

# EXHIBIT B

## Medical Officer Review of Supplemental NDA

NDA 13-217/S036  
Metaxalone (Skelaxin®)

Sponsor: Elan Pharmaceuticals

Re: Review of Complete Response to July 11, 2002 Approvable letter (S-036)  
Reviewer: M. Lourdes Villalba, M.D., M.O., HFD-550

Date of submission: July 19, 2002  
Date of review: August 27, 2002

**1. Background:**

Metaxalone is a muscle relaxant available for the treatment of acute, painful musculoskeletal conditions as an adjunct to rest, physical therapy and other measures for the relief of pain. The Agency issued an Approvable letter to NDA 13-217/s036 on July 11, 2002. The letter requested that the sponsor submit revised draft printed labeling, as well as a Safety Update report, including an analysis of post-marketing safety data with Skelaxin®.

**2. Review:**

This is the review of the Safety Update. As per Dr. Bashaw's review, inclusion of pharmacokinetic data as described in the sponsor's proposed label is acceptable.

Skelaxin® has been marketed for 40 years. The current submission contains a summary report of the last two-year reporting periods as well as a summary of adverse events from five recently conducted pharmacokinetic studies. In addition to the information provided by the sponsor, post-marketing safety information are available from a post-marketing safety review conducted by the Office of Drug Safety in August 2000, at the request of the Division of Pharmaceutical Evaluation III.

**2.1. Office of Drug Safety Post-marketing Safety Review (August 2000)**

From 1970 to August 23, 2000 a total of 52 cases of adverse events with metaxalone were reported to the AERS system. Of those, 29 were temporally related. Eighteen reported a serious outcome including one death. All events were unlabeled and involved the following body systems: cardiac (9), immune (6, including one death), hepatobiliary (1), hematologic (1), nervous (4), psychiatric (2), endocrine (2), reproductive (1) and others (3). None of the patients exceeded the maximum recommended daily dose of 3200

mg. The time of onset varied from immediate to greater than one day. Many were confounded by concomitant medication, preexisting medical conditions or lack of clinical detailed information. The safety evaluator concluded that the significance of these events could not be determined due to the small number of reports and the wide utilization of metaxalone over 30 years. (For a detail review see consult by Renan Bonnel, PharmD, M.P.H., OPDRA PID # D000565).

*The current Skelaxin label contraindicates its use in patients with prior history of hypersensitivity to metaxalone, known tendency to drug-induced hemolytic or other anemias and in patients with significantly impaired renal or hepatic function. These contraindications should be maintained. However, they should be in separate sentences. Also, the term "significantly impaired" should be better defined. The Adverse Reactions section also includes several events, all in a single paragraph. This section should follow the format of current labels and list AE's separated by organ system.*

2.2 Post-marketing review of last two annual reporting periods (3/1/00 to 2/28/01 and 3/1/01 to 2/28/02).

As noted in Table 1. Appendix 1, there has been an increase in the total number of adverse events over that last two year periods, particularly serious cases (from 2 to 14) and 15-day alert reports (from 2 to 13). This observation coincides with a slight increase in usage from year 2000 to 2001 (from approximately 250,000,000 to 310,000,000 tablets).

*Reviewer's comment:*

*As per review of the last two annual reports, the increase in serious AEs appears to be mainly in the Body as a whole, Digestive, Metabolic and Musculoskeletal systems. Still, the numbers are not extremely large, considering metaxalone usage over these periods. Of note, these are AEs submitted by the sponsor. A post-marketing review of the AERS system might yield higher numbers because of direct reports to FDA.*

2.2.1. March 1, 2000 to February 28, 2001 annual report - Case of interest.

a. Overdose

During this reporting period there was one report of intentional overdose (ID # SKEL 000027). This was a 44-year-old woman who took 200 to 250 400-mg Skelaxin tablets. Shortly after, she presented myoclonus, encephalopathy, hyperreflexia, tachycardia and diaphoresis. None of these events are included in the current Skelaxin label. At the time of the report (November 2000), five days after the suicidal attempt, she was still in the ICU in serious condition. No follow up report has been provided.

This patient had a history of depression and was taking Prozac (fluoxetine) at the time of the overdose. The prior history of depression and concomitant use of fluoxetine

may have contributed to the event of intentional overdose. However, there is no mention of fluoxetine overdose in the report. The large dose of Skelaxin, (80 to 100 g, when the maximum recommended dose is 3.2 g/day) most likely contributed to the

#### 2.2.2. March 1, 2001 to February 28, 2002 annual report - Cases of interest.

##### a. Overdose

During this reporting period there were three reports of death associated to intentional overdose with Skelaxin (SKEL 000052, 000078 and 000080).

- SKEL 000052 - A 37 year old woman died following a possible suicide attempt and overdose during the use of Skelaxin for the treatment of fibromyalgia. The patient filled a prescription for 240 tablets for Skelaxin on June 29, 2001. She died on June 30, 2001. According to the package insert, suicide attempt and overdose were not reported in patients during clinical development of Skelaxin.

