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# Psoriasis as the Marker of Underlying Systemic Disease

**A. S. Kourosh, BS[1]; A. Miner, BS[1]; A. Menter, MD[1,2]**

*[1]The University of Texas Southwestern Medical School, Dallas, TX, USA*
*[2]Division of Dermatology, Baylor University Medical Center, Dallas TX, USA*

## ABSTRACT

*Psoriasis is associated with comorbidities that include metabolic syndrome and increased cardiovascular risk. These conditions share etiologic features and health consequences that directly correlate with the severity of psoriatic disease. This disease, in both its skin and joint manifestations, may represent a relevant healthcare issue as an indicator of a broader, underlying disorder of systemic inflammation, and warrants more comprehensive study and multidisciplinary collaboration on its pathophysiology, epidemiology, and treatment in relation to its comorbid conditions.*

**Key Words:** Psoriasis, metabolic syndrome, cardiovascular risk, myocardial infarction, comorbidities, hyperlipidemia, type 2 diabetes mellitus

While heart disease remains a quiet killer, ignored for years by those at risk, psoriasis is a highly visible disease. Its impact on social interaction and quality of life can prompt earlier physician consultation. Psoriasis patients are frequently obese, and unknowingly at greater risk than the general population for myocardial infarction (MI), metabolic syndrome and other comorbidities.[1-4]

Patients who are obese, and those who have severe psoriasis, often share a common psychological experience.[5] However, beyond the social stigma, populations affected by psoriasis and/or obesity can similarly manifest insulin resistance, an aberrant lipid profile, and an increased cardiovascular risk.[4,6] A growing body of research suggests that these diseases may in fact share an etiologic link, which may permit them to join atherosclerosis, autoimmune disease, and other comorbid conditions as facets of a larger systemic disorder of inflammation.[4]

As a common Th1 mediated disease affecting 1%-3% of the world's population, psoriasis may serve as an external indicator of underlying immune and metabolic dysregulation.[4] A recent population-based study showed an increased risk of death at a younger age in patients with severe psoriasis.[7] Additionally, studies involving mice appear to support the role of obesity in Th1 mediated pathology where adipocytes are shown to secrete both hormones and cytokines. Of particular importance is the ability of adipocytes to secrete the proinflammatory cytokine tumor necrosis factor-α (TNF-α), as its overproduction is an important feature in the pathophysiology of psoriasis.[8] Further exploration of the biologic markers and systemic comorbidities of psoriasis, and their genetic influences, could aid in identifying patients who may be at higher risk for systemic disease, including cardiovascular risk, thus

ensuring that they receive timely diagnosis and care.

## Discussion of Statistics

Individually, the features of metabolic syndrome may be associated with increased cardiovascular events. Taken in combination, this risk may be synergistically increased. Metabolic syndrome is generally defined by the presence of or treatment for at least three of the following five criteria: hypertension, insulin resistance, decreased high-density lipoprotein, hypertriglyceridemia, and central obesity. (Table 1)

In a cross-sectional study of psoriasis patients, the body mass index (BMI) was calculated for each participant at 18 years of age and was, for most, normal (BMI <25). Subsequently, however, 78% of the patients in this group went on to become overweight or obese.[10] A recent review of hospitalized patients from Germany (controlled for age, smoking, alcohol consumption, and gender) found that metabolic syndrome was more likely to be found in psoriasis patients vs. controls (odds ratio [OR]=5.29; 95% confidence interval [CI], 2.78-12.8). The same report demonstrated that psoriasis is associated with type II diabetes mellitus (OR=2.48; 95% CI, 1.70-3.61) and coronary heart disease (OR=1.77; 95% CI, 1.07-2.93).[10] Thus, recognized sequelae of the metabolic syndrome are more prevalent in patients with psoriasis. A case-control study from Italy similarly demonstrated in its outpatient psoriasis population that more than 30% of patients had metabolic syndrome, compared with 20.6% of dermatologic controls over the age of 40 years (OR=1.65; 95% CI, 1.16-2.35). While the presence of three of the five components of metabolic syndrome was more common in the psoriasis population, abdominal obesity and hypertriglyceridemia were additionally more common as individual factors among the psoriasis patients.[2]

A historical cohort study in Sweden comparing cardiovascular mortality in patients hospitalized for psoriasis vs. outpatient controls found that inpatient psoriatics had a 50% greater risk of cardiovascular death.[11] This risk increased as the number of hospital admissions increased, and mortality was higher for those admitted at younger ages. Last year, a prospective, population-based cohort study conducted in the UK showed that psoriatic disease may confer an independent risk of MI, with the greatest relative risk residing in young patients with severe disease.[1] The cohort was adjusted for hypertension, hyperlipidemia, diabetes, history of MI, age, sex, smoking, and BMI.

