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M E M O R A N D U M

Date: February 27, 2006

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Re: Consult #819, received December 23, 2005 from HFD-130, and assigned on December 27, 2005 – This consult is for a review of the dermatologic aspects of the sponsor's response and provide comments to DPP.

Material Reviewed: Consult request, Sponsor briefing packet, NDA 20-717/S-019 safety update, dated 11/21/2005, and two recent safety updates dated 1/24/06 (#086) and 1/25/06.

Sponsor: Cephalon Inc.
Drug: Provigil and Sparlon (modafinil)
Indications: Treatment of ADHD in children and adolescents.

The consult will be organized as follows:

Summary of Findings

The safety data reviewed for modafinil includes 933 patients from eight completed ADHD studies, an additional 533 patients from an ongoing Phase 3 open label study (C1358/312/AD/US), and spontaneously reported postmarketing AEs. Appendix IV summarizes the treatment exposure in the studies.

There were 6 cases that appear to represent EM/SJS, two from clinical studies with modafinil (062338 and 315) which lacked confirmatory histopathology, and four from postmarketing spontaneously reported cases (US016653, Triage #202048, Triage # 163459, and US011480). Of the spontaneously reported cases, the first three have confirmatory histopathology and the fourth had a clinical presentation highly suggestive of and was clinically labeled as E. multiforme major but no histopathology was provided.

A second group of 15 cases had features somewhat suggestive of EM/SJS but histopathology and descriptive information that would confirm the diagnosis are lacking. These included three cases from clinical studies (18001, 18004, and 056003), and 12 postmarketing events: CEPH-1538-99-0019, US008164, US008404, US009106, US009878, US011315, US012666, US012767, US014352, US014893, US015766, and UK000630.

A third group of 16 cases had features resembling prodromal presentations for EM/SJS but without sufficient information for a firm diagnosis. These cases are mentioned here to complete the picture of the types of severe cutaneous AEs that have been reported for modafinil. This group includes 7 study cases and 9 spontaneously reported cases.

All of these cases reporting cutaneous AEs required treatment cessation and had positive dechallenge. A few of these cases required hospitalization. None of the cutaneous AEs led to death or severe disability. In the modafinil studies, there were no placebo treated subjects reported to have EM/SJS or any severe cutaneous AEs requiring treatment cessation.

Reviewers conclusions

1. The cutaneous adverse events reported for modafinil have been reviewed to identify cases of EM/SJS. The assessment of causality of cutaneous AEs is facilitated when the eruption is well documented in its morphology (photography, detailed clinical description, histopathology), in relation to the time of drug administration (improves after treatment cessation, reappears after rechallenge), and when skin tests are positive for the provoking drug.

The review has identified 6 cases that appear to represent cases of EM/SJS, and 15 additional cases that might represent cases of EM/SJS but the information provided is insufficient for a definitive determination. There are an additional 16 cases resembling a possible prodromal/incomplete presentation of EM/SJS.

These 41 cutaneous AEs ranged in severity, all required treatment cessation, a few required hospitalization, but none led to death or permanent disability. All resolved upon treatment cessation.

2. The incidence of EM/SJS in general is reported to be low, only a few cases per million. Therefore, the finding of a few cases resembling EM/SJS within the population studied is of concern.

3. Labeling for modafinil should include an update to the adverse events section and other sections as determined to be appropriate by the medical review team (e.g. WARNINGS and PRECAUTIONS). Parents of pediatric patients and patients should be informed to seek medical attention when a rash develops after starting therapy with modafinil. The labeling proposed by the sponsor appears to address this issue.

4. If future studies with this drug are contemplated, it might be useful to prospectively assess cutaneous reactions more thoroughly, including clinical description of the rash, serial photography, consultation with a dermatologist or other medical practitioner experienced in the assessment of cutaneous drug reactions, histopathology, and skin testing to ascertain causality.

5. With the current interest in Pharmacogenomics and Toxicogenomics, it could be of interest to save the appropriate samples for possible identification of at-risk populations, e.g. haplotype determination, in the investigation of severe cutaneous reactions developing during clinical studies, to identify subjects prone to these reactions.

Thank you for allowing the Division of Dermatologic and Dental Drug Products to assist you on this matter. Please do not hesitate to contact us with regard to any further questions or comments you may have.

Appendix I. Previous Dermatology Consult.

A consult (#773) was completed by Dr. Markham Luke on 10/11/05 and it included the following recommendations:

1) More specific evaluations regarding drug rashes may be requested in future studies with this drug. Drug rashes should be assessed by a qualified dermatologist. Skin biopsy where appropriate should be obtained. Photographs for documentation are encouraged.
2) Labeling for modafinil should include an update to the adverse events section and other sections as determined to be appropriate by the medical review team (e.g. WARNINGS and PRECAUTIONS). Parents of pediatric patients and patients should be informed to seek medical attention when a rash is evident after starting therapy with modafinil.

3) Follow-up for Case 1 could be conducted with regard to allergy to penicillin vs. modafinil. Follow-up of hypersensitivity reactions for sulfur/sulfone allergy could be conducted. These hypersensitivity reactions might be conducted via evaluation of serum from these subjects for elements associated with allergy, e.g. RAST testing for penicillin and sulfone.

Appendix II. Safety Data Request.

The following Specific Safety Request was sent from HFD#130 to the sponsor on 10/20/05:

We have several specific safety concerns that need to be further addressed:
1. Serious Rash.
There were 3 cases of clinically important rash among 933 patients exposed to modafinil in your modafinil/ADHD program.

-One of these was a 7 year old male (062338) who was noted to have a sore throat, fever and mild rash by day 16 of treatment with modafinil 340 mg/day. Amoxicillin was started on day 17, but apparently was limited to a single dose. The modafinil was also stopped by day 17. By day 19, the rash was spreading, and continued to progress, with blistering, peeling, and mucosal involvement (lips and urethral meatus). A dermatologist made a diagnosis of Stevens-Johnson. The rash appeared to resolve by day 30. No skin biopsy results were reported. Our consulting dermatologist suggested trying to obtain RAST testing for penicillin allergy for this patient. Given the limited data available, modafinil cannot be ruled out as a possible cause of this serious event.

-A second case involved an 11 year old female (315) with a maculopapular rash that developed on day 4 of treatment. The patient was treated with diphenhydramine, but the rash worsened and the patient was hospitalized on day 15. A dermatologist considered this to represent a morbilliform rash and treated it with an antihistamine. It resolved within a week.
-A third case involved an 8 year old male (18004) with mild fever, rash on the cheeks and severe blisters on the lips by day 14 of treatment. Modafinil was stopped at this point, and the rash resolved.