Around the time of her death, the patient was also receiving Zoloft (sertraline) for an unknown indication. The US package insert for Zoloft states that suicide ideation has rarely been reported although the possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. The psychiatric history of this patient is unknown, although it is conceivable that she had depression. In any case, the immediate cause of death appears to have been an overdose of metaxalone, not an overdose of sertraline.

- SKEL 000078. A 33 year old woman died as a result of a suicide from an intentional overdose during the use of Skelaxin for the treatment of an unspecified indication. The patient was found dead in bed with a suicide note.

The patient had a history of bipolar disorder and was taking Paxil (paroxetine) at the time of the suicide. The package insert for Paxil mentions that suicide attempt is inherent to depression and that fatalities associated with overdose of paroxetine have occurred. The autopsy revealed toxic levels of both, Paxil and Skelaxin. Therefore, both products may have been related to this patient's death.

- A 29 year old woman died following a suicide attempt during the use of Skelaxin for an unspecified indication. The date of death was January 21, 2002.

The autopsy revealed high levels of metaxalone as well as small levels of Celexa (citalopram) and alcohol. Again, it is unknown but conceivable that the patient may have had a history of depression. The package insert for Celexa states that suicide ideation is inherent depression and that suicide attempts have been reported in patients taking Celexa. Both metaxalone and citalopram may have been related to this patient's death.

*Reviewer's comment: In summary, deaths associated with overdose of metaxalone have been reported, particularly in patients taking concomitant antidepressants such as fluoxetine, sertraline, paroxetine and citalopram.*

*The only statement that refers to overdosage in the Skelaxin package insert is under the "Management of Overdose" section: "No documented case of major toxicity has been reported." Although the number of events is small (four over the last two years), the outcome of death in these young women is a strong signal for an event that should be included in the label.*

**b. Liver-related events**

There were three serious, liver related AEs: one liver necrosis/encephalopathy (000075) one fatty infiltration (000043) and one jaundice (000070).

- SKEL 000075 - A 42 year old male experienced flu symptoms followed by hepatic necrosis while on treatment with Skelaxin (400 to 800 mg/day) and diclofenac (50 - 100 mg/day) from December 12 to 21, 2001. He died of massive hepatic necrosis on January 12, 2002. Both diclofenac and Skelaxin may have been related to this death.
- SKEL 000043 - A 24 year old woman taking unspecified concomitant medications developed fatty liver infiltration after 3-4 months of treatment with metaxalone. There is very limited information in this case to draw any conclusions.
- SKEL 000070 - An adult male patient developed jaundice during the use of skelaxin for an unspecified indication. The start date and dose of Skelaxin is unavailable. The patient was taking concomitant rofecoxib and lisinopril. There is very limited information in this case to draw any conclusions.

*Reviewer's comment: The current Skelaxin label states under Precautions: "Elevation in cephalin flocculation tests without concurrent changes in other liver function parameters have been noted. Hence it is recommended that metaxalone be administered with great care to patients with pre-existing liver damage and that serial liver function studies be performed as required." This statement about the cephalin test appears outdated. The recommendation to check LFT's "as required" is pretty unspecific. A statement should reflect the lack of information related to patients with liver impairment.*

*A similar statement should be made regarding the lack of information in patients with renal impairment.*

2.3 A review of the summary of adverse events from five recently conducted pharmacokinetic studies (AN 151607-101, 102, 103, 104 and 106) reveals that headache is the most common AE associated with the use of metaxalone (up to 50% of patients in study 103).

**3. Conclusions/Recommendations:**

3.1. This supplemental application should be approved.

3.2. As per Dr. Bashaw's review, inclusion of data describing pharmacokinetic parameters is acceptable.

From the clinical point of view, the sentence stating that no documented cases of major toxicity have been reported should be eliminated from the label.

The potential risk of death associated with overdose, particularly in patients taking concomitant antidepressant medications should be included in the label.

The Skelaxin label should follow the format of other most recently approved muscle relaxants, including the name and order of the different sections and the listing of adverse events under different body system categories.

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Medical Officer, HFD-550

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Clinical Review of NDA 13-217  
Final Printed Labeling

NDA 13-217/S-036

**Submission date:** October 11, 2002  
**Receipt date:** October 15, 2002  
**Review date:** November 1, 2002

**Applicant:** Elan Pharmaceuticals, Inc.  
89 Headquarters Plaza North, Suite 1420  
Morristown, NJ 07927

**Applicant's Representative:** Ms. Linda B. Fischer  
Director, Regulatory Affairs  
(973) 294-2329

**Drug:** Skelaxin (metaxalone) tablets

**Pharmacologic Category:** Muscle relaxant

**Submitted:** Final Printed Labeling of the package insert, in response to the August 30, 2002, approval letter. The package insert refers to the 400 mg and 800 mg trade size tablets.

**Reviewer's comments:** The package insert in this submission is identical to the August 30, 2002 draft labeling (with the exception of acceptable sponsor differences highlighted in red) per telephone conversation held September 16, 2002 after discussion with and approval from the reviewing medical officers: