was seen in the 11 subjects in the vehicle treated group (p<0.001). Within the treatment group, clearance was 100% (15/15) in patients who required reduction to once or twice weekly therapy because of a brisk response to imiquimod. In those who were able to continue therapy at a frequency of three times weekly for 12 weeks, the clearance rate was 60% (6/10). All patients experienced local adverse effects ranging from mild to severe erythema, edema, erosions, vesicles, flaking and scabbing. One patient in the treatment group required a rest period of 10 days. All patients completed the 12-week treatment course. At the 1-year follow-up there was a 10% (2/25) recurrence rate in the treatment group.

In another clinical trial, 22 patients received imiquimod 5% cream three times weekly for 8 weeks (or until clearance) to one affected side of the body (either

Study	N	Treatment	Complete Response	Probability
Randomized double-blind vehicle-controlled study ⁴	25	t.i.w. for 12wks or until clear	84% (21/25) treatment group vs. 0% (0/11) placebo	p<0.001
Clinical trial Single side treated; other side vehicle control ⁵	22	t.i.w. for 8wks or until clear	Mean number lesions decreased 10.1 to 6.2 vs. 8.1 to 7.6 placebo	p<0.005
Open-label studies ⁶	25 pts with 33 CUs	t.i.w. for 4wks on/4wks off Max 3 cycles	ITT 82% (27/33)	Not reported
Phase III randomized, multicenter, double-blind, vehicle-controlled study ⁷	436	Once daily b.i.w. for 16 weeks	45.1% (97/215) treatment group vs. 3.2% (7/221) placebo	p<0.001
Phase III randomized, multicenter, double-blind, vehicle-controlled study ⁸	286	Once daily t.i.w. for 16 weeks	57.1% (84/147) treatment group vs. 2.2% (3/139) placebo	P<0.001

Table 1: Clinical trials results for imiquimod 5% cream. CU = cosmetic units, each containing 5-20 discrete AKs
CR = complete response
ITT = intention-to-treat analysis

Medication	Treatment Protocol	Complete Response
Imiquimod	Once daily b.i.w. or t.i.w. for 16wks ^{7,8} t.i.w. for 4wks cyclical therapy for 3 cycles total ⁶	45-57% (p<0.001) 82% (p<0.001)
Photodynamic therapy	2 treatment sessions in 12 wks ²⁶	73% (p<0.001)
0.5% 5-Fluorouracil	4wks of treatment ¹⁷	52% (p<0.001)
5% 5-Fluorouracil	b.i.w.-q.i.w. for up to 16wks ¹⁶	88.6% (no p value) Longer time to healing with b.i.w. regimen
3% diclofenac in 2.5% hyaluronic acid	30-90d of treatment b.i.d. ^{22,23}	30-50% (p<0.05 and p<0.001)

Table 2: Response rates of various therapies used to treat actinic keratoses.

face, arms, or legs) and vehicle to the other side.⁵ Application sites were randomized. Seventy-eight percent of patients (17/22) completed the study (8 weeks of treatment and 8 weeks of post-treatment observation). Among these 17 patients, the mean number of lesions decreased from 10.1 to 6.2 versus 8.1 to 7.6 for the vehicle-treated group at 8 weeks post-treatment. This reached statistical significance (p<0.005). Nine patients (53%) required one to two rest periods of 2 weeks' duration for local cutaneous reactions. Local side-effects were experienced by 14 patients (82%).

A third study examined the efficacy of cyclical imiquimod therapy.⁶ This was an open-label trial of 25 patients with 5-20 discrete AKs within one cosmetic unit: the scalp, the forehead and temples, or the cheeks. This contrasts with other studies, which have included the neck, arms, hands, and legs. Imiquimod was applied to the entire treatment area ("field treatment") three times weekly for 4 weeks followed by a 4-week rest period. The cycle was repeated a maximum of three times if needed. Of the 25 patients with 33 total cosmetic units, 20 patients with 30 cosmetic units completed treatment. In the intention-to-treat analysis (ITT) 82% total clearance was achieved after three treatment cycles. Four patients had severe reactions that required early rest periods at 2-3 weeks of treatment. Of note, subclinical AKs exposed to imiquimod became evident in the treatment field. Furthermore, AK clearance continued during the rest period when no imiquimod was administered.

