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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s) Rob Harris, M.D., Ph.D.
Review Completion Date

Established Name Baclofen Intrathecal
(Proposed) Trade Name Gablofen
Therapeutic Class Muscle Relaxant, Anti-spastic
Applicant CNS Therapeutics

Formulation(s) Powder in isotonic saline
Dosing Regimen 22 mcg (b) (4) IT
Indication(s) Severe spasticity
Intended Population(s) MS, TBI, SCI

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	5
1.1	Recommendation on Regulatory Action	5
1.2	Risk Benefit Assessment.....	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	6
1.4	Recommendations for Postmarket Requirements and Commitments	6
2	INTRODUCTION AND REGULATORY BACKGROUND	6
2.1	Product Information	7
2.2	Currently Available Treatments for Proposed Indications.....	8
2.3	Availability of Proposed Active Ingredient in the United States	9
2.4	Important Safety Issues With Consideration to Related Drugs.....	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission	13
2.6	Other Relevant Background Information	14
3	ETHICS AND GOOD CLINICAL PRACTICES.....	15
3.1	Submission Quality and Integrity	15
3.2	Compliance with Good Clinical Practices	15
3.3	Financial Disclosures.....	15
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	15
4.1	Chemistry Manufacturing and Controls	15
4.1.1	CDER CMC Synopsis	16
4.1.2	Novartis/Medtronic White Paper CMC CDER Analysis	16
4.1.3	Medical Reviewer CMC Conclusion.....	18
4.2	Clinical Microbiology.....	18
4.3	Preclinical Pharmacology/Toxicology	18
4.3.1	CDER Pre-Clinical Synopsis.....	18
4.3.2	Medical Reviewer Pre-clinical Conclusion.....	19
4.4	Clinical Pharmacology.....	20
4.5	Device	20
4.5.1	Device Issues.....	21
4.5.2	The Medtronic White Papers.....	24
4.6	Regulatory Issues Reviewed by Office of Combination Products (OCP) (b) (4)	27
	27
4.6.1	OCP	27
	(b) (4)	29
4.6.3	Reviewer Comment.....	29
5	SOURCES OF CLINICAL DATA.....	30
5.1	Tables of Studies/Clinical Trials	30
5.2	Review Strategy	30

5.3	Discussion of Individual Studies/Clinical Trials.....	30
6	REVIEW OF EFFICACY	31
7	REVIEW OF SAFETY.....	31
7.1	Methods.....	34
7.1.1	Sponsor’s NDA safety information	34
7.1.2	FDA Literature Searches.....	48
7.1.3	NDA Consult Performed by CDRH	49
7.2	Adequacy of Safety Assessments	49
8	POSTMARKET EXPERIENCE.....	49
9	APPENDICES	50
9.1	Literature Review/References	50
9.1.1	Search and Review Strategy.....	50
9.1.2	Overview of ITB Complications Literature.....	51
9.1.3	ITB and IT Inflammatory Masses	56
9.2	Medtronic Public Information	56
9.3	CDRH Consult.....	67
9.4	LABELING RECOMMENDATIONS	74
9.4	Advisory Committee Meeting.....	78

Table of Tables

Table 1: CNS AERS Database Search Demographics	35
Table 2: MedDRA Terms for ITB Complications With Incidence >1%.....	37
Table 3: Illustrative Overall Summary of ITB Complications.....	53
Table 4: Comparative labeling regarding FDA Request	76

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends an approval for Gablofen (baclofen intrathecal) for concentrations up to 2 mg/ml. (b) (4)



1.2 Risk Benefit Assessment

The available data indicate the risks of Gablofen will not likely differ from the reference listed drug product at doses up to 2 mg/ml. There is a small, possibly real risk of intrathecal mass formation at 2 mg/ml and below and is unknown in higher doses. The sponsor estimates at least 50,000 patients have received treatment with intrathecal Baclofen. There have been three reports of intrathecal masses uncertain etiology (possibly inflammatory masses or granulomas) (0.006%) occurring in patients receiving solely intrathecal Baclofen causing pump failure. The histology of the mass has never been established. All masses and associated symptoms disappeared with catheter repositioning or system replacement. Intrathecal mass formation should not preclude approval of doses 2 mg/ml and below, but a clinical study should be conducted for higher doses as suggested above.

Please see CDRH Review for additional information.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

An appropriate and effective post-marketing surveillance program would be key to monitor for intrathecal mass formation, (b) (4)

1.4 Recommendations for Postmarket Requirements and Commitments

An appropriate and effective post-marketing surveillance program is essential and a Registry of patients receiving Gablofen should be created to follow the patients systematically as long as they receive Gablofen. (b) (4)

It will take 2 – 6 years for an intrathecal mass to appear, so a post-approval study as recommended above would be essential. A registry may help elucidate these risks.

2 Introduction and Regulatory Background

Baclofen (Lioresal), a derivative of γ -amino-butyric acid (GABA), crosses the blood-brain barrier and diminishes spasticity. The oral formulation (10 and 20 mgs) has been marketed since the early 90's for treating spasticity initially as Lioresal. Following approval an intrathecal formulation to treat severe spasticity was marketed as a 0.05 mg/mL, 0.5 mg/mL, and 2 mg/mL solution. Given intrathecally at doses up to 2000 μ g/day, baclofen is useful for severe spasticity in patients resistant to oral doses. Intrathecal baclofen (ITB) also diminishes systemic side effects while providing higher CSF concentrations. Current intrathecal baclofen infusion use is directed primarily for spasticity associated with cerebral palsy (CP), spinal cord injury (SCI), traumatic brain injury (TBI), anoxic encephalopathy, and multiple sclerosis (MS).

Currently, Novartis manufactures the baclofen drug product for the pump device Medtronic manufactures. However, other sources of intrathecal baclofen delivery are available now with Codman also marketing an intrathecal drug delivery system. (b) (4)

Continuous infusion of intrathecal baclofen (ITB) via a subcutaneously implanted pump was introduced to the spasticity therapeutic regimen over 20 years ago by Dr. Richard Penn, a principal for this NDA. Over the last two decades, ITB has become a significant tool for spasticity management in various adult and pediatric neurological conditions. Putatively it acts more focally on spinal GABA receptors and seems to cause fewer systemic side effects than orally administered baclofen. The end result of ITB therapy is

enhanced daily patient care and relief from painful spasms consequent to spasticity. Over the 20 years of ITB use, newer applications along with potential new indications are emerging (b) (4)

The NDA for intrathecal Baclofen (NDA 020-075 . . . and its label) is owned by Medtronic, Inc. Medtronic distributes the product under the trade name, Lioresal®. Medtronic, Inc. Medtronic also manufactures and distributes the SynchroMed II and the SynchroMed EL intrathecal delivery systems (the latter no longer marketed) used for chronic delivery of Baclofen and other drugs into the intrathecal space. (b) (4)

Currently, high doses of ITB are being administered off-label for severe refractory cases of spasticity, but accurate data is not available. These doses must be compounded by local and national pharmacies which can be somewhat risky. In the IND and NDA submissions, the sponsor estimates (b) (4) of ITB is thus compounded. However this number is not verifiable and other anecdotal information suggests it is only (b) (4).

