Memorandum

To: San Mateo County Psychiatrists

From: Barbara Liang, PharmD, Mental Health Pharmacy Manager
Celia Moreno, MD, Mental Health Medical Director

Date: 2/13/2008

Re: FDA alerts of serious cutaneous reactions for Carbamazepine, Modafinil and Lamotrigine

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CARBAMAZEPINE

FDA issued an alert on December, 2007, recommending genetic testing prior to starting carbamazepine in Asian clients. Carbamazepine has been associated with severe and sometimes fatal skin reactions, such as Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These skin reactions are more common in clients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. The allele occurs almost exclusively in clients with Asian descent, including South Asian Indians. Asian clients should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started. Clients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from the drug.

Clients who test positive for HLA-B*1502 may be at increased risk of SJS/TEN from other anticonvulsant drugs, including lamotrigine. Therefore, in HLA-B*1502 positive clients, consider avoiding the use of other anticonvulsants associated with SJS/TEN. The FDA has not recommended screening for the HLA-B*1502 allele before starting treatment with lamotrigine; however, limited data suggest that HLA-B*1502 was associated with severe cutaneous reactions induced by phenytoin and lamotrigine as well.

Our contracted laboratory vendor LabCorp is able to test for HLA-B*1502, in a 2-step fashion. The clinician would need to request for HLA-B specific test, Test#167338, and note that you are specifically looking for B1502. If the client tests positive for the HLA-B 15 group, then the lab will perform high resolution typing test to see if B1502 is present. Altogether, these two tests cost approximately $360 per client. If you have further questions, please call the HLA line at LabCorp: 1-800-533-1037.

MODAFINIL

In Oct. 2007, the FDA approved product labeling updates in the warning section of modafinil, reflecting reports of serious rash reactions in postmarketing experience. Cases of life-threatening rash, including SJS, TEN, and drug rash with eosinophilia and systemic symptoms have been reported in adults and children worldwide. Angioedema and multiorgan hypersensitivity reactions have also been reported. Although benign rashes also occur with modafinil, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, Modafinil should be discontinued at the first sign of rash, unless the rash is clearly not drug-related.

Clients should be warned of rash, as well as signs and symptoms suggesting angioedema and multiorgan hypersensitivity, to notify the physician immediately.

Psychiatric adverse reactions (including anxiety, mania, hallucinations, and suicidal ideation) have also been reported. Modafinil is not approved for use in pediatric patients for any indication.

LAMOTRIGINE

In Sept. 2006, the FDA approved product information labeling revisions that highlighted the risk of hypersensitivity and multiorgan failure associated with lamotrigine.

The majority of serious rashes associated with lamotrigine occurred within 2 to 8 weeks of treatment initiation; however, isolated cases have been reported after prolonged treatment. Therefore, duration therapy is not an indicator of rash likelihood. The FDA advises that lamotrigine be discontinued at the first sign of a rash unless another etiology is confirmed. Cessation of lamotrigine therapy may not prevent a rash from becoming life-threatening or permanently disfiguring.

The FDA has also received reports of hypersensitivity reactions leading to clinical features of multiorgan failure/dysfunction. Early manifestations of hypersensitivity (eg. fever and lymphadenopathy) may occur in the absence of rash. Clients with these symptoms should be evaluated immediately, and lamotrigine discontinued. Clients should be warned of symptoms of hypersensitivity and rash, to notify the physician immediately.