There were also less significant rashes, and overall, the incidence of rash in the three phase 3 trials was 4% for modafinil and 2% for placebo.
We are also aware of 5 AERS reports of either erythema multiforme or Stevens-Johnson in adults treated with modafinil.

Comment: Finding even a single case of Stevens-Johnson in a small controlled trials experience is of concern, given how rare this event is as a background event. The finding of 5 AERS reports of either erythema multiforme or Stevens-Johnson adds to the concern that the Stevens-Johnson case in the controlled trial may have been related to modafinil use. We ask that you obtain whatever additional information might be available for this case, e.g., a skin biopsy if obtained and RAST testing for penicillin allergy, if feasible. We further note that the presence of excess levels of the sulfone metabolite in children compared to adolescents and adults suggests the possibility of sulfone allergy as a possible mechanism for this event, and you may consider further evaluation of this possibility. You may also consider getting your own expert dermatological consultation on these cases. Finally, we ask that you propose labeling to appropriately warn of the risk of serious skin rash. In the absence of a better understanding of these events, we consider a warning statement to be the appropriate level for this event, along with clear advice to seek medical attention at the first sign of a rash.

The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Appendix III. The Stevens Johnson Syndrome Spectrum.

To assess reported cutaneous adverse events as possible cases of Stevens - Johnson syndrome, it is appropriate to first summarize the current knowledge available for the syndrome. Such summary follows:

Historical Background:
Hebra first described Erythema Multiforme in 1866 as a relatively benign condition characterized by skin lesions with concentric color changes distributed symmetrically, mostly over the extremities. No mucosal involvement was described.

Stevens and Johnson in 1922 reported children with fever, conjunctivitis, stomatitis, and a generalized exanthem with purplish skin macules with necrotic centers.

In 1950, Thomas suggested that EM and SJS were variants of the same process and proposed renaming them as EM minor and EM major respectively.

In 1956, Lyell reported patients with a mucocutaneous reaction with widespread erythema, necrosis, and bullous detachment of the epidermis resembling scalding, which became known as Toxic Epidermal Necrolysis (TEN). Some of the original cases in this publication have later been reclassified as staphylococcal scalded skin syndrome and as bullous fixed drug eruption[23].

In 1968, Kennett described an oral disorder which was labeled as "EM affecting the oral mucosa."

In 1983, SJS was redefined to include those cases affecting at least two mucosal membranes[28].

Later, the EM major/SJS complex was subdivided into two types, one with target acral lesions -relabeled EM major- and another with widespread blisters on the chest arising over erythematous or purpuric macules - relabeled as SJS.

In 1993, an international group[18] reviewed a large series of cases and proposed a consensus classification which included the following clinical forms: Bullous EM, SJS, and TEN, but this classification is mainly based on morphology and bears no clear etiopathogenic correlation. A series of additional types and modifications have been added throughout the years and it is doubtful that there is currently a consensus on classification.

Cutaneous drug reactions are common, occurring in as many as 30% of hospitalized patients[1].

The WHO defines a serious adverse drug reaction as one that "results in death, requires hospitalization or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening [2].

These serious cutaneous AEs are thought to include SJS/TEN, and the more recently described Hypersensitivity syndrome (HSS) or Drug Rash with eosinophilia and Systemic Symptoms

(DRESS); there is no consensus on the definition of HSS or DRESS[3]. Some include SJS and TEN within HSS [4].

The WHO suggests that causality of a drug reaction be classified as certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassified[5]. Several algorithms have been developed for the application of these classifications but these algorithms have proven inconsistent with each other and are rarely used in clinical practice[36].
Because of the low incidence of SJS/TEN, few practitioners develop expertise[6] with this subject.

Etiology and Pathogenesis

There is no uniform etiology for the EM-SJS syndrome. Each of the different clinical types can be caused by multiple agents, from infectious to drugs and chemicals. In a particular case, it may be difficult to assign causality when multiple drugs are being taken simultaneously. A reaction to a drug can appear whether the drug has been taken once or for a long time; therefore, it would not be safe to assign a drug reaction to the latest drug added to one's treatment since a drug reaction could still be the result of one of the drugs taken for a longer time, the combination of several drugs, or other concomitant factors such as concurrent infections or other conditions that may alter the patient's response.

Among infectious agents, two appear more commonly implicated: Herpes simplex and Mycoplasma.

More than one hundred drugs have been associated with EM, SJS, and TEN [19]. In drug induced EM it is thought that reactive metabolites of the initiating drug induce the disease[7] but the mechanisms of damage are variable and do not appear to be the result of a delayed type hypersensitivity response[14]. Similar drugs have been implicated in both SJS and TEN[8].

The Erythema Multiforme spectrum comprises a cluster of closely related acute exanthematic skin reactions that represent the morphologic expression on the skin resulting from cytotoxic cells attacking epidermal cells. There is a drastic over expression of TNF-alpha in the epidermis and in serum, which may lead to apoptosis and to the attraction of more effector cells [14].

Causative drugs or their metabolites are thought to act as haptens and to render keratinocytes antigenic by binding to their surfaces[9]. Propensity for drug eruptions has been linked to defects of the detoxification systems of the keratinocytes[10, 11], which are thought to be arene oxides in the case of aromatic anticonvulsants, and hydroxyllamines in the case of sulfonamides [23]. Reactive metabolites[7] may act as haptens that bind covalently with cellular macromolecules such as serum proteins or cell surface membranes, resulting in large immunogens that may initiate an immune response[37]. These reactive metabolites might normally be reduced by glutathione and then excreted, or, under certain circumstances, the liver's capacity for glutathione conjugation might be exceeded.

The incubation time between a single drug intake and onset of SJS/TEN varies from a few days to 3 weeks. If a drug is taken daily, the risk of SJS/TEN is highest in the first weeks of administration and is then greatly reduced, as documented in recent case control studies[12]. In the

case of antiepileptics, the risk of developing SJS seems to be confined to the first 8 weeks of therapy [12.] A familial tendency has been reported in the case of anticonvulsants.

It has been suggested that since SJS/TEN is so uncommon, the patient background, for example HLA typing, may be a strong contributing factor[13]. There may be a genetic predisposition to EM for several haplotypes:[14]

-HLA-B15 (B62)
-HLA- B35
-HLA-A33
-HLA-DR53
-HLA-DQB1*0301

Some drugs, such as some anticonvulsants and sulfonamides, are known to cause a severe hypersensitivity syndrome (HSS) consisting of fever, rash, adenopathy, typically several weeks into therapy; the rash initially is a benign morbilliform eruption and may develop into frank exfoliative dermatitis[37].