## Pathophysiology

The nature of coronary artery disease as a chronic inflammatory condition is apparent in the histology of an atherosclerotic plaque.

| Abnormality | Out-of-Range Values |
|---|---|
| Abdominal obesity | Waist circumference<br>>102cm (>40in) males<br>>88cm (>35in) females |
| Impaired glucose regulation | Fasting glucose >5.55mmol/L |
| Hypertriglyceridemia | Triglycerides >1.69mmol/L |
| Low HDL-C | <1.03mmol/L males<br><1.29mmol/L females |
| Hypertension | >130/85mmHg<br>either systolic or diastolic |

**Table 1:** Metabolic Syndrome Criteria NCEP ATP III (3 or more)

HDL-C = High-density lipoprotein cholesterol

From: Statistical Fact Sheet of the American Heart Association http://www.americanheart.org/downloadable/heart/1136819875357META06.pdf

At its core are CD4+ cells and macrophages that potentiate plaque formation.[12] Its sites of rupture contain higher concentrations of these activated immune cells, as well as the inflammatory cytokines and proteolytic enzymes that weaken the cap and render it unstable.[12] Its local environment comprises the same cytokine milieu of TNF-α, IL-6, IL-8, and IL-17, as that found in the gut of a patient with Crohn's disease, in a psoriatic plaque, or in an arthritic joint, and its rupture is triggered by the same factors of infection and emotional stress that cause flares in these diseases. It resembles the pathology of a T-cell mediated disease. Thus, the concern that psoriasis and rheumatoid arthritis patients face a higher risk of premature cardiovascular mortality than others of the same age and background may be explained by the fact that the cell-mediated immune dysregulation associated with heart disease is already markedly elevated at baseline in patients with T-cell mediated diseases.[1,3,13-15]

Recent studies implicate IL-17, which is released by a subset of memory T-helper cells (Th17 cells) that are stimulated by IL-23, as a mechanistic link between T-cell activation and inflammation.[16,17] In contrast to normal skin, IL-17 is expressed in psoriatic skin lesions, and is known to induce the key psoriatic cytokines of TNFα, and IL-1, IL-6, and IL-8, among a cascade of inflammatory mediators. Its key role in driving epidermal activation in psoriatic plaques is evidenced by the mechanism of certain therapies. A recent clinical trial involving etanercept demonstrated the importance of the early inhibitory effects of this immunomodulator

on Th17 cells, in addition to those on Th1 cellular products and effector molecules which were reduced later in disease resolution.[18] IL-17 is also found in the inflamed joints of patients with rheumatoid arthritis and Lyme disease, as well as foci in inflammatory bowel disease, multiple sclerosis, collagen induced arthritis, experimental autoimmune encephalomyelitis, organ transplant rejection and ischemic stroke.[16,17,19] Notably, IL-17 is also seen at higher levels, along with IL6, IL-8, and C-reactive protein, in the plasma of patients who have suffered unstable angina and acute MI.[16] Theoretically, almost any cell could be a target, since the IL-17 receptor is ubiquitously expressed by activating an inflammatory response via a nuclear factor-κB associated pathway.[16] Thus, the inflammatory reaction seen in a psoriatic plaque may be a microcosm for what is simultaneously propagating in the joints, gut, vasculature or other sites, which further exposes the underlying systemic nature of psoriasis.

This has perhaps already been observed, not only in psoriatic arthritis, where a cutaneous disease progresses to include the joints as well, but also in the clustering of psoriasis with other autoimmune diseases such as Crohn's disease, systemic lupus erythematosus, multiple sclerosis, and diabetes mellitus types 1 and 2. The epidemiologic association of psoriasis and psoriatic arthritis with Crohn's disease, in particular, may arise from a genetic kinship, as both have been associated with the same organic cation gene transporter haplotype, and the PSORS8 locus of psoriasis overlaps with a Crohn's disease locus (CARD15) on the long arm of chromosome 16. Of intense research interest at present is the possibility that psoriasis and obesity may share common genetic alleles.[20-22]