A labeling contradiction for Gablofen, currently the focus of discussion, exists since Medtronic owns the label for the pump for intrathecal administration of Lioresal. The Medtronic pump is very specific that no baclofen concentration greater than 2 mg/ml is to be used in their pump. (b) (4)

These matters are detailed in Section 4.5 below.

2.1 Product Information

Gablofen (intrathecal baclofen), a selective agonist of GABA_β receptors, is to be marketed at the existing baclofen strengths (0.05 mg/ml, 0.5mg/ml and 2 mg/ml) (b) (4). The product functions as a muscle relaxant and antispastic. (b) (4)

Baclofen is currently approved in the United States for the treatment of spasticity in 2 forms:

- 10 mg and 20 mg tablets for *oral* administration, and
- as a sterile solution for *intrathecal* administration in concentrations of 0.05 mg, 0.5 mg, and 2 mg/mL.

While there are a number of approved applications for baclofen tablets, there is only a single approved application for Baclofen Intrathecal Injection. (b) (4)

(b) (4) In contrast to oral baclofen, there are no generic equivalents for intrathecal baclofen. As noted, CNS Therapeutics has (b) (4) submitted the 3 (b) (4) dose concentrations they also wish to market in this NDA.

While there are no product clinical trials submitted in this application, the sponsor's baclofen safety information has been updated. This was retrieved and reported from two sources:

- the Adverse Event Reporting System (AERS) Database from the Food and Drug Administration and
- a search of the published clinical literature from 2002 forward as agreed with the Division and discussed in detail in Review Section 9.10.

Regarding this product's 505(b)(2) NDA 22-462 for a 0.05, 0.5, 2.0 (b) (4) mg/mL Baclofen Intrathecal Injection, the RLD product is Lioresal/Medtronic NDA 20-075, the baclofen pump mentioned above. (b) (4)

The submission contains:

- No new information concerning absorption, distribution, metabolism or excretion of intrathecal baclofen.
- No new information concerning receptor binding or pharmacodynamic studies on intrathecal baclofen.
- No new information concerning the indications and efficacy of intrathecal baclofen in patients.
- No human or animal testing data of the new product has been conducted for this NDA.

Updated product CMC issues identified during the review cycle are addressed by CDER CMC in their review.

2.2 Currently Available Treatments for Proposed Indications

Only four drugs are currently approved by FDA as antispastic agents:

- baclofen,
- diazepam,
- dantrolene sodium, and
- tizanidine

(b) (4)

Baclofen is the main, (and one of oldest) spasticity drugs available in the United States. It is administered orally or intrathecally using a pump. Pump administration is reserved for the most severe cases, and is not a first-line therapy.

The main alternative to baclofen is tizanidine, a centrally acting α_2 -adrenergic agonist that was approved in 1996 in the tablet form, and in 2002 in the capsule form. A second alternative is diazepam (Valium), a benzodiazepine which may induce dependence and cause a withdrawal syndrome in cases of abrupt withdrawal. Finally, dantrolene, a muscle relaxant, remains available but is more rarely used because of possible severe hepatotoxicity.

For more focal treatment of spasticity, neural transmission blocks using botulinum toxin, local anesthetics or other chemical agents can also be used. (b) (4)

Maximum dosage limits its applicability in case of spasticity involving multiple muscle groups.

There are also non-pharmacological alternatives, such as muscle stretching, range of motion exercises, and other physical therapy regimens. Finally, surgery for tendon release or posterior rhizotomy can be applied in selected cases.

Two pump devices are currently approved by CDRH for intrathecal delivery of baclofen delivering up to 2 mg/ml as discussed:

- One device, the *SynchroMed® II Programmable Pump* is, like *Lioresal®*, also owned and distributed by Medtronic. The *SynchroMed® II Programmable Pump* was approved by CDRH in 1988 via a PMA, and, through a number of supplements, is currently approved for the chronic delivery of baclofen and other drugs into the intrathecal space.
- The other device is the *Codman 3000® Series* implantable pump, which is manufactured and distributed by Johnson & Johnson, and was approved in 1996 by CDRH for the intrathecal administration of several drugs including baclofen.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is widely available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

NDA 22-462 provides limited additional information to the vast clinical experience with baclofen, as there have been no new trials conducted for this NDA. Gilmartin, et. al., in 2000, reporting in *J Child Neurol*, reviewed intrathecal baclofen adverse events encountered during a multicenter trial evaluating management of spasticity in CP patients. The review of this study is typical of the numerous literature reviews that have been reported over the last two decades. 59% of the patients studied experienced an adverse event, though these were easily managed. The incidence of serious complications requiring surgical intervention associated with intrathecal delivery approaches 2.8-7.5%, with infection and catheter failure being the primary causes. When the intrathecal system fails, baclofen delivery is interrupted, causing a withdrawal phenomenon.

Withdrawal from oral baclofen is well known with various symptoms described such as agitation, insomnia, confusion, delusions, hallucinations, seizures, visual changes, psychosis, dyskinesia, hyperthermia, and increased spasticity. Withdrawal symptoms from IT baclofen, however, are less frequently reported and its diagnosis in this setting can be difficult.

The literature reports describe withdrawal from baclofen, either oral or intrathecal, as demonstrating a wide spectrum of signs and symptoms and can be life threatening. Most commonly hyperthermia, itching, and hypertonicity, often requiring emergency treatment with either an oral or an intrathecal baclofen bolus are reported. In the adult literature there are case reports of intrathecal baclofen withdrawal manifesting as periodic episodes of increasing spasticity, severe spasticity, multi-organ system failure, rhabdomyolysis, severe hyperthermia, neuroleptic malignant syndrome, cardiac failure, cardiac dysrhythmias, disseminated intravascular coagulation (DIC), pump infection requiring removal, seizures, in some cases, eventual death.

Clinical management of pump failures is described, beginning with a thorough workup for other causes. Failures have been attributed to battery failure, to baclofen refill errors, to catheter migration, and even catheter kinking secondary to an elastic bungee jump from a height of 140 m (reported by Al-Khodairy, et al, in *Am J Phys Med Rehab* in 1999). While a history of recent pump manipulation is important, the absence of this cannot rule out pump failure. As described next, recent reports of “granuloma” formation at the catheter tip can also lead to system failure producing symptoms of intrathecal mass effect or withdrawal.

Withdrawal treatment includes intravenous hydration, administration of oral baclofen, intravenous benzodiazepenes, dantrolene, and additional intrathecal baclofen administration. These steps may provide some improvement in clinical condition, but they fail to correct the underlying problem and are only supportive measures. First, the cause of the withdrawal must be discerned by pump interrogation, review of the

catheters radiographically, and imaging with nuclear isotopes and/or MRI. Finding the cause may even include surgical exploration and testing of the pump and catheter with removal/replacement as warranted.