There have recently been large phase III, randomized, multicenter, double-blind, vehicle-controlled studies examining the use of imiquimod 5% cream for the

treatment of AKs. The first of these published reports is a combination of two studies in which imiquimod 5% cream was applied once daily, 2 days per week for 16 weeks in 436 patients with 4-8 clinically diagnosed AKs on the face and scalp.⁷ Complete clearance, based on clinical assessment at 8 weeks post-treatment, was 45.1% (97/215) and 3.2% (7/221) for treatment and vehicle groups respectively (p<0.001). Dosing days were a minimum of 3 days apart. Local skin reactions were common in both treatment and vehicle groups. However, these were more severe in the imiquimod treated group and resulted in 2 patients (1%) discontinuing treatment.

The second published study examined three times weekly imiquimod 5% cream applied to the face or balding scalp for 16 weeks in 286 patients with 5 to 9 clinically diagnosed and histologically confirmed AKs.⁸ Dosing days were the same nonconsecutive days every week. At 8 weeks post-treatment, the complete clinical clearance rate was 57.1% (84/147) with imiquimod versus 2.2% (3/139) in the vehicle treated group (p<0.001). Adverse site reactions were reported by 46.3% (68/147) in the imiquimod group versus 11.5% (16/139) of patients using vehicle. Two patients using imiquimod (1%) discontinued therapy because of local side-effects.

Additional Treatment Options for AKs and Their Efficacy

There are no head-to-head trials comparing the efficacy of the various therapies used for the treatment of multiple actinic keratoses with that of imiquimod. Table 2 summarizes the response rates of various therapies that have been reported in the literature.

Cryotherapy is considered a standard treatment when patients present with a limited number of AKs (less than 15)⁹ or when there are multiple scattered lesions.¹⁰ The commonly used cryogen is liquid nitrogen (-195.8°C), which may be applied with techniques ranging from cotton-tip application to cryospray or cryoblast.¹¹ The open-spray technique, with a freeze time of 5 to 10 seconds is effective.¹² Prospective randomized controlled trials examining the efficacy of cryotherapy are lacking. Based on an observational study in which a 20 to 45 second total thaw time was used, a cure rate of 98.8% was achieved based on a recurrence rate of 12 out of 1,018 treated lesions in 70 patients followed for 1–8.5 years.¹⁰ Local side-effects such as blisters, scarring, and textural and pigmentary changes can rarely occur with cryotherapy.⁹

In patients with multiple AKs, the therapies listed below may be employed.

5-Fluorouracil (5-FU) is a structural analog of thymine that competes for enzymes with normal metabolites, such as uracil. Its cytotoxic effects are mediated by integration into RNA and inhibition of DNA synthesis by blockade of thymidylate synthetase.¹³ Typically the medication is applied twice daily for 3-4 weeks for facial lesions and 4-6 weeks on arms and hands until the lesions inflame and erode. In an effort to reduce the often intolerable side-effects of continuous therapy, the efficacy of pulse 5% 5-FU therapy has been examined in two studies. The earlier of these showed efficacy with once or twice weekly 5-FU applied for an average 6.7 weeks,¹⁴ while the other demonstrated little efficacy with intermittent therapy.¹⁵ Recently, a single-arm open-label study examined intermittent 5% 5-FU for up to 16 weeks in 53 patients with a total of 83 AKs on the face or scalp.¹⁶ All patients were initially treated 4 times per week (q.i.w.—twice daily on two consecutive days). After the first week, patients could switch to twice weekly application (b.i.w.—twice on a single day) if they experienced intolerable discomfort. Fifty patients (98%) with 79 lesions (95.1%) completed therapy. A total of 74.6% of lesions (59/79) were treated q.i.w., while 25.3% of lesions (20/70) were treated b.i.w. Complete healing was seen in 88.6% of lesions. Efficacy was not reduced as a result of less frequent application (complete clearance rates of 88.1% [52/59] and 90% [18/20] with q.i.w. and b.i.w. treatment respectively). Mean time to healing, however, did increase with decreased frequency of 5-FU application (7.4 weeks versus 10.2 weeks in the q.i.w. versus b.i.w. groups respectively).

