CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-256

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	January 14, 2009
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # **Supp #**	N 22-256
Applicant Name	Cypress Bioscience, Inc. Forest Laboratories, Inc.
Proprietary / Established (USAN) Names	Savella Milnacipran hydrochloride
Dosage Forms / Strength	Tablet 12.5 mg, 25 mg, 50 mg and 100 mg
Proposed Indication(s)	1. Treatment of fibromyalgia syndrome 2. Treatment of the pain associated with fibromyalgia
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding milnacipran (MLN) and the reader should refer to the reviews in the action package for a more detailed discussion. MLN is a selective norepinephrine and serotonin reuptake inhibitor that was originally approved for marketing in France (by Pierre Fabre Medicament) in 1997 as an antidepressant and is currently approved for use in depression in many foreign countries (Europe, Asia and South America). Cypress Bioscience and Forest Laboratories are partnering with Pierre Fabre for this application.

This NDA was submitted for the two indications listed above after discussions with the Agency. These discussions occurred within the Division of Anti-Inflammatory, Analgesic and Ophthalmology Drug Products (DAAODP). During the development program of this application, there was an OND reorganization, and this product is now housed within the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP). Along with the reorganization, there has been an evolution of thinking within DAARP such that the indication for a drug in use for fibromyalgia patients is a more general one, 'Management of fibromyalgia' instead of language such as that above that carves out different aspects or symptoms of the disease. This more general indication is the one that was given to the other two products that have approval for use in fibromyalgia which are Lyrica (pregabalin) and Cymbalta (duloxetine). DAARP has, however, felt that the development program of this application incorporated the necessary endpoints for this indication which has allowed review.

Overall, there is sufficient evidence that milnacipran at 100 mg and 200 mg a day has efficacy and an appropriate safety profile to allow approval of this application. This is not entirely surprising as MLN is in the same class and has a similar mechanism of action as one of the

already approved product, duloxetine. As such, I was prepared to take an approval action at the original PDUFA goal date.

However, on October 7, 2008, which was shortly before the PDUFA goal date, I received a forwarded e-mail that had an attachment of a letter from an organization that defends whistleblowers. This attachment contained allegations from that an anonymous informant to the whistleblower organization that a drug study of MLN submitted to us may have been compromised. As such, I felt a complete for cause investigation was warranted before MLN could be approved for marketing. DSI was contacted and agreed with this assessment. Due to the magnitude of the claim, and the amount of work necessary to fully investigate, it was clear that we would not be able to resolve this issue prior to the PDUFA date. Since it was unknown whether the data upon which my conclusions were based could be relied upon, and therefore I did not know whether the sponsor would have adequate data, or if they would need to perform additional studies if some of their data could not be relied upon, I chose to miss the PDUFA date instead of taking a complete response action (if I were to take an action, a complete response would have been the only option as it was clear that MLN could not be approved until the allegation was fully investigated).

A DSI for cause investigation was performed on site at Forest Research Institute as they were the contract research organization (CRO) and this is where the data was held. Between December 1, 2008 and December 3, 2008, Ms. Dawn Wydner, Dr. Michelle Chuen, and Dr. Thomas Permutt (present December 1 and 2, 2008), representing the FDA, met with staff from Forest and reviewed the conduct of Protocol # FMS-031 entitled "A Phase III Pivotal, Multi-center, Double-Blind, Randomized, Placebo-Controlled Mono-therapy Study of Milnacipran for Treatment of Fibromyalgia", and MLN-MD-02 entitled "A Phase III Pivotal, Multicenter, Double-Blind, Randomized, Placebo-Controlled Monotherapy Study of Milnacipran for Treatment of Fibromyalgia") of milnacipran hydrochloride (Savella). To assure all relevant issues were explored the additional step of including Dr. Thomas Permutt, who is not a member of DSI but is Director of the Division of Biometrics II and an experienced statistician that works with DAARP and had knowledge of this application, was included on the investigational team.

According to the informant, it was discovered by study personal that 57 study participants did not have personal electronic device (PED) data at the three month primary study endpoint. The study personnel made the decision to make every effort to retrieve all the missing PED data. However, the informant became aware that only the PED data of the 23 patients known to be positive responders were recovered. The letter I received by e-mail indicated that the informant felt the data was associated with positive responders "known to be positive responders to milnacipran", and if this was true, may have introduced bias favoring the study drug if the sponsor were only seeking to include positive responses to those on milnacipran. This would also indicate that the blind had been broken, allowing the sponsor to 'cherry-pick' what data to include in the analysis.