Recently, intrathecal administration of baclofen for spasticity has been scrutinized by the Agency for two reasons: 1) intrathecal mass formation and 2) a recent increase in AERS reports associated with ITB administration:

1. Firstly, the development (first reported in 2006) of *intrathecal mass formation* associated with ITB treatment. Previously reported cases have been described only for intrathecal delivery of opioid and admixed off-label products via the system. The opioid literature documents inflammatory mass formation at the tip of the catheter, many of which have been excised and examined histologically and inflammation confirmed. However, as detailed below, there is no histological confirmation of the nature of the intrathecal mass with baclofen as the sole agent, and all 3 cases responded to pump catheter repositioning and/or device replacement.

As presented in the Device Section of the Review (4.5) and in the Appendices, FDA reviews note that intrathecal masses at the intrathecal catheter tip cause:

- a) Decreased therapeutic response (worsening spasticity, return of spasticity when previously well controlled, withdrawal symptoms, poor response to escalating doses, or frequent or large dosage increases),
- b) Pain,
- c) Neurological deterioration

Upon review of the ITB literature, there are only 3 reported intrathecal mass cases with baclofen as the sole drug agent. As further discussed below, the intrathecal masses were not operated upon and no tissue was ever obtained for histopathological confirmation of inflammation. MRI imaging was used to classify the intrathecal masses as inflammatory, which is highly problematic diagnostically.

Other possibilities include precipitation of baclofen at the catheter tip or even reactive arachnoid cysts forming around the catheter tip in response to the tubing and/or drug product. Furthermore the masses disappeared without even excision when a pump/catheter was changed or the intrathecal catheter was simply repositioned. The only certainty is that MRI evidence of some sort of mass at the intrathecal catheter tip was present. MRI cannot make a tissue diagnosis. ITB mass formation with compromised pump function prompted a recall by CDRH and a Dear Doctor Letter in January 2008 alerting physicians to this possibility (See Appendix Review Section 9.2.2). Later that year, CDRH consulted CDER's Division of Pharmacological Vigilance in the Office of

Surveillance and Epidemiology for a review and analysis of the AERS database for baclofen intrathecal mass formation.

The DPV review of the AERS database search captured 13 cases of inflammatory mass/granuloma reported in association with intrathecal baclofen/Lioresal® Intrathecal including the three literature reports. One non-literature case had surgical intervention and documented inflammatory mass excision. We retrieved the case report form and determined that there were several other drug products being infused intrathecally in this case, including opioids. So this was not a case of baclofen as the sole drug placed in the pump system.

The DPV analysis further showed histopathologically unconfirmed “inflammatory masses/granulomas” have occurred when baclofen was the sole intrathecal drug administered without regard to concentration or whether commercial or compounded product was utilized. But there is no absolute tissue diagnostic confirmation in any case, and therefore “granuloma” is an inappropriate term to describe what is really, at this point, an intrathecal mass of unknown type.

2. The other reason for FDA concern with intrathecal administration of baclofen has been *the significant increase in weekly AERS reports* describing and apparent increase in deaths and re-operations for the existing baclofen intrathecal system. A special Task Force was convened with representatives from CDRH, OSE, and the Division to further analyze these reports.

The Division culled the AERS database for the reports of clinical deterioration and death in patients being treated for chronic spasticity with ITB. In addition, CDRH and DNP met with Medtronic in this regard as noted next. These various reviews and scrutiny of each CRF individually revealed there were changes in Medtronic’s reporting system, capturing accurately patients that had not been previously reported. Most all of the patients reported were very sick, the product was being administered correctly, and the complications were typical of those found in treating these patients. Most of the patients who suffered severe or fatal complications were seriously ill at the outset from their disease. This matter is detailed in Review Section 8, Post-Marketing Experience and Review Section 9.1.3 (the Literature Review/Reference Section of the Appendices).

Additional safety issues with intrathecal baclofen include its association with a withdrawal syndrome, discussed in the Warnings section of the package insert. Patients have experienced a rebound increase in spasticity, hallucinations, seizures, confusion, and elevated temperature. FDA added a Boxed Warning and strengthened the Warnings section of the prescribing information of Lioresal Intrathecal (baclofen intrathecal), indicated for use in the management of severe spasticity of cerebral and spinal origin. This warning informs healthcare professionals about rare cases of

intrathecal baclofen withdrawal that can lead to life threatening sequelae and/or death in patients who abruptly discontinue therapy.

In the original NDA 17-851 studies for *oral* baclofen tablets, the most common adverse reaction was transient drowsiness (10-63%). Other common adverse reactions were dizziness (5-15%), weakness (5-15%), nausea (4-12%), confusion (1-11%), hypotension (0-9%), headache (4-8%), and fatigue (2-4%). Similar adverse events occurred with intrathecal administration as well as noted in NDA 20-075, the original intrathecal baclofen administration submission.

In pre- and post- marketing *intrathecal* baclofen clinical trials, the most commonly observed adverse events associated with use of LIORESAL INTRATHECAL (baclofen injection) not seen at an equivalent incidence among placebo- treated patients were: somnolence, dizziness, nausea, hypotension, headache, convulsions and hypotonia. The incidences were similar whether the spasticity was of spinal or cerebral origins.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND (b) (4) was opened by the sponsor in 2008 requesting a pre-NDA meeting in preparation for submitting a 505 (b)(2) application intra-thecal baclofen NDA. They sought approval of its Baclofen Intrathecal Injection (Gablofen) as a *drug product*, and not a *drug-device combination product*, indicating they would not co-package their product with a pump. They wished to market (b) (4) concentrations of baclofen injection: 0.05 mg/mL, 0.5 mg/mL, 2 mg/mL (same as currently approved) (b) (4)

At the 2008 meeting the clinical team expressed initial safety and efficacy concerns for the sponsor to address in the NDA. If the sponsor's argument was considered satisfactory, no new clinical studies would be required, assuming the non-clinical data do not identify any cause for concern.

FDA acknowledged the doses delivered would be the same as for the approved product, (b) (4)

Based on these considerations, the sponsor was told:

- To address another FDA worry: the reduced volume of drug delivered possibly having an impact on the diffusion of baclofen to its targeted areas in the spinal cord. FDA believed that a case could likely be made based on CSF physiology. Nevertheless, the Division reminded the sponsor that they must present a compelling argument in the NDA.

Other Division concerns voiced included:

- 
- (b) (4)
- The recall for the Medtronic Neuromodulation SynchroMed EL, SynchroMed II and IsoMed Implantable Infusion Pumps after the pump manufacturers and FDA received reports of inflammatory mass formations at or near the distal tip of intrathecal catheters infusing opioids, baclofen, or chemotherapy drugs into patients.
 - A Dear Doctor Letter, released with the recall, included a recommendation to administer the *lowest effective dose and concentration* of intrathecal opioids [*Emphasis added*]. It also stated that “in patients treated with Intrathecal Baclofen Therapy, physicians should closely monitor their patients in order to identify the prodromal clinical signs and symptoms of inflammatory mass, *especially if using pharmacy-compounded drugs [Emphasis added]* or baclofen admixtures that include opioids.” While the letter did not include a recommendation to use the lowest concentration of intrathecal baclofen, it is unclear how much experience was available at higher concentrations, or if the concern for using pharmacy-compounded drugs was related to a higher baclofen concentration in these preparations.