One-half percent, 1%, and 2% concentrations of 5-FU have been developed. The one-half percent 5-FU cream was shown in two pooled, phase III studies of 384 patients to result in total AK clearance in 52.9% (45/85) of patients versus 1.6% (2/127) in the placebo group after 4 weeks of treatment ($p < 0.001$).¹⁷ In terms of comparative studies, chemical peel with Jessner's solution (resorcinol, lactic acid, and salicylic acid) combined with trichloroacetic acid and 5% 5-FU twice daily for 3 weeks were equal in efficacy.¹⁸ Photodynamic therapy has also been found to be equivalent in efficacy to 3 weeks of 5-FU treatment.¹⁹

Diclofenac is a nonsteroidal, anti-inflammatory drug that inhibits cyclo-oxygenase-2 resulting in reduced prostaglandin synthesis.²⁰ Raised prostaglandins have been linked with sun damage and AKs.²¹ In a randomized, double-blind placebo-controlled study of 96 patients treated twice daily with 0.5 grams of topical 3% diclofenac in 2.5% hyaluronic acid for 90 days, 50% of patients showed complete resolution of all target lesions compared with 20% in the placebo group ($p < 0.001$).²² Another multicenter, double-blind, placebo-controlled study of 195 patients treated twice daily for 30 or 60 days with the same formulation of diclofenac achieved total lesion clearance of approximately 30% (in both 30- and 60-day treatment groups) versus approximately 10% in the placebo group.²³ Adverse events included mild-to-moderate local pruritus, erythema and rash. The medication was well tolerated overall.²⁴

Photodynamic therapy (PDT) employs aminolevulinic acid (ALA), a prodrug that is intracellularly metabolized to protoporphyrin IX, a photosensitizing molecule.²⁵ When this is activated by exposure to light, free radicals and reactive oxygen species are generated.²⁵ These are cytotoxic. A recent phase III, multicenter, investigator-blinded, randomized controlled trial examined the efficacy of ALA topical solution versus vehicle followed by blue light in the treatment of multiple AKs on the face and scalp in 243 patients.²⁶ Following initial treatment, remaining target lesions were retreated at 8 weeks. Complete response rates achieved at 8 and 12 weeks were 66% (109/166) and 73% (109/149) respectively ($p < 0.001$). In the vehicle treated groups, complete responses were achieved in 11% (6/55) and 8% (4/52) at 8 and 12 weeks. Moderate-to-severe stinging and burning were reported in 90% of patients during treatment, but this decreased after 24 hours. Additional side-effects of PDT include erythema and edema, which improve over 1-4 weeks. Pruritus, crusting, scaling, hyperpigmentation, and

hypopigmentation may also be seen. This therapy is indicated for non-hyperkeratotic AKs.

Dosage and Adverse Effects

Imiquimod 5% cream is supplied in single-use sachets containing 250mg of the cream (12.5mg imiquimod).²⁷ Each sachet can cover an area between 150 and 200cm².²⁸ Patients are instructed to apply imiquimod nightly, leave on for 6-10hrs, and then wash off. Hands should be washed after imiquimod application.