DRESS has been said to typically develop 2-6 weeks after a drug is first used, and is said to often be due to one of the following: an aromatic antiepileptic agent, sulfonamide, allopurinol, gold salts, and minocycline.

When due to a drug, re-exposure is said to usually lead to a more severe recurrence.

Epidemiology
SJS/TEN cases are rare, the reported incidence being 1-4 cases per million.

Clinical Presentation:
Cutaneous AEs generally present as transient erythematous maculopapular rashes, but these rashes can be the initial presentation of serious mucocutaneous reactions such as SJS or TEN[15].
Cutaneous AEs may vary from benign maculopapular rash to TEN and depend mainly on the host response to a single drug[16].

The following morphologic groups have been defined:

EM minor
- Lesions symmetric over extensor surface of arms and legs.
- Target-like and bullae, may be itchy.
- Mucous membrane involvement limited to one site, usually oral mucosa, presenting as superficial erosions.
- Oral lesions (anterior) may be alone (no skin involvement) or precede skin lesions, or present as ulcers. Lips often swollen and cracked, bleeding crusted.
- May have fever, malaise.
- May range from very mild to very severe.

EM major
-Multiple mucosal involvement.
-Lesions symmetric over extensor surface of arms and legs, similar to E. minor, but also on face and lesions less typical, more widespread (usually less than 10% BSA), more bullous.
-Affects anterior part of the mouth and gingivae, as a result of rupturing small papulovesicles.
-Swollen lips may present blood stained crusted erosions.
-Oral lesions may precede or follow cutaneous lesions by several days.
-Mucosal involvement may be the most prominent element of the disease[27].

SJS
-The prodromic signs of SJS are very non-specific and include: "flue-like symptoms, sore throat, cough, nausea and or diarrhea, headache, arthralgias, myalgias, fever, rhinitis, a macular morbilliform rash develops on the face, neck, chin and central trunk, may be bullous, pneumonia, nephritis and myocarditis. These usually last 1-14 days.
- A phase of progression may follow and can last 4 or more days, depending on the half life of the drug. The acme phase takes from a few days to 2 weeks, with hemodynamic shock, myocardial infarction, and even septicemia [22].
-Initial signs and symptoms are soreness and burning sensations, followed by edema and erythema, then by blisters that rupture to form hemorrhagic dull-red erosions or shallow aphthous-like ulcers.[27]
-Initially, the eyelids may be swollen, erythematous and crusted.
- A concomitant conjunctivitis may appear[17], and conjunctiva involvement may range from mild inflammation to severe eyelid swelling, hyperhemic bullae may occur but are rarely visualized.
- Widespread lesions develop over mouth, eyes, pharynx, esophagus, skin, genitals, and anus, and then spread to extremities and to the rest of the body.
-Skin lesions flat, atypical targetoid or purpuric, affecting less than 10% BSA[7]. At times, they are raised and coalesce[22].
-Skin detachment <10%.
-Before the skin lesions become confluent, it may be confused with a generalized morbilliform drug eruption [27].

SJS-TEN overlap
- Between 10-30% BSA.
-Widespread macules (erythematous and pruritic) or flat atypical targets.

TEN without spots
-Skin detachment >10% BSA with large epidermal sheets and without any macules or targets.
- With or without blisters.

TEN with spots
- Blisters.
- May be strikingly similar to scalded skin syndrome [22].
- More than 30% BSA.
- Widespread purpuric macules or flat atypical targets.
- Systemic symptoms more pronounced here than in SJS, more respiratory involvement with sloughing of tracheal and bronchial mucosa leading to obstruction, bronchopneumonia and even

acute respiratory distress syndrome, and gastrointestinal tract involvement with diarrhea, pain, bleeding and colonic perforation [22].
-The ocular sequelae can be indistinguishable from those of SJS [26].

Oral EM
- To some, it is a distinct but less well-recognized variant of the EM spectrum[27].
- Intraoral bullae and erosions that may interfere with mastication, swallowing, and speech.
- May involve the lip vermillion.
- Most patients have oral lesions. Oral and lip lesions seen in 1/3 of cases; Cutaneous involvement seen in 25% of patients.
- More common in adolescents and young adults.
- Difficult diagnosis because it may present with extremely variable features that can mimic other inflammatory and bullous diseases. A biopsy here mostly helps to exclude the other entities[27].

DRESS has tentatively been defined as follows:
-Cutaneous drug eruption.
-Eosinophilia $\geq 1.5 \times 10^9$/L or atypical lymphocytes.
-Systemic involvement : adenopathy, or hepatitis, or nephritis, or interstitial pneumonitis, or carditis.

Attempts has been made to classify cutaneous AEs into several types[18] but many individual cases do not fit well into any of the types. It remains to be determined whether each group in the classification represents distinct etiopathological entities[14]. In large reviews of EM cases, often they are assigned to a type different from the one originally assigned to by the clinician, and many cases end up labeled as unclassifiable [19,20].

Patients have been seen who will look like E minor at one time, and like E. major at another time[14], suggesting both forms are related. Lack of clear diagnostic criteria has caused the term EM to be widely used to characterize a large variety of cutaneous eruptions, with and without mucosal involvement, and to include even cases of mucosal involvement without skin lesions[21].

Most authors agree that EM major, SJS and TEN are identical processes which differ only in severity and extent of involvement [22], representing a continuous spectrum of increasingly severe manifestations of a single disease entity[28] and are viewed as a continuum spectrum of disease [23] with cases evolving from one category to another within this group [19], and with transition cases where lesions progress from atypical to typical, or cases where lesions of different types coexist on different parts of the body[3, 29]. A unified term has been proposed for these cases: exanthematic necrolysis[24] or acute disseminated epidermal necrosis[25]. A criticism made for the grading system of SJS, SJS-TEN overlap, and TEN is that it does not take into account the evolution of the disease in the early phase [22].

Some consider EM, SJS and TEN severity variants within the so-called erythema multiforme spectrum[18] Some consider that TEN in its early phases is indistinguishable from the epidermal type of EM[26]. It has been said that EM major and SJS represent a bridge in the continuum of EM[27]. Some consider SJS to be synonymous with EM major[28].