The Division concluded the IND meeting agreeing that pharmacokinetic data would not be needed. CNS therapeutics was informed that if they intended to submit a 505(b)(2) application relying for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, CNS must establish that such reliance is scientifically appropriate. Furthermore CNS must submit data necessary to support any aspect of the proposed drug product representing modifications to the listed drug(s).

2.6 Other Relevant Background Information

Medtronic, in collaboration with Novartis (the drug product manufacturer), also recently published a “white paper,” detailing their CMC investigations using other than the approved concentrations of baclofen. Their investigation demonstrated at high concentrations, baclofen can precipitate in the tubing and/or otherwise clog the pump system. These studies were not refereed nor confirmed by independent investigators.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of this submission is good and was submitted in paper and electronically via CD-ROM using eCTD Headings. The information was well-organized, complete, and did not necessitate further queries for additional data to perform the review.

3.2 Compliance with Good Clinical Practices

No new trials were conducted as part of this NDA. CNS Therapeutics certified it did not use, in any capacity, the services of any person debarred under Section 306(a) or (b) with this NDA in a communication dated 11/19/08. Similar statements from other companies involved in development of this product were obtained and attached to the CNS Therapeutics communication.

3.3 Financial Disclosures

The sponsor states In accordance with 21 CFR Part 54, they determined that no financial disclosure is appropriate for this application. There are no “covered clinical studies” in this submission.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the full Chemistry Review. The sponsor also recently provided catheter and pump stability data on 12/4/09, which was reviewed by Dr. Akm Khairuzzaman of CMC. His summary synopsis is presented next (Review Section 4.1.1), followed by the White Paper synopsis that has generated concern. He critiqued in detail the White Paper as presented in Review Section 4.1.2. Please see the detailed CDRH review for their assessment as well. Note: CMC believes the investigatory technique used for the Novartis White Paper was flawed, as described below. This limits meaningful conclusions regarding baclofen precipitation and its consequences in this system. Please see the CDER CMC and CDRH (4.1.1 and 4.5 sections of this review) for further details.

4.1.1 CDER CMC Synopsis

(b) (4)

The pump-drug product compatibility (using the *Medtronic SynchroMed® II* pump) 6 months' data (at 37 °C) also showed good physical and chemical stability inside the pump. The applicant has also performed a temperature cycling study in response to our CMC question and showed that the precipitation starts at -4 °C and sponsor agreed to include a statement, "Do not Freeze" in the label. The applicant has also performed a compatibility study with the pump catheter for 117 hours at 37 °C and data showed no physico-chemical incompatibility.

4.1.2 Novartis/Medtronic White Paper CMC CDER Analysis

From the published Novartis/Medtronic White Paper on the CMC issues with use of higher dose Baclofen, the following is quoted verbatim:

"Solubility and physical stability of **3 and 4 mg/mL aqueous baclofen** solutions were evaluated in a study undertaken by Novartis Pharmaceuticals Corporation, manufacturer of Lioresal® Intrathecal (baclofen injection), to determine if a formulation of baclofen at concentrations higher than those commercially available is a safe, viable option for further development. The results of the study demonstrate that **precipitation occurs in concentrations above 2 mg/mL, independent of several variables** evaluated in the study.

Consequently, there are numerous unsubstantiated risks associated with formulation of intrathecal baclofen above the commercially available 2 mg/mL concentration. Of particular concern are the unknown risks associated with:

- inaccurate dosing due to an altered concentration of the drug solution in the pump or
- potential clogging of the pump filter by precipitate.

Given the unknown nature of these risks, use of intrathecal baclofen solution with SynchroMed® Programmable Drug Infusion Systems at concentrations higher than the commercially available 2 mg/mL is *unadvisable.*”

Dr. Khairuzzaman, of CDER CMC, reviewed the White Paper, pointing out several observations which make concluding anything definite from this paper problematic:

- First, the white paper itself says, *“The saturation solubility of baclofen in aqueous media is still controversially discussed in the literature, data range from 2.09mg/mL to 7.5mg/mL. Therefore the feasibility of a higher-than-commercially-available strength cannot directly be derived from existing literature data.”*
 - Note: This equilibrium solubility experiment was done at room temperature (25° C) (b) (4)
The intrathecal mass formation observed from the compounded Baclofen at hospital setting may be due to either in-appropriate solubilization or may be due to other co-administered therapeutic agent which we don’t know. This impairs our ability to derive a meaningful conclusion.
 - The Medtronic/Novartis, however, acknowledges in the White Paper: *“...firm evidence that the incidence or severity of the formation of inflammatory masses at the catheter tip is related to this higher concentration is lacking when baclofen is the sole therapeutic intrathecal agent”.*
- Dr. Khairuzzaman also notes the Medtronic/Novartis experiment was done for 118 hours and at the end of that time the saturation value obtained was 4.6 mg/mL and since no equilibrium solubility was determined after 118 hr., the experiment was abandoned and continued for the most desired concentration 3 and 4 mg/ml.
 - While they have observed precipitation from this concentration, it could be due to poor solubilization or could be left over micr/nano drug crystals remaining in the prepared solution that got passed through the filter and led to precipitation. But that is his own hypothesis.
 - On the other hand, he points out, there is lots of data from CNS and we don’t see any precipitation at all, not in pump, not in drug product, not on stability storage. And their experimental methodology is standard.

Dr. Kairuzzaman, then concludes his comparison of the CNS data and The Medtronic/Novartis data in the White Paper:

- No apparent CMC issue regarding precipitation and compatibility with pump and catheter can be defined. This does not guarantee no mass formation will occur with actual use in humans. That remains unanswered until monitoring for this in humans is conducted.

4.1.3 Medical Reviewer CMC Conclusion

No apparent clinical concerns are raised, (b) (4). This may have to await actual exposure to human (vs artificial) CSF. Similarly, concerns about long-term changes to the catheters and pump may also require monitoring. The 3 (b) (4) dose CMC evaluations are the same as the RLD. The product can be safely prepared commercially at (b) (4) proposed strengths.

4.2 Clinical Microbiology

Please see Denise A. Miller's review in DARRTS for details. No issues were identified in their review and Microbiology recommends approval from the quality microbiology standpoint.

4.3 Preclinical Pharmacology/Toxicology

Please see the pre-clinical review of the 4 non-clinical Beagle dog studies submitted to the NDA which have been reviewed by Dr. D. Charles Thompson. These studies had limitations as he and the CDTL describe and are summarized below.

4.3.1 CDER Pre-Clinical Synopsis

The 4 submitted pre-clinical studies reviewed were:

- 069-001: "Maximum Tolerated Dose (MTD) Toxicity Study of Baclofen Via Continuous Intrathecal Administration in Beagle Dogs"
- 069-002: "28-Day Safety Study of Baclofen Via Continuous Intrathecal Lumbar Administration in Beagle Dogs"
- 069-003: 28-Day Safety Study of High Concentration Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs
- 069-004: 28-Day Safety Study of High Concentration Baclofen via Continuous Intrathecal Lumbar Administration in Beagle Dogs.