In general, imiquimod is well tolerated. Local cutaneous adverse effects are common, however, and include pruritus, burning, pain, erythema, erosions, edema, scabbing, induration, and ulceration.²⁷ Erythema is the most common adverse reaction. In many of the above studies, dosing adjustments were required due to local reactions. Pretreatment counseling along with adequate follow-up will facilitate patient compliance with therapy. Serious systemic effects have not been reported.²⁷ There are no known contraindications to treatment and no known drug interactions.²⁷

Conclusions

Imiquimod is a reasonable treatment option in patients with multiple AKs. Health Canada has approved the treatment course at twice weekly for 16 weeks. Other treatment regimens can also be considered after the above treatment schedule. A key component in the management of AKs remains the adoption of sun protective behaviors and sunscreens as a preventative strategy.²⁹

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The Surgical Correction of Protuberant Ears

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ABSTRACT

While prominent ears are considered a sign of good fortune in the Far East, Western society looks upon prominent ears in a far less positive manner. Children with prominent ears are often the subjects of verbal and at times physical abuse by their peers, resulting in adverse psychological effects. Advances in otoplasty have made it possible not only to “pin back” the ears, but also to reshape them, reduce their size, or make them more symmetrical. For a dermatologic surgeon, an otoplasty may be an unfamiliar surgical procedure, however, the surgery itself does not significantly differ from ear wedges or cartilage removal procedures for skin cancer, procedures with which the dermatologic surgeon is quite familiar.

Keywords: prominent ears, otoplasty

Otoplasty is the surgical correction of protuberant ears and ear deformities. Like other forms of cosmetic surgery its goal is to enhance the patient’s appearance. Specifically, it is aimed at making the protuberant ears less apparent by restoring them to a normal form and position in a symmetrical fashion. It is a surgical procedure being performed by several surgical specialties and for the dermatologic surgeon, an otoplasty may be an unfamiliar surgical procedure. The procedure itself, however, does not significantly differ from ear wedges or cartilage removal procedures for skin cancer, procedures with which the dermatologic surgeon is quite familiar.

Historical Background

In 1845, Diffenbach reported the first surgical approach for the correction of prominent ears.¹ He combined simple excision from the posterior sulcus with sutures subsequently fixing the ear cartilage to the periosteum of the mastoid. Subsequently, multiple surgical techniques have been described, with over 170 being reported in the literature. These can be basically categorized into three groups:

- 1) leaving the cartilage intact and using only sutures to reconstruct the ear, as used in the permanent suture insertion of the Mustarde technique² and the incisionless otoplasty of Fritsch³
- 2) incising the cartilage in order to make it more pliable, without resecting it (e.g., the Converse’s cartilage incision technique⁴ and the anterior approach technique described by Chongchet⁵ and Stenstrom⁶)
- 3) a technique that includes excision of the cartilage.

There is also a relatively new nonsurgical approach that is effective when prominent ears are noted in infancy. The use of external temporary appliances to set the ears in a correct position for several months results in a successful permanent correction.⁷⁻⁹ The drawback with this method is that it takes highly motivated parents to follow the protocol.

Surface Anatomy of the External Ear

A thorough knowledge of the anatomy of the ear is essential for performing a safe and successful otoplasty. Although it comprises a small anatomic area, the surface anatomy of the external ear is quite complex (Figure 1). The external ear consists of the auricle and the external auditory canal. The helix rim arises anteriorly and inferiorly from a crus extending horizontally above the external auditory meatus, thus creating the outer frame of the auricle. The helix merges inferiorly into the cauda helices and connects to the lobule. The region located between the crura of the antihelix is referred to as the triangular fossa, while the scapha lies between the helix and