More broadly, certain single nucleotide polymorphisms in the promoter regions of TNF-α and IL-6 have been linked with greater relative production of these cytokines in some individuals, rendering them more sensitive in their response to the same inflammatory stimuli, whether infectious or intrinsic, than carriers of other variants.[21,23,24] This allelic predisposition to higher levels of both cytokines has been seen with increased risk of coronary heart disease, particularly in the setting of type 2 diabetes and obesity, which are features of metabolic syndrome.[21,23-25]

The role of obesity in this picture of inflammation and heart disease emerges in the concept that adipose tissue can function not only as an endocrine organ, but also as a component of the immune system. Since adipocytes express toll receptors that are involved in the innate immune response, these cells can directly react to foreign pathogens via the release of inflammatory cytokines, such as macrophages, which are derived from the same mesothelial origin.[26] This group of adipocytokines, or 'adipokines', includes adiponectin, leptin, resistin, and plasminogen activator inhibitor type 1 (PAI-1), as well as known key mediators of psoriatic lesions, such as IL-6 and TNF-α. These two cytokines also induce insulin resistance, dyslipidemia, endothelial production of monocyte adhesion molecules, and subsequent adherence of monocytes, illustrating how adipocytes contribute to the formation of foam cells. Thus, adipocytes are not simply "dormant" cells "bulking up" the abdomen; rather, they act as an increased cellular store, as found in obese patients, that may amplify the processes, which breed both psoriatic and atherosclerotic plaques.[4]

Additionally, both cytokines promote thrombosis. TNF-α raises levels of PAI-1, which inhibit tissue plasminogen activator, causing impaired fibrinolysis and uninhibited clot formation, while IL-6 promotes hepatic release of fibrinogen and C-reactive protein (CRP), and augments a procoagulant effect on platelets.[15,23,27,28] Circulating markers of inflammation, such as CRP and erythrocyte sedimentation rate have demonstrated value as adjunct predictors to the established risk factors for coronary artery disease and heart failure, respectively.[29] In addition to traditional factors such as infection or autoimmune vasculopathies, for which their elevations are monitored, both markers are found to be elevated at baseline, not only in psoriasis patients, but also in those who are obese.[30] Secretion of IL-6 and TNF-α by adipocytes may contribute to these elevated levels of CRP, which further portrays obesity as a condition of chronic inflammation connected with both psoriasis and heart disease.[30,31]

## Future Considerations

Since the first study on susceptibility of psoriasis and genetic loci, much has been uncovered regarding the polymorphisms and human leukocyte antigen (HLA) associations of chronic diseases.[32] Greater attention is necessary to understand their underlying genetic relationships and how these give rise to the epidemiologic clustering of many inflammatory and metabolic diseases, with an eye toward gene therapy. Also, since chronic disease morbidities are often difficult to distinguish from the long-term side-effects of their systemic therapies, the effects of medications such as methotrexate and biological agents on metabolic syndrome and cardiovascular risks must be assessed in patients with psoriatic disease, including the full spectrum of skin and joint involvement.

Most chronic diseases are managed by primary care doctors. Psoriatic disease is an exception, in that specialists, i.e., dermatologists and rheumatologists, often diagnose and manage this chronic disease with its now known systemic implications. With the evidence indicating that a higher incidence of obesity (BMI >30) occurs in these patients, and that joint disease usually appears 8–10 years post-onset of skin disease, it is

critical for dermatologists to identify at-risk patients and initiate an interdisciplinary approach to the screening and management of their comorbidities.

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# Novel Agents for Intractable Itch

C. B. Lynde[1]; J. N. Kraft, MD[2]; C. W. Lynde, MD, FRCPC[1]
[1]*Faculty of Medicine, University of Toronto, Toronto, ON, Canada*
[2]*Division of Dermatology, Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada*

**ABSTRACT**

*There exists a multitude of medical conditions that cause intractable itch, or pruritus. The successful management of this symptom depends explicitly on establishing the underlying cause. Studies have shown that drugs not traditionally used in the treatment of cutaneous disorders, such as opiate receptor antagonists, antidepressants, and antiepileptics, can provide symptomatic relief of intractable itch. These novel antipruritic agents will be explored in this review.*

**Key Words:** Intractable itch, pruritus, opiate receptor antagonists, antidepressants, anticonvulsants, antihistamine, phototherapy, thalidomide

Itch, or pruritus, refers to an unpleasant sensation in the skin that provokes scratching. Arguably, all humans experience an itch at some point in their lives. One-fifth of the population is thought to suffer from some form of itch at any given moment.[1] The intensity of pruritus ranges from mild to severe, and can have a significant psychosocial impact on patients, by interfering with their sleep and daily activities. Itch is one of the most common symptoms associated with cutaneous disorders that require treatment from dermatologists. Its management presents a treatment challenge, as many therapies are often tried to no avail.