Diagnosis

To attempt classification of a cutaneous AE, it is important to identify the types of lesions present in the rash. These definitions have been proposed for the types of lesions that can be present in EM/SJS cases:

- Targets have been defined as <3 cm round lesions with well defined borders and three defined concentric zones, one ring of palpable edema paler than the central disk.
- Raised atypical targets defined as round, edematous, palpable lesions resembling EM but with only two zones and a poorly defined border.
- Flat atypical targets, similar to Raised atypical targets but non-palpable, with a potential central blister.
- Macules with or without blisters defined as non-palpable, erythematous or purpuric lesions with irregular size and shape, often confluent.

The diagnosis is mainly clinical. After review of large series of cases, it has been said that at least 1/3 of all cases admitted to the hospital for a suspected diagnosis of EM or SJS had initially been misdiagnosed[29]; in some review series, often there has been lack of agreement among clinicians as to how to classify individual cases[19].

Generalized Fixed Drug Reaction can be indistinguishable from TEN[26]. Before bullae develop, SJS/TEN may be indistinguishable from other drug reactions[13], but the detection of high serum levels of sFasL could be useful distinguishing SJS/TEN[13], particularly in the early stages.

Histopathology can be quite variable, is most helpful in excluding other diagnosis, but it does not help to establish whether a disease is drug induced[3]. Dermal and epidermal types of EM have been described histologically[30], but it has been said that these types of EM may actually represent different stages of lesion development and reflect different skin sites[31]. The frequent suggestion that the presence of eosinophiles point to a drug reaction was not supported after the review of a large series of cases [42]. Immuno staining is thought to be non-specific.

It may be difficult to distinguish an initial herpetic lip lesion from a lip lesion of EM[32]. The prodromal stages and early mucocutaneous disease of SJS/TEN may be misdiagnosed as an infectious illness, and a drug eruption should always be considered in a child in whom an exanthem and fever develop shortly after initiating treatment with a drug [23].

There are no specific tests for EM.

Testing for cutaneous drug reactions has been recommended as a tool to diagnose cutaneous drug reactions. Guidelines have been published to standardize skin testing procedures[33] but their reliability and the drug concentrations needed for testing are generally unknown for most drugs[39]. Testing may include patch tests, prick and intradermal tests, and provocative tests. Positive relevant tests have been reported in the 25-67% range [33].

Testing for cutaneous drug reactions should be conducted 6 weeks to 6 months after complete healing of the reaction, and at least 1 month after discontinuation of any systemic steroids or immunosuppressive therapy, and preferably not during pregnancy. Testing should be done with

the commercialized product, with active and excipient ingredients. To minimize severe reactions, skin testing should be preformed in the following sequence: patch tests with an immediate reading at 20 minutes, then prick tests and, if negative, delayed reading are recommended for all theses tests.

Patch tests: These should be performed on normal and on affected skin, and read at 20 minutes and at Day-2, Day-4, and at Day-7 if negative at earlier readings. Patch tests appear to be less useful in cases of vasculitis or SJS/TEN[33].

Prick tests should be preformed on the volar forearm skin, starting at very low concentrations and, if negative, increasing the test concentration of the drug by 10 fold at each of three consecutive tests.

Intradermal Skin Tests are recommended when Skin Prick tests are negative but they are contraindicated in patients who had SJS/ TEN or leukocytoclastic vasculitis [33]. These tests may be more useful for IgE mediated reactions[34].

Negative results may have several explanations: a) the final responsible agent could be a drug metabolite that is not formed in the skin when the native drug is applied there, b) no immune mechanism is involved in the cutaneous reaction, or c) concomitant factors that are responsible in inducing a transient oral drug intolerance –such as a viral infection- are not present at the time of testing; thus, a negative test does not exclude the responsibility of the drug. False positive reactions have also been observed in intradermal tests[35].

Today, the provocative test is considered as the "gold standard" to confirm whether a suspected culprit drug is responsible for a particular eruption, because it not only reproduces the allergic symptoms but also any other adverse clinical manifestations irrespective of mechanism[36]. However, rechallenge may not be appropriate in the investigation of severe drug reactions [3, 22].

The European Academy of Allergology and Clinical Immunology recommends the use of provocative test to confirm drug hypersensitivity reactions when skin tests and biologic tests are not available and after balancing the risk-benefit ratio in the individual patient[36]. Cautious rechallenge may be considered if the reaction was not consistent with an IgE-mediated event and if it did not involve serious organ damage[37]. In large series, drug provocation tests reproduced the original drug reaction symptoms, albeit milder and of shorter duration[38].

In drug provocation tests, the drug used is either the suspect drug itself, an alternative drug, or a structurally related drug[39]. If a provocative test is positive, rechallenge with a placebo is also indicated –to rule out the "nocebo effect"[40], and if this is negative, testing should be repeated again with the suspect drug [36]. The predictive value of provocative test depends on the type of reaction and on the type of drug; some subjects with negative provocative tests have been reported to react again upon re-exposure to the drug[41].

In vitro testing methods are mainly available as a research tool. The RAST method for detection of drug-specific IgE antibodies is not very sensitive and its usefulness is unclear [37]. Lymphocyte blast transformation in response to a specific drug can be measured but its role in clinical patient

evaluation is unclear[37]. Some individuals may have specific metabolism defects that enhance their responsiveness to the metabolites formed from the drug. Once we are able to determine the patient's drug metabolism phenotype, the LBT test may become more useful[37].

Differential Diagnosis

The following conditions may resembled EM/SJS and need to be differentiated:

- Drug-induced EM-like eruptions, which cannot be satisfactorily classified and should be considered imitators of EM[22].
- Generalized bullous fixed drug eruption, may be hard to distinguish from SJS[22].
- Kawasaki disease (no oral lesions or swollen lips).
- Toxic shock syndrome.
- Staphylococcal scalded skin syndrome (cannot be differentiated from SJS clinically [42], subcorneal blisters rather than full thickness skin necrosis).
- Acute pustular psoriasis.
- Drug-induced exanthematic pustulosis (high PMN count, initially erythematous/edematous rash that progresses to multiple non-follicular small pustules, which can be hard to differentiate from SJS if they coalesce into large sheets of epidermal detachment, histopathology shows subcorneal spongiform pustules) .
- Acute paraneoplastic pemphigus.
- Linear IgA bullous dermatosis.
- Edematous erythroderma.
- Graft-vs.-Host disease may be indistinguishable from TEN.
- Exfoliative dermatitis.
- Lupus erythematosus.

Appendix IV. Review of Submitted Safety Data.