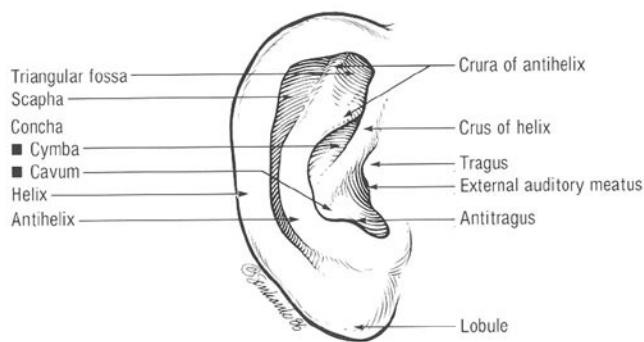


Figure 1: Anatomy of the external ear

antihelix. The antihelix borders medially to the rim of the concha and the concha proper. The concha is composed of the conchal cyma superiorly and the conchal cavum inferiorly, which are separated by the helical crus and meet the antihelix at the antihelical rim. The intertragic notch separates the tragus and antitragus. The lobule does not contain cartilage and displays a variety of shapes and attachments to the adjacent cheek and scalp.

The superficial temporal and posterior auricular arteries preserve the arterial supply of the external ear. The sensory innervation involves the anterior and posterior branches of the greater auricular nerve and is reinforced by the auricular temporal and lesser occipital nerves. A portion of the posterior wall of the external auditory meatus is supplied by the auricular branch of the vagus nerve.

Surgical Correction Techniques

External ear deformities are very diverse, with protuberant ears being the most common complaint of patients. Ear prominence is generally the result of one or more of the following anatomic malformations: failure of antihelical folding, overdeveloped conchal

cartilage, protrusion of the upper third of the ear and/or protrusion of the earlobe.¹⁰⁻¹¹ For adequate surgical correction, the surgeon must recognize and address all of the anatomic malformations contributing to the patient's ear prominence. Surgical correction of these common ear deformities will be discussed briefly.

The antihelix is commonly unfolded giving the appearance of prominent ears. In this case, simple pressure in the scaphoid region toward the scalp will define the antihelix and superior crus. A further increase in pressure will elevate the conchal rim, outlining the excess conchal rim. This excess conchal rim cartilage and skin is removed, creating an antihelix and a normal appearing ear.

Conchal enlargement represents another common ear deformity. The excess conchal cartilage can extend throughout or be confined to a particular region. The removal of the excess cartilage in the appropriate areas resolves the abnormal contour of the ear.

The auricle and the earlobe generally meet the adjacent scalp tissue at an angle of approximately 30 degrees. An angle over 40 degrees usually results in protrusion of the ear. To achieve proper surgical correction, the skin of the posterior earlobe and posterior auricle, as well as the skin over the mastoid, needs to be dissected and then sutured together. Dissection of the lobule skin alone will change the anatomy of the lobule, without improving the protrusion of the ear.

Complications

The most common immediate postoperative complication of otoplasty is the formation of a hematoma, requiring immediate, meticulous treatment.¹² Generally, if a patient complains of increasing, persistent pain under the dressing, a hematoma must be suspected. If a hematoma is present, immediate evacuation should be performed, and the patient should be started on oral antibiotic therapy in order to diminish the incidence of perichondritis. Inadequate correction, contour distortion, and an asymmetric correction are the most common untoward outcomes of otoplasty.¹³ Even though some degree of retroprotrusion can be expected with most otoplasty techniques, it appears to be particularly common and significant when permanent sutures alone are used to reconstruct the ear. For that reason and in order to obtain optimal cosmesis, we favor the technique that includes excision of cartilage. This is a simple surgical procedure, which provides the best and most reliable results, making the deformity less apt to recur.



Figure 2: Anterior view; A) Pre-operative B) Post-operative



Figure 3: Posterior view; A) Pre-operative B) Post-operative

Surgical Correction for Children

Children with protruding ears are often the subjects of verbal, and at times physical, abuse by their peers, resulting in adverse psychological effects. These psychological concerns often cause parents to be the first to initiate the steps toward surgical correction of the prominent ears. However it is very important to have the child voice his or her desire for surgery, because the child is best able to judge the degree of distress this condition imposes. Nevertheless, the patient's age plays an important role in the decision for or against surgery. Eighty-five percent of the final size of the ear is achieved by age of 3 years, and surgery prior to school age could result in marked inhibition of auricular growth. For these reasons, we prefer to limit otoplasty in our office to patients who have achieved adolescence or adulthood without completely adjusting to their appearance, as they are more capable than young children of describing the auricular features of concern to them and their desire for correction. Thus, successful correction of the protuberant ears can be of significant help to a patient's social life and self-esteem.