Causation can sometimes be easily established, such as a primary dermatological disease (e.g., atopic dermatitis, psoriasis, urticaria), underlying renal or hepatic disease, or a drug-induced reaction (e.g., opiates). However, in many cases resolution of the symptom does not follow even after the etiology has been established; this is especially true for chronic disorders. Tables 1 and 2 summarize dermatologic and systemic disorders that can cause intractable itch.

| Dermatologic Disorders | |
|---|---|
| Local | Generalized |
| • Dermatitis (atopic and contact)<br>• Prurigo nodularis<br>• Urticaria<br>• Insect bites<br>• Lichen planus<br>• Dermatitis herpetiformis<br>• Lichen simplex chronicus<br>• Infection (candidiasis, varicella) | • "Winter itch"<br>• Pruritus of senescent skin<br>• Infestations (lice, scabies)<br>• Drug eruptions (opiates, ASA)<br>• Psychogenic states |

**Table 1:** A summary of dermatologic disorders that can cause intractable itch.

| Sytemic Disorders | |
|---|---|
| **Endocrine** | • Hyper/ hypothyroidism<br>• Diabetes mellitus |
| **Hematologic** | • Iron deficiency anemia<br>• Polycythemia rubra vera<br>• Hemochromatosis |
| **Hepatic** | • Obstructive biliary disease<br>• Cholestatic liver disease of pregnancy |
| **Infectious** | • HIV<br>• Hepatitis C<br>• Trichinosis |
| **Neoplastic** | • Cutaneous T-cell lymphoma<br>• Hodgkin's/ non-Hodgkin's lymphoma<br>• Leukemia<br>• Carcinoid<br>• Multiple myeloma<br>• Internal malignant tumors (i.e., lung, breast, gastric) |
| **Neurologic** | • Peripheral nerve injuries<br>• Post-herpetic neuralgia<br>• Psychosis<br>• Depression<br>• Multiple sclerosis |
| **Renal** | • Chronic renal failure |
| **Miscellaneous** | • Gout |

**Table 2:** A summary of systemic disorders that can cause intractable itch.

## Pathophysiology

The neuropathways responsible for relaying pruritus to the brain are well-known. The itch sensation is carried to the brain by a dedicated subset of nociceptive C

| Agent Class | Examples and Typical Dosing | Uses in Literature | Strength of Evidence |
|---|---|---|---|
| **Opioid Agonists/ Antagonists**<br>*Proposed Mechanism of Action:* inhibition of itch transmission based primarily on direct relationship of increased opioidergic tone and pruritus at the spinal level (μ-opioids are pruritic, κ-opioids are antipruritic) | **Butorphanol**<br>• μ-opioid receptor antagonist, κ-opioid receptor agonist<br>• 2mg intranasal spray every 4-6 hours | • severe opioid-induced pruritus<br>• intractable pruritus associated with inflammatory skin diseases or systemic diseases | D[3]<br>D[4] |
| | **Naltrexone**<br>• μ-opioid receptor antagonist<br>• 50mg po daily | • cholestatic pruritus<br>• intractable pruritus associated with inflammatory skin diseases or systemic diseases<br>• uremic pruritus | A[5]<br>B[6], C[7]<br>B[8] |
| **Antidepressants: Selective Serotonin Reuptake Inhibitors**<br>*Proposed Mechanism of Action:* reduces pruritus signaling through alteration of neurotransmitter concentrations within the central nervous system (CNS) | **Paroxetine**<br>• 20mg po daily<br>**Sertraline**<br>• 75-100mg po daily<br>**Fluoxetine**<br>• 10mg po daily | • malignancy<br>• polycythemia vera<br>• pruritus associated with a variety of underlying conditions (e.g., solid tumors, hematological malignancies, drug-induced pruritus [none opioid induced], paraneoplastic pruritus, and cholestatic pruritus)<br>• cholestatic pruritus | D[9]<br>C[10]<br>A[11]<br>B[12] |
| **Antidepressants: Norepinephrine and Serotonin Enhancer**<br>*Proposed Mechanism of Action:* reduces pruritus signaling through alteration of neurotransmitter concentrations within the CNS | **Mirtazapine**<br>• 15-45mg po daily | • inflammatory skin diseases and severe nocturnal pruritus<br>• cholestasis, renal failure and malignancies | E[13]<br>E[14] |
| **Anticonvulsants**<br>*Proposed Mechanism of Action:* blocks neuropathic afferent pathway | **Gabapentin**<br>• 300mg po daily and titrating to effect up to 1800mg po daily over 3-4 weeks | • brachioradial pruritus<br>• multiple sclerosis - induced itch<br>• uremic pruritus<br>• cholestatic pruritus - negative effect | E[15, 16]<br>E[17]<br>A[18]<br>A[19] |
| **Glutamic Acid Derivative**<br>*Proposed Mechanism of Action:* hypnosedative effects (penetrates CNS); direct effects on neural tissue; and immunomodulatory and anti-inflammatory effects (e.g., antagonism of histamine) | **Thalidomide**<br>• 100-200mg po qhs | • prurigo nodularis<br>• chronic pruritus (psoriasis, eczema, nodular prurigo, senile pruritus and primary biliary cirrhosis) | E[20]<br>D[21] |