The safety data provided for review includes 933 patients from the completed ADHD studies. An additional 533 patients were enrolled in C1358/312/AD/US, an ongoing Phase 3 open label study (data cutoff 2/28/05). The worldwide literature search provided by the sponsor includes new safety information on modafinil for published reports between January 1, 2002 and September 30, 2005, for the indications ADHD, sleep apnea, chronic schizophrenia, shift-work sleep disorder, and Parkinson's disease. The sponsor states that the safety profile of modafinil noted in these publications is similar to that previously reported for modafinil. The sponsor has provided safety updates dated 1/24/06 (#086) and 1/25/06.

The eight completed studies included 420 patients treated with modafinil and 213 treated with placebo and were:

– C1538d/309/AD/US: A 9-Week, Flexible-Dosage (up to 425 mg/day) study.
31 subjects treated with ≤ 255 mg/day, 22 with 340 mg/day, 78 with 425 mg/day

– C1538d/310/AD/US: A 9-Week, Fixed-Dosage (340 or 425 mg/day) study including a 2-Week (Blinded) Withdrawal Period.
44 subjects treated at 340 mg/day, 81 at 425 mg/day

– C1538d/311/AD/US: A 9-Week, Flexible-Dosage (up to 425 mg/day) study.
31 subjects treated with ≤ 255 mg/day, 36 at 340 mg/day, 97 at 425 mg/day

- C1538a/207/AD/US: A 5 or 6 Weeks per Part, Crossover Study followed by an 8-Week Open-Label Extension. 47 subjects treated at 100-400 mg/day, 30 subjects in the extension.

– C1538a/213/AD/US: A 4-Week, Study Followed by an 8-Week Extension.
197 subjects treated at 300-400 mg/day for 4 weeks, 220 in the extension.

- C1358/312/AD/US: open study, at dosages of 170-415 mg/day. 9unclear what the exposure has been in this study up to date of safety data update)

Two studies were conducted in France: E1044 (14 subjects treated for up to 49 days) and E1047 (24 subjects treated for 56 days). Additionally, there were a 2 week single dose and an 12 week dose ranging and pk studies.

The sponsor states that a worldwide literature search covering 1/1/1998- 4/1/2005 includes publications covering about 500 adult subjects, treated with 50-800 mg/day and 62 children treated with modafinil at 50-400 mg/day, reporting no deaths and only 4 serious adverse events, all of them in adults.

1. Review of Study Subjects with Severe Cutaneous Adverse Events leading to treatment discontinuation:

This review has been hampered by the scarcity of information available for review. In general, photographs have not been provided, morphologic descriptions of the rashes observed and histopathology have been provided in very few cases, and no testing has been done to establish whether the treatment drug could have been responsible for the rash observed except in a few cases where retreatment reproduced the cutaneous AE. Another difficulty is that a particular case may appear labeled differently in different reports, making it difficult to decide whether several reports

refer to the same or different patients; for instance: a recent safety update identifies a patient as # 99 from study 312 in one place, as #062338 elsewhere, and as US013240 in another, a patient was designated as both 056003 and (056180). In many cases, we are told that the adverse event led to treatment discontinuation and that it resolved upon dechallenge. We are also told that although some cases required hospitalization, no case experienced lasting or permanent disability. In a couple of cases, we are told that treatment was restarted, either by mistake or purposefully, and the AE reappeared. Where several clinicians have been involved in the care of patients developing severe cutaneous AEs, often the diagnosis offered by each clinician has either been different or has varied with the passage of time. For many of these cases, accurate information is lacking regarding the initial dose, or when the dose was increased.

This reviewer has identified some cases that are likely to represent Stevens-Johnson-EM syndrome, other cases which appear compatible with/suggestive of early forms of EM-SJS, and still a group of other cases where at best one could consider the case history to be suspicious for an incipient case of SJS. The cases are described next:

1. Study cases that represent EM/SJS:

Case # 1.1

Patient id	062338 (US013240 in recent safety update)
Study id	C1538d/311/AD/US
Age	7
Gender	Male, Caucasian (changed to Asian in safety update)
Initial dose	Not given
dose started	3/20/04
Dose change on	Day-15
Dose changed to	Up to 340 mg (up to 425 in recent update)
Concomitant meds	none
AE start date	Day-16 Mother stopped Provigil
AEs	Sore throat Fever of 101.9 F Mild rash worsened to entire body (labeled EM by investigator) Safety update states on Day 16 rash was "significant, extensive, severely itching, involving most of the body, with swollen red crusty lips, inflamed meatus and difficulty urinating, later involving palms and soles" One dose amoxicillin Rapid strep test neg Erythromycin prescribed but not taken (taken for 2 days in recent safety update)
New AEs date	Day 19
New AEs	Multiple pruritic areas over stomach and arms Pediatrician thought it unrelated to amoxicillin
New AEs date	Day 22
New AEs	Rash spread to face Extensive skin peeling Burning on urination, involvement of both lips, considered the onset of SJS Dermatologist called EM by Hx, most likely SJS
Action taken on	Day 18. Treatment stopped
AE assessment	Rash related to drug Pharyngitis considered viral Narrative includes a statement that SJS was probably secondary to viral pharyngitis
	Day-26 Mother gave one more Provigil dose, and itching worsened

	Day 42 patient seen by investigator and referred to dermatologist and by this time the rash appeared to be resolving
	Dec 29, 05 Percutaneous skin test for penicillin G and for Modafinil negative for immediate-type hypersensitivity (per recent safety update)
Rash description	no
Bx available	no
Improved on dechallenge after days	Day 30, resolved Day 31, additional dose given by mother (medwatch says last dose at Day 27 No info on whether rash recurred Withdrawn from study on day 44, SJS was resolved but EM was still continuing *Reviewer comment: this contradicts the earlier statement that rash had resolved by day-30*
Narrative available	yes

Reviewer comment: My personal impression is that this case most likely to represent EM/SJS, and that the symptoms that were initially interpreted as a viral process were most likely part of the "prodrome" for EM/SJS. There is a contradiction in statements that the adverse events had resolved by Day-30 the SJS had resolved by Day-44, but the EM was continuing at Day-44. Percutaneous testing does not take into account the metabolism of the study drug and may therefore be negative even if the study drug was actually responsible for the skin rash, as the sponsor recognizes in the Conclusions and Recommendations within the report. Therefore, a negative percutaneous test with modafinil does not rule out its being responsible for the AE. The sponsor is accepting this case as compatible with SJS.