Inflammatory changes were found in the intrathecal space, but the exact nature and cause of this cannot be determined with certainty from the submitted studies. Chronic administration of both the RLD and the proposed drug product formulation appeared to show similar biological responses, namely pyogranulomatous inflammation, in the intrathecal space of the dog.

But there were certain study problems, principally the Medtronic Synchronomed II pump and the Medtronic Indura intrathecal catheter (#8711) proposed for Gablofen administration were not evaluated in the animals, rather an external syringe pump for intrathecal delivery was used. Six additional study limitations identified included:

1. the dose range-finding study was inadequate based on inclusion of only two male animals and absence of any control group;
2. the dose groups and the numbers of animals were not uniform across the three 28-day studies, such as an RLD-dosed group being absent in the first 28-day study (069-002), present with only 2 dogs/sex in the second study (069-003), and present with 4 dogs/sex in the third study (069-004);
3. only spinal cord tissue was examined;
4. the 28-day study duration was sub-optimal based on current state of the science for a chronic IT dog study and may be too short to evaluate time-dependent phenomena;
5. a 'Device Control' group was only included in the first two studies as an afterthought, by protocol amendment, while such a 'Device Control' group was included by original protocol design in the third study (069-004), but then the spinal cord tissue from these animals was not even examined microscopically; and
6. adequate sampling to conduct a thorough kinetic analysis of baclofen levels in CSF, or even plasma, was not included in any of the studies.

Despite preclinical study limitations summarized above, Dr. Thompson recommended approval provided CMC quality and stability standards are met. He noted the proposed limit of (b) (4)

(b) (4) exceeds the ICH qualification threshold, but observed that this issue has subsequently been adequately addressed to the satisfaction of CMC reviewers.

4.3.2 Medical Reviewer Pre-clinical Conclusion

(b) (4)

4.4 Clinical Pharmacology

This submission contains no new information concerning receptor binding or pharmacodynamic studies on intrathecal baclofen. Information found in the current Lioresal® labeling provides the basis for this submission.

4.5 Device

This NDA is the first 505 (b) (2) application for a generic neurologic drug product to be used in an existing previously approved intrathecal pump. (b) (4)

(b) (4) They will (b) (4) qualify their product for use only for use with the Synchromed II Programmable Pump already approved for the Intrathecal delivery of Baclofen at this time (b) (4). No device clinical trials and no data were submitted to the IND that preceded this NDA.

Essentially two drug/device issues have required time and discussion to resolve for this first 505 (b) (2) neurologic drug product for use in a device manufactured by a generic competitor. The first question is whether the (b) (4) concentrations of Gablofen that are identical to the RLD Lioresal require further testing before approval. (b) (4)

(b) (4) No pre-clinical or clinical studies evaluating these issues are submitted in this NDA.

(b) (4)

CDER considers the .05, 0.5 and 2 mg Gablofen product to be identical in all respects to the RLD, Lioresal. (b) (4)

(b) (4)

(b) (4)
The Division is satisfied the (b) (4) doses, however, are identical and qualify for generic regulatory approval.

4.5.1 Device Issues

Summarized here, briefly, are several device issues, principally from the CDRH perspective as delineated in the numerous memos and e-mails from the CDRH lead reviewer, Lana Shiu, M.D. Appendix 9.2.3 contains her initial consult and correspondence for review. (b) (4)

(b) (4) She recommends they meet the CDRH policy device-drug delivery system requirement to show successful drug delivery of the product for the life-cycle of the system. This includes the pump itself and the associated catheters and connectors.

To meet that demand, more animal and human clinical data would be required for a period up to 7 years for the (b) (4) dose formulations that are equivalent to Lioresal. Please see her several extensive reviews for details. I have summarized these next.

There are 4 categories of concern to her:

1. *Inadequate Drug-Device Compatibility Testing*: her reasons outlined:
 - a. Static vs. Dynamic testing was incomplete – the sponsor’s testing of their drug product was under static conditions, not under flow (dynamic) conditions.
 - b. Multiple catheter testing was not done – Dr. Shiu points out there are multiple catheters that can be used for Synchronomed intrathecal pump infusion but the sponsor tested only one (Model 8711).
 - c. The time interval for full pump evaluation is too short – Since pumps are implanted for up to 7 years, the pump/drug combination should be evaluated for a period equal to the expected pump life, rather than the typical CDER approach for this situation for chronically administered drugs. CDER typically permits safety data extrapolation from a limited but practical duration of use (i. e., up to one year) to support chronic use.
 - d. The sponsor’s use of simulated CSF *in vitro*, is inadequate to delineate the origins of protein aggregation within the catheter system – She believes a preferable evaluation would be in vivo, using a large animal (sheep), and of sufficient duration with dynamic flow simulating the fluid dynamics throughout the whole system.
 - e. Refill Kits require thorough testing with Gablofen – Lioresal is supplied in refill kits specifically designed for refill with the Synchronomed System.

Gablofen would need further testing of the (b) (4) needle insertion into the reservoir assessing coring and leakage in the pump. The sponsor notes their plan is similar to what is done with other drugs using the Synchronmed pumps.

- f. The intrathecal mass formation issue and the possibility of drug precipitation at the catheter tip as an etiology, have not been properly explored – Dr. Shiu reviewed the literature (b) (4)
- (b) (4) Novartis, the Lioresal drug product manufacturer, has published a sponsor's white paper in which they claim higher concentrations of 3 and 4 mgs/ml could form precipitates, thereby clogging the pump filter, (b) (4)
2. *Labeling Concerns:* Dr. Shiu indicates one-way labeling could create confusion in the clinic because a contradiction exists with the pump label. The pump label clearly states that Lioresal is the only approved product to be used in the Synchronmed II Pump and that the maximum dose to be used is 2 mg/ml. (b) (4)
- (b) (4)

To resolve these difficulties, CNS should contact Medtronic and for their permission to allow Gablofen to be indicated in their pump. Clearly collaboration between the two firms would be ideal. However, the firms are competitors and this is not likely to happen. FDA does not have regulatory authority to impose this either.

3. (b) (4)
4. *Specific Concerns for the use of the 2 mg and 0.5 mg/ml dosage strengths:* Dr. Shiu believes CDRH does not have enough data on the effect of manufacturing residual chemical causing a different permeation drug profile along the fluid path, including the internal pump tubing for even this equivalent dose of baclofen. The sponsor only tested one approved catheter model and this was only a static, not dynamic test. Furthermore she is concerned about the influence of the various types of holes present at the delivery end of the intrathecal catheter (multiple side-holes vs. open-end). She is worried that the Gablofen formulation, despite being exactly the same to Lioresal at the lower doses, could lead to protein deposition with clogged filters, pumps, or catheters.

She suggests Gablofen's sponsor would have to either design their own comparable validated test methods or send their drug product to Medtronic to be

tested thoroughly with the device. Since the Gablofen sponsor has no binding agreement with the Medtronic pump manufacturer then any minor changes in the materials or design of the pump could lead to severe adverse events in the patients receiving Gablofen due to drug/device incompatibility resulting in public health safety issues.