**Table 3:** Summary of novel agents for intractable itch. A=double-blind study; B=clinical trial ≥20 subjects; C=clinical trial <20 subjects; D=series ≥5, <20 subjects; E=anecdotal case reports.

neurons. Like the pathways for pain and temperature, the message is relayed to the spinal cord, then crosses the midline and ascends via the lateral spinothalamic tract to the thalamus, and then finally travels to the cerebral cortex.

There are many peripheral mediators of pruritus, which include histamine, cytokines (IL-2), tryptase, substance P, serotonin, and opioid peptides. The most potent from this list is histamine, which is released by dermal mast cells via many triggers (i.e., IgE crosslinking, substance P, complement C5a). This biogenic amine acts mainly as a neurotransmitter and plays a major role in skin reactions associated with urticaria, urticaria pigmentosa, and insect bites. Its role in other skin diseases (e.g., atopic dermatitis) is debatable.

## Traditional Topical Agents

Topical agents provide symptomatic relief. However, it must be stressed that successful management depends on establishing the underlying physiologic imbalance.

- Menthol 1%, compounded in an aqueous cream or in a moisturizer base, sensitizes thermal receptors to cold and is considered a safe remedy that has been used for centuries.
- Doxepin 5% cream is a topical tricyclic antidepressant that relieves pruritic symptoms associated with atopic dermatitis. Patients being treated with doxepin should be cautioned regarding adverse side-effects, such as systemic absorption and drowsiness.
- Capsaicin 0.025%-0.3% cream is derived from chili peppers, and triggers the release of substance P from C nociceptors, which desensitizes nerve fibers. Local irritation can result.
- Topical corticosteroids are only considered when there is a primary dermatosis, due to the potential for local side-effects (i.e., telangiectasia, atrophy, striae).
- Topical anesthetics are seldom used as they are associated with an increased risk of allergic sensitization.
- Other topical agents that may be of benefit include: moisturizers, oatmeal-based agents, calamine lotion, aloe and camphor.

## Systemic Agents

Systemic agents are tried if there is a specific indication or if the more conservative measures are ineffective. Antihistamines are predominantly used for treating urticaria, but are otherwise rarely effective for itch. The first generation antihistamines are sedating, but are generally considered to be the most effective when compared with its subsequent counterparts. Due to its potential to affect performance, sedating antihistamines should be administered at night. The addition of successive generations (second or third) may be helpful for daytime relief as they are minimally sedating. Tranquilizers have been used, but they only serve to sedate the patient and do not directly address the pruritic symptoms.

## Phototherapy

For patients who are unresponsive to traditional topical or systemic therapies, UV light (UVB or PUVA) may be an option. For example, UVB has been shown to be of benefit in the treatment of pruritus associated with chronic renal disease.[2] After 2 weeks of three treatments per week, improvement can be seen. If no improvement is detected following this treatment regimen, phototherapy should be reconsidered. Clinical experience seems to indicate that maintenance therapy is not required.