Case #1.2

Patient id	315	
Study id	C1538a/207/AD/US	
Age	11	
Gender	female	
Initial dose	100 mg for day-1, 200 mg for days 2-7 100 mg days 8-15	*Why was dose decreased at day-8?*
Concomitant meds	Somatropin for Turner's syndrome Desmopressin for enuresis	
AE start date	Day-4	
Aes	Fever Abdominal pain diarrhea	Persisted for 9 days
AE start date	Day-8 (from 3.1.3)	
Aes	Urticaria, not in narrative	
New Aes date	Day-14	
New AEs	Generalized pruritic urticaria believed to be contact dermatitis	
Action taken on	ER visit, diphenhydramine	
New AEs date	Day 15	
New AEs	Hospitalized as SJS hydroxyzin Study treatment stopped	
AE assessment	Dermatologist changed Dx to moderate morbilliform rash (3.1.3 calls it "serious") Probably drug related	
Rash description	No mucosal blisters or erosions	

Bx available	no	
Improved on dechallenge after days	Rash resolved within 1 week	
Narrative available	yes	

Reviewer comment: Urticaria is listed in table 3.1.3 but not reflected in the narrative. It is unclear whether the observation of urticaria by Day-8 was the reason for the decrease of dose to 100 mg on Day-8. The subject was hospitalized with a diagnosis of SJS. This diagnosis was later changed to "moderate morbilliform rash" but in table 3.1.3 the rash is labeled as "severe." It is unclear whether the dermatologist who changed the diagnosis to "morbilliform rash" saw the patient when the eruption was at its most severe manifestation. The sponsor is accepting this case as compatible with SJS.

2. Study cases that are compatible with/suggestive of early forms of EM/SJS:

Case # 2.1

Patient id	18001
Study id	C1538/213/AD/US
Age	6
Gender	male
Initial dose	200 mg
dose started	3/6/02
Concomitant meds	none
AE start date	Day-3
AEs	Decreased appetite
New AEs date	Day-8
New AEs	Severe rash
New AEs date	Day-9
New AEs	fever
New AEs date	Day-11
New AEs	vomiting
Action taken on	Day ?? diphenhydramine ibuprofen given for the rash
Action taken on	Day-14 Treatment stopped
AE assessment	Possibly related
Rash description	none
Bx available	no
Improved on dechallenge after days	?? number of days
Narrative available	yes

Reviewer comment: The rash was labeled as "severe" and was accompanied by vomiting, requiring treatment cessation which was followed by symptom resolution. Although no firm conclusion can be drawn, the case is compatible with the prodromal presentation for EM/ SJS.

Case #2.2

Patient id	18004
Study id	C1538/213/AD/US
Age	8
Gender	male
Initial dose	200 mg
dose started	4/5/02
Concomitant meds	Chewable vits
AE start date	Day-14
AEs	Mild fever Moderate rash on cheeks
New AEs date	Day-17
New AEs	Lip blisters (in 3.1.3, labeled "severe")
Action taken on	Day-18 Treatment stopped Cephalexin Acetaminophen with codeine for fever and rash related-pain
AE assessment	Possibly related
Rash description	no
Bx available	no
Improved on dechallenge after days	Yes after ?? days
Narrative available	yes

Reviewer comment: The presentation of "moderate rash" on the cheeks with "severe" lip blisters and fever is suggestive of EM/SJS. The differential diagnosis here would mostly be herpes infection, which would be unlikely if no antiherpes antibodies are detected.

Case #2.3

Patient id	056003 (056180)
Study id	C1538d/312/AD/US
Age	9
Gender	male
Initial dose	85 mg
dose started	2/25/04
Dose change on	Day-10
Dose changed to	340 mg
Concomitant meds	none
AE start date	Day-13
AEs	Fever, Urticaria, Swollen eyes, vomiting
Action taken on	Withdrawal at Day 14 Treatment given for fever
AE assessment	Probably related
Rash description	none
Bx available	no
Improved on dechallenge after days	Day-23
Narrative available	yes

Reviewer comment: The presentation of fever, urticaria, swollen eyes, and vomiting, requiring treatment cessation and positive dechallenge suggests a drug reaction and could represent the prodromal stage of EM/SJS without further progression because the offending drug was quickly discontinued.

3. Study cases with insufficient information but with a history resembling the prodromal presentation of EM/SJS:

Case #3.1

Patient id	019137
Study id	C1538d/309/AD/US
Age	10
Gender	female
Initial dose	unknown
dose started	11/12/03
Dose change on	Day 8
Dose changed to	titrated up to 255 mg
Concomitant meds	none
AE start date	Day 3
AEs	mild pharyngitis mild upper respiratory infection
New AEs date	Day 16
New AEs	Mild rash, Fever, Headache Tremor, Panic attack
Action taken on	Day 17
Action taken	Dose decreased Dose stopped
AE assessment	Probably related
Action taken on	Day 21
Action taken	Discontinued from study
Rash description	Not given
Bx available	no
Improved on dechallenge after days	
Narrative available	yes
Added info needed	Unknown course after Rx stopped

Reviewer comment: The presentation of pharyngitis, upper respiratory infection, mild rash, fever, and headache, severe enough to warrant treatment cessation, with positive dechallenge, and labeled as "probably related" are compatible with the prodromal presentation of EM/SJS.

Case #3.2

Patient id	031149
Study id	C1538d/310/AD/US
Age	8
Gender	female
Initial dose	340 mg
dose started	2/4/04
Concomitant meds	none
AE start date	Day 8
AEs	Reddening of sclera, Blurred vision Dry mouth, Pruritus, Headache
Assessment	Probably related
Led to	Study discontinuation
Rash description	no
Bx available	no
Improved on dechallenge after days	By day-15, except for conjunctivitis
Narrative available	yes

Reviewer comment: The presentation of "conjunctivitis" with pruritus, headache, and dry mouth, severe enough to warrant treatment cessation, with positive dechallenge except for conjunctivitis, and labeled as "probably related" are suggestive of the prodromal presentation of EM/SJS.

Case #3.3

Patient id	08012
Study id	C1538/213/AD/US
Age	9
Gender	male
Initial dose	200 mg
dose started	4/25/02
Concomitant meds	none
AE start date	Day 14
AEs	Moderate rash
Action taken on	diphenhydramine
Action taken on	Day 16 Treatment stopped
AE assessment	Definitely related
Rash description	no
Bx available	no
Improved on dechallenge after days	2 days
Narrative available	yes

Reviewer comment: The information available is too scant to make any assertions. However, a rash severe enough to warrant cessation of treatment, with positive dechallenge, and labeled as "definitely related" should not be ruled out entirely as a prodromal EM case.

