

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022462Orig1s000**

**SUMMARY REVIEW**

## MEMORANDUM

DATE: November 18, 2010

FROM: Russell Katz, M.D.  
Director  
Division of Neurology Products/HFD-120

TO: File, NDA 22-462

SUBJECT: Action Memo for NDA 22-462, for the use of Gablofen (baclofen injection) 0.05 mg/ml, 0.5 mg/ml, 2 mg/ml, (b) (4)

NDA 22-462, for the use of Gablofen (baclofen injection) 0.05 mg/ml, 0.5 mg/ml, 2 mg/ml, (b) (4) was submitted by CNS Therapeutics, Inc., on 3/27/09. Gablofen is intended to be administered intrathecally for adults and pediatric patients ages 4 years and older with severe spasticity. Currently, Lioresal (baclofen injection) is approved for this same indication. This application contained CMC (including drug-pump compatibility studies) and non-clinical data. CNS performed no clinical studies, and proposed that the previously available clinical data with Lioresal supported approval of this NDA (this NDA was submitted under section 505(b)(2) of the FFD&C Act).

The application has been reviewed by Drs. Steven Pollack, Dinesh Patwardhan, and Ji Guo, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health (CDRH), Anthony Watson, Office of Device Evaluation (ODE), CDRH, Dr. Lana Shiu, Office of Combination Products and ODE, Debbie Beitzell, SEALD, Dr. Charles Thompson, DNP pharmacologist, Dr. Lois Freed, DNP pharmacology supervisor, Dr. John Duan, Office of New Drug Quality Assessment (ONDQA), Dr. Akm Khairuzzaman, chemist, Denise Miller, microbiologist, Drs. Kristina Toliver and Loretta Holmes, Division of Medication Error Prevention and Analysis (DMEPA), Dr. Rob Harris, DNP medical officer, and Dr. Eric Bastings, DNP deputy director and neurology team leader.

Dr. Bastings's two memos provide extensive and comprehensive reviews of the relevant data in the application and chronology of the review process.

In brief, this application has been the subject of numerous meetings between staff of CDRH and CDER in which the specific requirements for drug-pump compatibility studies have been discussed. Initially, staff of CDRH had requested extensive such testing (as noted above, the sponsor had done several such studies with the Synchroned II pump, one of the pumps for which Lioresal is approved for use, but had not studied the compatibility of Gablofen in the pump under dynamic conditions; that is, while the pump was operating). Further, the duration of the studies that the sponsor performed was also an issue of concern for CDRH (the maximum duration of testing performed by the sponsor was 6

months). Ultimately, however, CDRH and CDER agreed that additional compatibility testing for Gablofen strengths up to and including 2 mg/ml was not necessary, due to the (essential) identity of the Gablofen and Lioresal preparations. (b) (4)

A concern also addressed during several of the meetings between CDRH and CDER staff related to the possibility that Medtronic (the sponsor of both the pump and Lioresal) might change the pump in some way, at some future date, such that Lioresal would no longer be compatible with the current pump, and that, therefore, Lioresal might need to be reformulated to be compatible with the new pump; without similar changes, under this scenario, (unchanged) Gablofen might no longer be compatible with that new pump. Because CNS Therapeutics and Medtronics have no business relationship, concerns were raised that CNS Therapeutics might not be aware of any such changes to the pump, and that, as a result, Gablofen might be marketed with labeling that states it should be used with a pump with which it was no longer compatible. In his last memo (September 30, 2010), Mr. Anthony Watson, Director, Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices, ODE, CDRH, agreed that no more compatibility/stability studies need be done for Gablofen strengths up to 2 mg/ml, but he expressed his personal concerns about potential changes to the pump.

In response, Dr. Bastings has made several observations.

First, the only changes to the pump that raise any potential concerns would be those that would result in the current Lioresal formulation being incompatible with the new pump. Any new pump with which current Lioresal is still compatible will also be compatible with (current) Gablofen, given the similarities in both formulations.

If, in the unlikely case that Medtronic did need to reformulate Lioresal to be compatible with a new pump, CDER would be aware of such a change, because it would require the submission of a supplement to the Lioresal NDA. Therefore, the Agency would be in a position to inform CNS Therapeutics that Gablofen would need to be re-formulated, and Dr. Bastings describes the various mechanisms that would be available to require such a re-formulation. He also notes that in such a case, it would be very likely that (“old”) Lioresal would continue to be marketed while the “new” Lioresal was being introduced (that is, there would be a period of overlap of the two Lioresals); such a scenario is another reason why the availability of a new Lioresal is likely to be a very public matter.

Questions have also been raised about the consistency of the label for the pump itself, and the proposed label for Gablofen. Specifically, the pump label mentions its approved use with Lioresal (baclofen injection), and not with other baclofen

preparations, while the proposed Gablofen label states that it can be used with the Synchroned II pump (and any other pump with which it would be approved for use, though none are contemplated at the moment). Further, the pump label specifically states that it should not be used with baclofen preparations of greater than 2 mg/ml (this last statement is based on data generated by Medtronic that demonstrates that concentrations of baclofen greater than 2 mg/ml are not compatible with the pump, and post-marketing reports of complications when the pump has been used with compounded baclofen with that concentration).

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

I agree entirely with Dr. Bastings's conclusions and recommendations.

Specifically, I agree that the Gablofen NDA should be approved for concentrations up to and including 2 mg/l, [Redacted] (b) (4)

[Redacted]

For this reason, [Redacted] (b) (4) the application [Redacted] (b) (4) (NDA 22-462, Original 1 [up to 2 mg/ml], [Redacted] (b) (4)). I will issue an Approval letter for Original 1 with labeling with which the sponsor and we have agreed [Redacted] (b) (4).

APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUSSELL G KATZ  
11/19/2010