The Division remains unconvinced that further testing of the 0.5 and 2.0 mg/ml formulations is required, however, since they are the identical molecule in identical solutions (saline).

Please see Dr. Shiu's e-mail of 1/13/2010 listing the detailed information she would require. Summarized here is an outline of her requests for additional Gablofen data:

1. Test data evaluating Gablofen in the reservoir, cycled for at least 2 refills at maximum stability cycle, the presence or absence of molecules/particle formation that would clog the 0.22 micron filter and lead to pump failure. This should be sampled all along the drug/fluid path from reservoir to catheter tip.
2. Test data should be generated under dynamic conditions so that neutral ion pair formation altering permeation with subsequent corrosion and pump failure can be assessed.
3. Bench and animal test data (preferably large animal sheep – emulating human anatomy and CSF flow conditions demonstrating that Gablofen does not precipitate in the various models and designs of the SynchroMed catheters and their associated catheter tips. This should include catheters no longer marketed.
4. Additional data evaluating refill kits. During the review cycle, the sponsor opted to only use the Medtronic refill kit, so testing others is unnecessary
5. Sixty months of continuous run reliability data with flowing Gablofen through the pump and during refills at expected refill intervals. This should contain data for dispensing accuracy, system patency, and failure analysis. The sampling analysis intervals should be justified and explained.
6. Testing results supporting any adjustments to the initial refill period that would be considered due to loss of drug on initial fill that could result in overdosing on subsequent refills. If adsorption interactions are identified during stability testing, then CNS should provide any data for any recommended adjustments.
7. Labeling recommendations for procedures required should the physician switch the patient from Lioresal to Gablofen, (b) (4)
[REDACTED].

These matters have been discussed by the rest of the review team. One unanimous CDER opinion is that detailed study of Gablofen at the 0.5 and 2.0 mg/ml is not needed since this is the identical preparation to the RLD. (b) (4)
[REDACTED]

(b) (4)

4.5.2 The Medtronic White Papers

Appendix Review Section 9.2.2 discusses Medtronic's one published "White Paper" with Novartis on inflammatory masses, concluding that ITB mass formation was principally an opioid phenomenon as discussed previously. And, during this Review Cycle, Medtronic and Novartis coincidentally published 2 more pertinent "White Papers" concerning their Lioresal Intrathecal Product. The "White Papers" are discussed in this review section since they directly relate to the CDRH consult. Three areas were studied as noted below.

The first topic discussed addressed catheter occlusions resulting from pH & salt concentration gradients between the delivery solution and CSF. The second presented their data derived from Synchromed EL & Synchromed II pump corrosion from non-indicated drug formulations which caused permanent pump stalls. The third, and most recent, looked at the solubility and stability of ITB in high concentrations and its implications for chronic use in their pump system.

While these may be interesting and germane to this submission, they also refer to their Medtronic and Novartis laboratory data, and have not been independently confirmed, to my knowledge. The actual 3 documents, only summarized in my review, are available online at this URL:

<http://professional.medtronic.com/interventions/intrathecal-drug-delivery/clinical-outcomes/index.htm>

Key points from the White Papers are briefly summarized here:

1. *Intrathecal Distal End Catheter Occlusions as a Result of pH & Salt Concentration Gradients Between Delivery Solution & Cerebrospinal Fluid (CSF),*

The paper suggests (based on unconfirmed, unverified Medtronic engineering analyses) using both indicated and non-indicated drug formulations, collections of protein in the intraspinal end of the catheter lumen are possible. They further suggest that the proteinaceous catheter collection is greater with "non-indicated" formulations, causing catheter occlusion with loss of patency and subsequent cessation of the therapeutic regimen. They state they have identified CSF proteins in returned catheters that are occluded at the intrathecal end.

The sponsor notes mixing of the drug and cerebrospinal fluid (CSF) normally occurs in and around the distal end of the intrathecal catheter. They hypothesize the mechanism for these depositions and occlusions are consequent to

(b) (4)

(b) (4)

But this, in my mind, is speculative at the moment and would need independent confirmation. Continuing the pH argument, they mention that the pH of lumbar CSF is 7.3 and all intrathecally indicated drugs have a pH > 4.0.

Medtronic reminds White Paper readers: “Non-indicated formulations are not approved for use with the infusion systems. Use of non-indicated drugs or fluids may result in increased risks to the patient due to permanent damage to the catheter requiring surgical replacement and a loss or change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug under-dose. Non-indicated drug formulations include drugs not listed in the Indications labeling, admixtures, compounded drugs, and unapproved drug concentrations. Indications labeling is provided with the pump and catheter systems.”

The timing of the publication of this information is interesting. Gablofen could be considered a “non-indicated drug.” Nevertheless, at the (b) (4) dose concentrations, the osmolality and pH of Gablofen are essentially identical. The non-clinical studies performed by CNS did not demonstrate catheter occlusion, but no human studies are available to confirm this. There is no question in my mind that compounding introduces risk attendant not only for the resultant infusion product, but also to pump system as related above.

2. *SynchroMed® EL & SynchroMed II Pump Corrosion from Non-indicated Drug Formulations Resulting in Permanent Pump Stalls*

In this non-refereed document, Medtronic says their engineering analyses confirmed “use of non-indicated drug formulations can compromise the performance of the SynchroMed® EL and SynchroMed® II infusion systems.” Their research attributes corrosion of the SynchroMed Systems that come from non-indicated formulations’ corrosive agents which “permeate the pump tubing as neutral ion pairs between drug species and counter ion (e.g., chloride, sulfur). After permeating through the pump tubing, the neutral ion pair can dissociate and cause corrosion to the pump’s internal components. Neutral ion pair formation can be caused by drug formulation conditions such as pH. Mixing drug solutions or compounding drugs are some of the mechanisms that can result in adjustments to the formulation pH. The concentration of ion pairs in solution is affected by (but not limited to) the following: additives, impurities, pH adjustments, and concentration adjustments.”

Medtronic describes “Labeled Lioresal® Intrathecal (baclofen injection) at formulation pH 6 is highly dissociated from the chloride ion (corrosive agent). At

labeled formulation the permeation rate of chloride associated with drug is negligible over the life of the pump. If the pH is adjusted below the formulation pH (non-indicated), the formation of ion pairs with baclofen increases. The amount of permeation across the pump tube over the implant life of the pump increases as well. It is the chloride carried by baclofen that causes the pump corrosion.”

(b) (4) Gablofen could be considered non-indicated, (b) (4) doses corresponding to approved Lioresal, the specifications are identical. This mitigates against any of these concerns for the pump or its internal tubing, catheters, and connectors used for intrathecal baclofen infusion. Gablofen, a small molecule, would therefore not have a greater chance for incompatibility as noted in large molecule drugs.

3. *Solubility and Stability of Intrathecal Baclofen Solutions at High Concentrations: Implications for Chronic Use in the SynchroMed Infusion System*

The third topic reports Novartis’ evaluation of both the solubility and physical stability of 3 and 4 mg/ml aqueous baclofen solution. The stated objective was to determine if concentrations higher than the approved formulation would be safe and worthy of further development. Their study demonstrated precipitation occurring in concentrations > 2 mg/ml. This study has not been replicated independently.