The primary responder analysis was of a composite. To be a responder, a patient had to have a favorable global impression and a favorable pain score. According to Dr. Permutt, his investigation revealed that the 23 subjects in question were those that had favorable global

impressions and therefore might be responders if they also had favorable pain scores. Dr. Permutt's investigation revealed that the subjects were evaluated without regard to whether they received the active drug or placebo, and were evaluated in a blinded fashion. This would avoid any concern with bias. The other 34 participants, since they had unfavorable global impressions, were correctly put into a no response category regardless of their pain scores. Dr. Permutt's opinion was that it was entirely appropriate to try to retrieve pain data for the 23 subjects that were responders, and appropriate to not make additional efforts to retrieve pain data for the remaining 34 participants that would be classified as nonresponders anyway. He noted that none of the 34 nonresponders were left out of the analysis. In Dr. Permutt's review dated January 9, 2009, he notes:

I believe xxxxx[1] misunderstood the protocol and the documents xxxx[1] passed on. The 23 patients were not "known to be positive responders to milnacipran." They were possible responders based on the other component of the primary endpoint, whereas the other 34 were known not to be responders regardless of the pain score. Furthermore, there is no suggestion that any of this discussion took place after unblinding the treatment allocations, so that the patients in question are possible responders to *treatment*, whether with milnacipran or placebo.

It is also important to note that 22 of the 23 subjects noted above were eventually put in the nonresponders category as the sponsor was not able to obtain the protocol required data or the pain scores turned out not to be favorable. The remaining subject that favorable pain data was obtained for, was taking placebo, and was correctly counted as a responder in the placebo group, which would have been detrimental to the sponsor's attempt to demonstrate efficacy, and would seem to also speak against any bias in the evaluation, but would indicate following the protocol appropriately.

As such and considering the above discoveries from the investigation, Dr. Permutt and the DSI investigators felt that the handling of missing data was in keeping with good practice and DSI will issue a letter stating that the sponsor adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations.

I have had many interactions with the DSI representatives and Dr. Permutt regarding the evaluation of the data integrity allegations. I am confident that a complete and thorough investigation of this issue has occurred. The results of this thorough investigation are that we can place confidence that the data was obtained following good clinical trial practices and therefore can be relied upon to make regulatory decisions regarding the marketability of MLN.

Efficacy

This has been thoroughly covered in Drs. Filie, Kashoki and Buenconsejo's reviews. The evaluation for efficacy is rather complicated and is based on two studies, FMS-031 and MLN-MD-02. The efficacy was determined using a composite endpoint consisting of the domains:

1) pain

[1] Person's name or reference to gender edited out by myself to maintain autonomy.

2) patient global assessment
3) physical function

As stated above, this evaluation was complicated and has many caveats, multiple evaluations and the reader should look at the reviews listed above for all the nuances. As an overview, the efficacy evaluation of the originally requested indication of 'treatment of pain associated with fibromyalgia' was done using a composite endpoint consisting of the domains: 1) pain and 2) patient global assessment. The efficacy evaluation for 'treatment of fibromyalgia syndrome' was done using a composite endpoint consisting of three domains which were the two listed above with the addition of physical function. MLN demonstrated efficacy for these composite endpoints in the studies, with most secondary endpoints supporting this conclusion. This has given the review team comfort in recommending approval for the overall indication of 'management of fibromyalgia'. I do note that the individual component domains of pain (evaluated on a VAS scale) and function (evaluated by SF36-PCS) demonstrated little evidence of efficacy based on their own accord in either study. The individual component for patient global assessment does demonstrate statistical significance in study MLN-MD-02 and probably drove the results for the primary efficacy endpoint, but does not demonstrate efficacy when compared to placebo in study FMS-031. This is summarized in the table below (from Dr. Buenconsejo's review, Page 9).

Table 1: (Primary) Endpoint Analyses at 3 months landmark

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
STUDY MLN-MD-02			
	N=401	N=399	N=396
Pain Domain Only	101 (25%)	124 (31%) 1.34 (<1.0, 1.8)	119 (30%) 1.28 (0.9, 1.8)
Global Domain Only	92 (23%)	125 (31%) 1.53 (1.1, 2.1)	129 (33%) 1.62 (1.2, 2.2)
Function Domain Only	86 (21%)	108 (27%) 1.37 (<1.0, 1.9)	89 (22%) 1.10 (0.8, 1.6)
Composite Pain	66 (16%)	91 (23%) 1.50 (1.1, 2.1) p=0.0252	98 (25%) 1.68 (1.2, 2.4) p=0.0037
Composite Syndrome	35 (9%)	58 (15%) 1.79 (1.1, 2.8) p=0.011	55 (14%) 1.75 (1.1, 2.8) p=0.015
STUDY FMS-031 (UPA Analysis Population)			
	N=223	N=224	N=441
Pain Domain Only	62 (28%)	76 (34%) 1.34 (0.9, 2.0)	155 (35%) 1.42 (<1.0, 2.0)
Global Domain Only	60(27%)	74 (33%) 1.34 (0.9, 2.0)	145 (33%) 1.33 (0.9, 1.9)
Function Domain Only	61 (27%)	71 (32%) 1.28 (0.8, 2.0)	131 (30%) 1.18 (0.8, 1.7)
Composite Pain	43 (19%)	61 (27%) 1.55 (<1.0, 2.4) p=0.0554	118 (27%) 1.54 (1.0, 2.3) p=0.0323
Composite Syndrome	27 (12%)	44 (20%) 1.84 (1.1, 3.2) p=0.0277	85 (19%) 1.80 (1.1, 2.9) p=0.0175