Conclusion

Otoplasty is a simple surgical procedure with which the dermatologic cosmetic surgeon should be familiar. It is performed in an out-patient setting and under local anesthesia with or without conscious sedation. With minimum complications and risks, a successful otoplasty can be of significant help to a patient's social life and self-esteem.

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Erratum

In Table 4 on page 4 of "A Review of Systemic Retinoid Therapy for Acne and Related Conditions" by R. A. Kunynetz, published in Volume 9, Number 3, the number of suicides/suicide attempts for isotretinoin should be 1.7/100,000 patients, not 17/100,000 patients.

Erratum

On page 6 of "Clinical Use of RESTYLANE®", by J.S. Dover, A. Carruthers, J. Carruthers and M. Alam, published in Volume 10, Number 1, the legend for Table 1 should read:

Table 1: Adverse events in RESTYLANE®/ Zylplast® study²

Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Antipsoriatic Agent</i>	Alefacept <i>AMEVIVE™</i> Biogen Idec	TPP Canada approved this biologic therapy in October 2004, for the treatment of patients with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.
<i>Anti-arthritis Agent</i>	Infliximab <i>Remicade®</i> Schering-Plough	The European Medicines Agency (EMA) granted approval in October 2004, for this product to be used in combination with methotrexate for the treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying antirheumatic drugs.
<i>Dermal Fillers</i>	Hylan-B Gel <i>Hylaform® Plus</i> Inamed	The US FDA granted marketing approval in October 2004, for this dermal filler for the correction of moderate-to-severe facial wrinkles and folds.
<i>Anti-acne Agent</i>	Clindamycin 1% + Tretinoin .025% Gel <i>Velac®</i> Connetics	The US FDA accepted a New Drug Application in October 2004, for this investigational new drug as a potential new topical treatment for acne.
Drug News		
<i>Drug Warning</i>	Important new information on side-effects associated with the use of Bextra, a COX-2 selective non-steroidal anti-inflammatory drug that is indicated for the treatment of osteoarthritis, rheumatoid arthritis, and dysmenorrhea was reported in December 2004 by the US FDA. A “boxed” warning will be added to the label, stating that patients taking Bextra have reported serious, potentially fatal skin reactions, including Stevens-Johnson Syndrome and toxic epiderma necrolysis. These skin reactions are most likely to occur in the first 2 weeks of treatment, but can occur at any time during therapy. In a few cases, these reactions have resulted in death. The labeling advises doctors that Bextra should be discontinued at the first appearance of a skin rash, mucosal lesions, or any other sign of allergic reactions. The warning also states that Bextra contains sulfa, and patients with a history of allergic reactions to sulfa may be at a greater risk of skin reactions.	
<i>Risk Minimization Actions Plan for Anti-acne Agent</i>	The US FDA announced in November 2004, that the risk minimization actions plan (RiskMAP) for Accutane® (isotretinoin) and its generic equivalents is being enhanced in order to reduce the risk of birth defects associated with fetal exposure to isotretinoin. Under the new program, sponsors will obtain registration of not only prescribers, but also pharmacies that dispense and patients who use isotretinoin. The program also includes documentation of a negative pregnancy test before giving isotretinoin to women who are capable of becoming pregnant. The registration system will be built to incorporate physician and patient identification codes that will also protect the privacy of the patients. The innovator and generic sponsors of isotretinoin have jointly contracted with Covance, Inc. to design, build, implement and operate a single strengthened isotretinoin RiskMAP incorporating these elements.	

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