Novartis concluded there are, as yet, unknown risks linked to inaccurate dosing because of varying concentrations of the higher dose drug within the pump. Furthermore, they report, the potential for clogging of the pump filter by a precipitate exists. They state unequivocally that use of intrathecal baclofen solutions in the Synchromed pump systems > 2 mg/ml is not advised.

The paper continues to describe Novartis’ testing of both 3 and 4 mg/ml preparations following storage at room temperature and 8° C. They state that after 24 both solutions began forming insoluble particulates, but this did not occur in the 2 mg/ml control formulation. The latter solution remained clear without such particulates.

(b) (4)

Upon review of all this device section information and the various reviewers’ concerns as reported in previous sections of the review, I believe the 2 mg/ml and lower concentrations of Gablofen are identical to the RLD and these concentrations are

acceptable for marketing. (b) (4)

4.6 Regulatory Issues Reviewed by Office of Combination Products (OCP) (b) (4)

As this product consists of both a drug (Gablofen) and a device (Medtronic's Synchromed II pump) and is administered intrathecally, Dr. Patricia Love of the Office of Combination Products was consulted. Please see her consults and internal meeting notes, which are only summarized here. Because of the labeling issues raised by the drug manufacturer (CNS Therapeutics) using a competitor's pump product (Medtronic Intrathecal Lioresal) (b) (4)

Please see official meeting minutes for details of their opinions.

4.6.1 OCP

Medtronic's Lioresal Intrathecal is a combination product with inadvertent one-way labeling. This restricts use of the device to their Lioresal drug at a maximum concentration of 2 mg/ml and warns against use at higher doses, with other formulations, and other unapproved modifications due to adverse clinical events and possible device malfunction as a consequence. So 2 issues are raised right away:

- the SynchroMed is not approved for use with Gablofen, and (b) (4)
- (b) (4)

Introduced here are other concerns as well:

- Possible confusion between prescribing and administering health care provider when they are not the same individual.
- Confusion could lead to patient overmedication 5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
- A serious medication error could result in consequence if the infusion rate is not decreased and a higher than intended higher drug concentration is delivered to the brain.

- (b) (4)

(b) (4)

Furthermore, Medtronic could make changes to its pump in the future rendering the pump unsafe and/or ineffective with Gablofen. There is no business agreement between the CNS Therapeutics and Medtronic; Medtronic does not have to inform CNS of the changes to their pumps. This introduces an incompatibility risk between their pumps and Gablofen, potentially leading to serious patient injury.

Dr. Love points out Medtronic reported the numbers of adverse events associated with the compounded drugs is increasing. Therefore, it is crucial to be sure Gablofen can be used safely and effectively in the SynchroMed pump and that users can clearly understand how each drug (CNS Therapeutics' Gablofen (b) (4) vs. Medtronic Lioresal at 2-mg/ml) is to be used with the SynchroMed pump.

She reminds us that the technology and assay methodology with appropriate testing expertise ensuring compatibility of drugs in the Medtronic pump resides with Medtronic, not CNS.

Finally, two more uncertainties are identified:

- “If the two labels are inconsistent, how would a user know which label to follow? How might a hospital purchasing department respond? For example, might the Hospital order a different pump that is not compatible with Gablofen and thereby make the wrong pump available to the Hospital? Could an end-user prescribe the wrong pump because of the label differences?”
- “What if Medtronic’s updated its label to warn/contraindicate the use of their device with Gablofen and provide data to support their claim? This would create an untenable situation. We need both labels to be clear and to avoid misleading information.”

Dr. Love offered the following recommendations to address the identified concerns:

- (b) (4)
- Determine if CNS has a mechanism in place for detecting the changes to the SynchroMed pump
- Determine if the labeling inconsistencies could be reasonably addressed in one label (Gablofen) or whether more specific cross-labeling is needed to protect the public health by minimizing inconsistencies. For example, in making the approvability determination of safety and effectiveness, consider whether the proposed labeling or reasonable modification is sufficient

If concerns about undue user confusion persist that could be resolved with/without SynchroMed relabeling, then the Centers could consider whether a Human

Factors/User comprehension study would be of benefit to address outstanding concerns.

(b) (4)

(b) (4)

4.6.3 Reviewer Comment

The reader should note both the Medtronic and Codman approved intrathecal delivery pumps are used (often off-label) for a variety of drug products, from opiates to chemotherapeutic agents.

(b) (4)

There are only a few practitioners implanting pumps and managing refractory spasticity.

(b) (4)

On the other hand, the 2 mg/ml and lower doses of Gablofen are identical to Lioresal, so no safety, efficacy, or labeling concerns are identified for this dose. Other products are dissimilar to Lioresal (i.e. Ziconotide) and they are used in the Medtronic pump. Any pump changes affecting Lioresal would therefore affect Gablofen similarly.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

No clinical trials were performed for this 505(b)2 submission. No new clinical data was obtained.

5.2 Review Strategy



For safety, the sponsor researched the available literature, focusing on principally the issue of inflammatory mass formation and its consequences, as the Division requested at the pre-NDA meeting. The sponsor also performed an AERS database review as well.

I corroborated the sponsor's reviews, independently confirming their information. As outlined in Review Section 9.1, we conducted our own AERS database search in consultation with DPV and an additional PubMed Search and with the assistance of Mrs. Joanne Berger of the Biosciences Library, searching other databases as described. I also reviewed the DPV-CDRH Consult reviewing the AERS Database for intrathecal mass formation done for CDRH and CDER last year.

5.3 Discussion of Individual Studies/Clinical Trials

No new data was acquired for this 505(b)2 submission.

6 Review of Efficacy

Efficacy Summary

No new data was acquired for this 505(b)2 submission. (b) (4)

(b) (4) Information on the clinical efficacy of intrathecal baclofen is found in the current Lioresal® labeling. However, there is substantial published literature on intrathecal baclofen with the 0.05, 0.5, and 2 mg/mL formulations that are commercially available and the sponsor references the literature for this 505(b)2 NDA.

7 Review of Safety

Safety Summary

No new data was acquired for this 505(b) 2 submission. No trials or other safety data were conducted/generated during development for this product. (b) (4)

(b) (4) The sponsor is relying on FDA's prior finding of safety along with an extensive literature review they conducted for the NDA. (b) (4)

(b) (4)

The Division also discussed other concerns associated with intrathecal administration of baclofen and other drugs, in particular:

(b) (4)

- The recall for the Medtronic Neuromodulation SynchroMed EL, SynchroMed II and IsoMed Implantable Infusion Pumps after the pump manufacturers and FDA received reports of inflammatory mass formations at or near the distal tip of intrathecal catheters infusing opioids, baclofen, or chemotherapy drugs into patients.
- A Dear Doctor Letter, released with the recall, included a recommendation to administer the *lowest* effective dose and *concentration* of intrathecal opioids [*Emphasis added*]. It also stated that “in patients treated with Intrathecal Baclofen Therapy, physicians should closely monitor their patients in order to identify the prodromal clinical signs and symptoms of inflammatory mass, *especially if using pharmacy-compounded drugs* [*Emphasis added*] or baclofen admixtures that include opioids.”