So while there are greater point estimates for pain and global domains for MLN compared to placebo in both studies, these individual domains do not achieve statistical significance and the combination composite response is necessary to demonstrate efficacy. It is somewhat curious to me that we required a demonstration of efficacy in each study by two different composites (composite pain and composite syndrome) that each share two out of the three domains (composite pain=pain domain & global domain; composite syndrome=pain domain & global domain + function domain). It is unclear to me why we would not have been satisfied to have either a two or three domain composite, instead of requiring a two AND three domain composite, where two of the three domains were common to each composite. I note that the primary endpoint used in the duloxetine studies was change from baseline to endpoint in average pain. Be that as it may, this program was discussed with the sponsor and agreements made regarding evaluation protocols, and a demonstration of efficacy was achieved with

replicate evidence of efficacy for the 200 mg/d dose and sufficient support, when viewing the totality of the data, for the 100 mg/d dose.

Safety

The safety issues with MLN are well document in the clinical reviews and are, for the most part, those that would be expected with selective norepinephrine and serotonin reuptake inhibitor agent. Those that deserve some discussion are:

1) Effects on blood pressure
2) Effects on heart rate
3) Effects on mood

MLN demonstrated a mean increase in systolic and diastolic blood pressure of approximately 3 mmHg and a heart rate increase of 7 beats per minute (bpm) above placebo for the 100 mg/day and 200 mg/day doses. These are known effects from the NSRI class of medications and the blood pressure effects of MLN seem to be line with other approved agents, including duloxetine which is approved for management of fibromyalgia, but should be considered by clinicians and monitored.

Regarding effects on mood, while these trials did enroll patients with a history of depression, they did not study MLN in fibromyalgia patients with a current major depressive episode, moderately severe depression, or those anticipated to acutely require antidepressant therapy. The cumulative data indicated that in subjects with a history of depression, MLN may have an increased risk of suicidal ideation and psychiatric adverse events such as anxiety and insomnia compared to placebo. This is not unexpected and would require similar labeling as already exists for this class of drugs.

A consult with CSS noted that MLN may cause physical dependence. As noted in Dr. Kashoki's review, there are case reports of patients treated for depression where abrupt discontinuation of the MLN produced a potential withdrawal syndrome. This was not seen in this clinical trial database of fibromyalgia patients, which included abrupt withdrawal of the agent. However, it is well known and documented that SNRI (and other centrally acting agents), with abrupt discontinuation, may result in symptoms of withdrawal. As such, labeling should warn against abrupt discontinuation.

Conclusions and Recommendations

MLN has demonstrated efficacy for the management of fibromyalgia. It is interesting that in the original analysis for study FMS-031, efficacy was not demonstrated and a post-hoc analysis demonstrated that efficacy was demonstrated only when subjects with moderately severe depression (Beck Depression Inventory > 25) were excluded (analysis not discussed in my review but thoroughly covered in Dr. Kashoki's review). This screening was incorporated in the protocol for MLN-MD-02 where efficacy was confirmed. This, and other analysis performed by the team and documented in their reviews, should give us some reassurance that the efficacy demonstrated by MLN was not due to an antidepressant effect or that subjects

misdiagnosed with depression instead of fibromyalgia were included in the study and drove the analysis.

I do note that for most of the studies, there is little separation for the 100 mg and 200 mg dosages when viewing point estimates on composite endpoints. However, there does seem to be some dose ordered separation in efficacy when viewing discontinuation rates based on therapeutic failures and some secondary pain response profile analyses. This taken in the context that the 100 mg dose also seems to, perhaps, have a slightly improved adverse event profile (while, perhaps, having slightly less evidence of efficacy based on composite pain results), should allow for labeling that indicates both dosages such that patients with adverse events while taking a 200 mg dose will have an option for continued therapy.

The safety profile for MLN appears to be similar to that of other NSRI agents, including duloxetine which is already approved for fibromyalgia management.

Data integrity allegations had been brought to our attention, fully investigated and all issues resolved.

In conclusion, it would seem that MLN has an appropriate risk:benefit profile for the management of fibromyalgia and I recommend approval.

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/s/

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