## Novel Agents

In the past, if traditional agents were not effective, dermatologists had few other options. The emergence of a new understanding of the pathophysiology of itch has led to novel uses of existing therapies to treat pruritus, which include opiate receptor antagonists, antidepressants, and antiepileptics. The addition of these drugs to the dermatologist's therapeutic arsenal provides options to patients who are inadequate responders to traditional agents. Table 3 provides a summary of these unconventional antipruritic agents.

## Conclusions

Pruritus is a very common symptom that is associated with many dermatologic and systemic conditions, and can be challenging to treat. Conventional therapies such as topical agents and antihistamines are often not effective. Novel therapies such as opioid antagonists, antidepressants, and anticonvulsants are emerging as promising treatments for intractable itch.

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| Class | Name/Company | Approval Dates and Comments |
|---|---|---|
| *Anti-psoriatic Agent* | **Ustekinumab**<br>*CNTO 1275*<br>Centocor, Inc./ Janssen-Cilag International | The US FDA and European Commission (EMEA) received a Biologics License Application (BLA) and Marketing Authorization Application, respectively, in December 2007 for approval of this novel, fully-humanized monoclonal antibody for the treatment of chronic moderate-to-severe plaque psoriasis. In February 2008, the US FDA accepted the BLA. |
| *Anti-arthritic Agent* | **Tocilizumab**<br>*Actemra*®<br>Hoffmann La-Roche/ Chugai Pharma | The US FDA and EMEA received a BLA and Marketing Authorization Application, respectively, in November 2007 for approval of this humanized interleukin-6 receptor-inhibiting monoclonal antibody for the treatment of moderate-to-severe rheumatoid arthritis. |
| *Neurotoxin* | **Botulinum Toxin Type A**<br>*Reloxin*®<br>Medicis Pharmaceutical Corp./ Ipsen Ltd. | The US FDA received a BLA in December 2007 to market this neuromuscular blocking agent for esthetic indications. In January 2008, the FDA ruled the BLA as incomplete. Medicis is working with the agency to address the deficiencies. |

## Drug News

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| *Atopic Dermatitis* | The National Institute for Health and Clinical Excellence (NICE) in the UK announced the development of comprehensive guidelines in December 2007 aimed at improving the quality of life (QoL) and treatment of atopic dermatitis (AD) in children from birth to 12 years of age. Children's needs and preferences, along with those of their healthcare providers, parents, and caregivers, are all factors that should be considered when dispensing best practice advice and making decisions regarding management and therapy. Furthermore, attention should be accorded to cultural considerations, and encouraging program access to those with disabilities or those who encounter language barriers. Key guideline recommendations include: avoidance of a uniform approach in disease assessment by considering individual QoL (i.e., daily activities, sleep and psychosocial wellbeing); adoption of a stepped approach for management by tailoring treatment steps to disease severity; healthcare providers will devote time to educating patients, parents, and caregivers about AD and its treatment; and clinical assessment will involve identification of potential triggering factors. It is estimated that 80% of AD cases seen by general practitioners are for mild forms of this skin condition. The intent of implementing these new guidelines is to substantially reduce unnecessary referrals for more specialized services by providing primary care physicians and affected individuals with an evidence based and supportive approach to successfully managing children with AD. The complete guidance report may be found at: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11901. |
| *US FDA Alert* | The US FDA issued an alert in December 2007 regarding the link between severe or possibly fatal skin reactions following the use of carbamazepine by patients with Asian ancestry. Carbamazepine (Carbatrol®, Shire; Equetro®, Validus; Tegretol®, Novartis; and generics) is an anti-seizure medication used for the treatment of bipolar disorder, epilepsy and neuropathic pain. The life-threatening cutaneous reactions include Stevens-Johnson syndrome (e.g., rash, blistering and inflammation of the mucous membranes) and toxic epidermal necrolysis. These severe adverse reactions, though rare, are significantly more common in this segment of the population due to the presence of a specific human leukocyte antigen (GLA) allele, HLA-B*1502. Although the gene occurs almost exclusively in those with an Asian ancestry, all patients should undergo a blood test for risk assessment prior to start of therapy. Patients treated for several months with carbamazepine and exhibit no symptoms, even with the HLA-B*1502 marker, are at low risk for ever developing the side-effects. Of the treatment population affected, it is estimated that 5% are of Asian descent. The products' labeling will be required to carry the new safety information in the boxed warning section. More details on this FDA alert can be found at: http://www.fda.gov/cder/drug/infopage/carbamazepine/default.htm. |

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