Case #3.4

Patient id	24004
Study id	C1538/213/AD/US
Age	8
Gender	female
Initial dose	100/200 mg
dose started	3/28/02
Dose change on	4/9/02 stopped
Concomitant meds	none
AE start date	Day-13
AEs	Severe rash
New AEs date	??
New AEs	Leukopenia, probably related
AE assessment	Definitely related
Rash description	no
Bx available	no
Improved on dechallenge after days	Resolved ?? days
Narrative available	yes

Reviewer comment: The information available is too scant to make any assertions. However, a rash severe enough to warrant cessation of treatment, with positive dechallenge, and labeled as "definitely related" should not be ruled out entirely as a prodromal EM case.

Case # 3.5

Patient id	029015 (029169)
Study id	C1538/312/AD/US
Age	7
Gender	male
Initial dose	85 mg
dose started	4/22/04
Dose change on	
Dose changed to	Titrated to 340 mg by Day-10
Concomitant meds	none
AE start date	Day-24
AEs	Mild rash benadryl Medrol (for a mild rash?)
Action taken on	Between days 26 and 33 Treatment stopped Treatment re-started on Day 34 and rash reappeared on the same day. Treatment stopped again
AE assessment	Definitely related
Rash description	no
Bx available	no
Improved on dechallenge after days	Day-29, first time Day 39 second time
Narrative available	yes

Reviewer comment: The information available is too scant to make any assertions. It is of interest that although the rash was labeled as "mild," treatment with Medrol was given, suggesting the rash severity was not properly categorized. A rash severe enough to warrant cessation of treatment, with positive dechallenge and positive re-challenge, and labeled as "definitely related" should not be ruled out entirely as a prodromal EM case.

Case #3.6

Patient id	2007 (2281)
Study id	C1538d/312/AD/US
Age	9
Gender	male
Initial dose	85 mg
dose started	4/1/04
Dose change on	Day-15
Dose changed to	425 mg reduced to 340 mg on Day 29 because of headaches
Concomitant meds	
AE start date	Days 8-17 Red blotches on tongue
AEs	Nausea day 6-16
New AEs date	
New AEs	Headaches day 8-8 Page 94 of 517 Day-14: Sore throat, Increased AST, ALT Moderate Myalgia Day 15-27 Day 32-33 cough and fever, fatigue, leading to dose reduction Gastroenteritis Day 83 moderate decreased absolute monocytes day 35- 42, moderate decreased percent monocytes day 35-49

	moderate increased lymphocytes day 35-104. All of these adverse events resolved with no residual effect and were considered by the investigator to be possibly related to treatment with study drug.
Rash description	no
Bx available	no
Narrative available	yes

Reviewer comment: The presentation of headaches, red blotches on the tongue, myalgia, cough, fever, fatigue, and gastroenteritis, severe enough to warrant treatment cessation with positive dechallenge are compatible with prodromal EM/SJS.

Case #3.7

The following case, listed in one of the tables, describes the presence of a vesico-bullous eruption accompanied by fever. This reviewer has not been able to identify a narrative for this case.

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Listing 10
Adverse Events by Site

Site: 02 (SAMUEL W. BOELLNER, MD)

Patient ID	_Study Day^_ Start	Stop	Duration	Description	Preferred Term	Body System	Serious	Severity	Action Taken Medication	Other	Other Specify	Relation to Study Med	Outcome
02037/[redacted]	32	63	32	BLISTERS ON FEET	VESICULOBULLOUS RASH	SKIN	NO	MODERATE	NONE	MED		NOT RELATED	RESOLVED NO RESIDUAL EFFECT
	38	55	18	INSOMNIA	INSOMNIA	NER	NO	MODERATE	INTERRUPTED			POSSIBLE	RESOLVED NO RESIDUAL EFFECT
	38	55	18	SEPARATION ANXIETY	ANXIETY	NER	NO	MODERATE	INTERRUPTED			POSSIBLE	RESOLVED NO RESIDUAL EFFECT
	61	61	1	FEVER	FEVER	BODY	NO	MILD	NONE	MED		NOT RELATED	RESOLVED NO RESIDUAL EFFECT

^Study Day: Day relative to the start of open-label medication.

Source: j:\biostats\provigil\213o1\cpstats\pgms\1213AE.sas Programmer: [redacted] Data Extract: 11/27/02 12:30 Table Generation: 01/21/03 15:57

Reviewer comment: Some of these events could represent cases of EM/SJS. Because the early manifestations of EM/SJS can be so variable, with the available information the diagnosis of EM/SJS cannot be confirmed or excluded in many cases reported to have adverse reactions.

The onset of the rash occurred approximately 3 through 24 days after starting modafinil treatment. Systemic symptoms were rarely reported. None of these patients were on concomitant medications. The rashes resolved upon discontinuation of study drug treatment. A dose relationship is difficult to establish because most patients started on a low dose and were titrated upward within a short time. Most reported cases are younger than 11 years old but this may be reflective of the study population.

2. Postmarketing Cutaneous Adverse Events:

The sponsor has provided information on spontaneous postmarketing cutaneous AEs in Appendix E (listing 2.7.4 page 180) and in the safety update dated 1/25/06. These cases will be presented in three categories, similarly to the study subjects presented above.

1. Spontaneously reported cases that represent EM/SJS:

Case 1.1. US016653.
A 42 year old female who was treated with Risperdal and Lexapro, and then Provigil was added. After 14 days, she developed pruritus and "black spots" over her entire body that progressed to a "pimple-like rash" and was then treated with Benadryl, and later with Prednisone. The patient was hospitalized a week later, presenting blisters over a "significant percentage of the total body area" (later assessed as 30% of BSA), with ocular, oral and nasal mucosa involvement, 2-4% of the skin being denuded and open, and greater than 20% of the skin sloughing and with flaccid blisters, erosions and crusted blisters, and a diagnosis of SJS with TEN was made and all three drugs were discontinued. Histopathology showed full thickness epidermal necrosis overlying re-epithelialized skin.
Reviewer comment: This case is probably the one most representative of EM/SJS. Although the eruption developed soon after initiating treatment with Provigil, the possible role of the other two drugs administered cannot be ruled out.

Case 1.2. Triage unit sequence # 202048.
A 27 year old female who took Provigil for an unspecified period of time. No information is given about concurrent medications. She developed for one week a sore throat which progressed to swelling of the oral cavity and dysphagia, fever. At the time of hospitalization, she presented severe sloughing of the oral and vaginal mucosa. A clinical and histopathology diagnosis of EM/SJS was made.
Reviewer comment: Although the information provided is limited and outcome is unknown, this presentation is easily accepted as representative of EM/SJS. However, causality is difficult to assign with the information provided.

Case 1.3. Triage # 163459.
A 28 year old female with a 3 year history of systemic lupus being treated with low dose prednisone and Plaquenil, and also receiving Zoloft, was treated with Provigil during 2/25/02-

3/2/02 and developed itchy eyes, skin and mucous eruption consistent with SJS, and was hospitalized and treated with high dose steroids. Histopathology reported as positive for erythema multiforme.

Case 1.4. US011480.
A 68 year old female took Provigil 200 mg, daily for 2 weeks, and developed sore throat, mouth swelling with ulcers, and a rash over her body, which required hospitalization and treatment with oral and topical corticosteroids and was labeled as Erythema multiforme major. Positive dechallenge.
Reviewer comment: Although the information provided is very limited, it is very suggestive of EM/SJS.

2. Spontaneously reported cases that are compatible with/suggestive of early forms of EM/SJS:

The following twelve cases include insufficient information for a definitive classification but the information provided is suggestive for EM/SJS:

CEPH-1538-99-0019. Age: 54. Dose: 100 mg. Duration of treatment: 29 days. Rash developed with severe swelling of face, hands and legs, which led to treatment discontinuation. Positive dechallenge.
US008164. Age: 32. Dose: 200 mg. Duration of Treatment: 1 day. Anaphylactic shock, angioedema, urticaria. Positive dechallenge
US008404 Age: 50. Dose: 100 mg. Duration of treatment: 1 day. Rash, hives, itching, swelling of tongue, anaphylactoid reaction. Positive dechallenge
US009106 Age: 46. Dose: 200 mg. Duration of treatment: 3 days. Angioedema. Positive dechallenge.
US009878. Age 23. Dose: 100 mg, AE at 400 mg. After 1 day, face felt hot and tender, brown urine, nausea. Positive dechallenge.
US011315 Age: 36. Dose: 100 mg. Duration of treatment: 1 week. Urticaria, total body edema, headache. Positive dechallenge.
US012666 Age: 48. Dose 200 mg. Dose: unknown. Duration of treatment: unknown. Anaphylactic reaction Concomitant: Keflex
US012767. Age: 38. Dose: 200 mg. Duration of treatment: 10 days. Severe allergic reaction. Positive dechallenge
US014352 Age: 25. Dose 200 mg. Duration of treatment=0. Fever, severe joint pain, rash, swelling. Positive dechallenge. Concomitant: interferon
US014893 Age: 22. Dose: 100 mg. Duration: 2 weeks. Pain in throat, itchy rash on hands and feet. Positive dechallenge
US015766 Age: 21. Dose unknown. Duration of treatment: 0. Lupus like eruption. Positive dechallenge
UK000630 Age: 40. Dose 300 mg. Duration of treatment: 5 weeks, 4 days. Arthralgia, sweating, headache, nausea, vomiting, flue-like symptoms. Positive dechallenge and rechallenge

Reviewer comment: Some of these events are likely to represent cases of EM/SJS.

3. Spontaneously reported cases with insufficient information but with a history resembling the prodromal presentation of EM/SJS:

The following nine cases include insufficient information for a definitive classification but the information provided resembles the prodromal presentation of EM/SJS:

CEPH-1538-99-5064. Age: 25. Dose: 40 mg. Duration of treatment: 13 days. Fever, vomiting, body pain, eyes photosensitive. Positive dechallenge
US010549 Age: 50. Dose 150 mg. Duration: 0. Red flushing of the skin, not resolved
US011060 After 3 days, pruritus. Positive dechallenge
US012623 Age: 51. Dose: 100 mg. Duration: 1 day. Itching, pain in extremities. Positive dechallenge.
US012983 Age: 52. Dose: 200 mg. Duration: one dose. Swollen tongue, blurred vision, increased thirst, dizziness. Positive dechallenge
US013490 Age:57. Dose: 200 mg. Duration: a few days. Peripheral edema. Positive dechallenge
US013627 Age 48. Dose 400 mg. Duration of treatment: 4 years. Rash, unspecified. Positive dechallenge
US013912 Age:52. Dose: 100 mg. Duration of treatment: 0. Fever, myalgia, nausea, vomiting, Positive dechallenge, positive rechallenge
US014715 Age 51. Dose: 200 mg. Duration of treatment: 3 weeks. Erythematous rash and stinging pain. Positive dechallenge

Reviewer comment: Six cases appear likely represent true cases of EM/SJS, including 2 study cases and 4 spontaneously reported cases.
An additional 15 cases are highly suggestive for EM/SJS but the information provided is insufficient for a definitive classification. These include 3 study cases and 12 spontaneously reported cases.
For a supposedly rare event such as EM/SJS, the number of reported cases is of concern. Because of this concern, one should not disregard the additional 16 cases, 7 study cases and 9 spontaneously reported cases with a suggestive but very incomplete clinical description.

3. Labeling:
The sponsor was asked to provide copies of labeling in other countries were modafinil is being marketed. The labeling for Modiodal, as is marketed in Mexico has been provided. This labeling includes the following text in relation to cutaneous adverse events:

Allergic Reactions:

- Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

In the incidence of adverse events table, the following is included:

- Skin Herpes simplex 1% 0%
- Skin Appendages Dry skin 1% 0%

The following text is included after the table (cutaneous effects underlined here by the reviewer):

Events for which the MODIODAL incidence was at least 1%, but equal to or less than placebo are not listed in the table. These events included the following: infection, back pain, pain, hypothermia, abdominal pain, flu syndrome, allergic reaction, fever, asthenia, accidental injury, general edema, tachycardia, palpitations, migraine, ventricular extrasystole, bradycardia, dyspepsia, tooth disorder, constipation, flatulence, increased appetite, gastroenteritis, Gl disorder, ecchymosis, anemia, leukocytosis, peripheral edema, increased weight, increased SGOT, myalgia arthritis, arthralgia, somnolence, thinking abnormality, leg cramps, sleep disorder, hallucinations, hyperkinesia, decreased libido, increased cough, sinusitis, bronchitis, pneumonia, rash, sweating, pruritus, skin disorder, psoriasis, ear pain, eye pain, ear disorder, taste perversion, dysmenorrhea', urinary tract infection, pyuria, hematuria, cystitis and disturbed menses'.

Reviewer comment: The labeling for Mexico under represents the cutaneous adverse events for Modafinil.

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