While the letter did not include a recommendation to use the lowest concentration of intrathecal baclofen, it is unclear how much experience was available at higher concentrations, or if the concern for using pharmacy-compounded drugs was related to a higher baclofen concentration in these preparations.

The sponsor was asked to also address these questions in the NDA. The sponsor addressed these issues through a series of observations and descriptions to support their position, which is incomplete and unscientific in my opinion. The firm’s response to the effect of concentration on intrathecal mass formation was addressed in the pre-clinical beagle dog studies. But, as has been pointed out, there were significant issues with the studies (See Drs. Thompson’s and Bastings’ reviews). (b) (4)

Please see CMC review for details. The sponsor notes in its argument, “In its concentrated form the CNS product *should* behave like any other water soluble molecule introduced into the intrathecal space. It is distributed primarily by convective CSF flow both due to the pulsation of the CSF and its steady turn over.” Emphasis added. “Should” is not “does,” so the final answer awaits further study.

In responding to the CSF physiology inter-relationship with the high concentration, the sponsor simply notes, “A significant advantage to the intrathecal pump lies within the biopharmaceutical and pharmacology of delivery to the intrathecal space. In this case, drug is delivered more closely to the site of action and is not compromised by absorption, protein binding, or the blood brain barrier. This targeted delivery allows for administration of 100-fold lower doses and it is more effective.” (b) (4)

Finally, I also attempted to determine what is known about the use of higher concentrations of baclofen intrathecally by reviewing material from 4 sources:

- The sponsor's safety information from their own literature review and AERS database review
- Our own independent literature review with the assistance of the FDA Biosciences Library.
- The prior DPV and CDRH consults addressing this matter.
- The recent Medtronic/Novartis white papers discussing CMC investigations into the pump and high-dose baclofen, but were NOT referenced by CNS in this submission. These papers addressed:
 - Intrathecal Distal End Catheter Occlusions as a Result of pH & Salt Concentration Gradients Between Delivery Solution & Cerebrospinal Fluid (CSF)
 - SynchroMed® EL & SynchroMed II Pump Corrosion from Non-indicated Drug Formulations Resulting in Permanent Pump Stalls and
 - Solubility and Stability of Intrathecal Baclofen Solutions at High Concentrations: Implications for Chronic Use in the SynchroMed Infusion System

These sources are discussed as separate review arms for this NDA. In general, the CNS and FDA DPV *AERS database* searches were essentially harmonious as corroborated in this review. Generally no significant new papers were identified in the *literature review databases* when considered collectively by FDA, CNS, or Medtronic, with one glaring omission: The CNS literature search did not capture nor reference the Novartis/Medtronic White Paper presenting their precipitation/solubility data for high dose baclofen in their pump system.

The *first* arm of my NDA review, evaluated the CNS *sponsor's NDA safety information*, which was retrieved and reported from two sources:

- the Adverse Event Reporting System (AERS) Database from the Food and Drug Administration and
- a search of the published clinical literature.

To establish value and pursuant to prior direction from the Division, the CNS search surveyed all relevant information from 2002 forward. As noted, the CNS search failed to capture the Novartis/Medtronic White Paper presenting those firms' assessment of high dose baclofen in their pump systems.

For the *second* arm of my NDA review, additional safety material was obtained independently of the CNS sponsor, as outlined in Review Section 5.2, Review Strategy just above. This included *our own literature searches* using several additional databases

(Web of Science, TOXLINE, and International Pharmaceutical Abstracts) and obtaining articles describing use of high dose intrathecal baclofen in spastic patients. I also reviewed the numerous post-marketing reports to AERS for pertinent complications of intrathecal baclofen as summarized in the Review Section 8, Post-marketing Experience.

For the *third* arm of the NDA review, I studied the *prior consults conducted by DPV and CDRH* as they relate to this product and its safety concerns. All of this information is collected and reproduced for future reviewer convenience in Review Section 9.2

7.1 Methods

No new data was acquired for this 505(b)2 application; the sponsor relies on the Baclofen Intrathecal RLD for their product as well as their own literature and AERS database searches for safety information (b) (4)

Here I present the summary information developed for the (b) (4) arm approach analyzing available safety for intrathecal baclofen introduced just above. Please see Appendices 9.1 (literature review/references and 9.2 for details and the pertinent consults and other material we obtained to provide safety data for this product.

7.1.1 Sponsor's NDA safety information

No new data was acquired for this 505(b)2 application; the sponsor relies on the Baclofen Intrathecal RLD for their product. For the NDA section CNS Therapeutics had a consultant (b) (4) review the FDA Adverse Event Reporting System (AERS) Database. Another consultant, (b) (4) searched the published clinical literature from 2002 onward following previously provided DNP guidance.

7.1.1.1 Sponsor's AERS Database Review

This was searched for all AEs pertaining to ITB Lioresal preparations between 1 January 2002 and 30 Sept 2008. A total of 2,578 AE reports were returned for all ITB products, 94% of US origin. Most of these were sent by the device maker Medtronic. Almost all of the AEs were associated with appropriate, labeled uses for treatment of spasticity. 98% of the manufacturers forwarding baclofen AERs reports came from 1 of 2 companies: Medtronic 92.5% and Novartis (5.3%). Another 13 companies, such as Ivax, Lederle, Acorda, Pfizer and others) forwarded between 1 – 4 AE reports.

Most reporting was spontaneous, but there was also a large amount of literature reporting. Over half of the reports were sent by physicians. While almost all ITB AE reports had 1 or more indicators for "Serious." But upon closer scrutiny, they found ¾ of

the reports contained the serious marker “required intervention” with much lower proportions associated with hospitalization and death. The serious criterion, “Disability,” occurred in < 1% of cases.

The sponsor’s AERS Database search returned the following demographic information:

Table 1: CNS AERS Database Search Demographics

Metric	Intrathecal Baclofen (N=2,578)
Report Counts (% , No.)	
Electronic reports	4.2% (N=107)
Non-electronic reports	95.7% (N=2,467)
Unknown	0.2% (N=4)
Age (Yrs)	
Mean age when known	39.0
Median Age When Known	40.0
Age Distribution (% , No)	
0 -- <18 Years	5.6% (N=144)
0 -- <2 Years	0.0% (N=0)
2 -- <6 Years	0.2% (N=6)
6 -- <12 Years	1.9% (N=48)
12 -- <18 Years	3.5% (N=90)
18 -- <35 Years	4.8% (N=123)
35 -- <50 Years	5.3% (N=137)
50 -- <65 Years	6.1% (N=158)
65 -- <80 Years	2.1% (N=54)
Age 80+ Years	0.4% (N=11)
Age Unknown	75.7% (N=1,951)
Gender Distribution (% , No)	
Female	40.7% (N=1,050)
Male	51.7% (N=1,333)
Unknown	7.3% (N=195)
M:F Gender Ratio	1.27

Interestingly, the age evidently was not reported for over ¾ of the patients in the AERS database, but the few reported had a mean age of 40. Slightly more males than females are found in AERS.

The following groups of AEs were commonly reported after ITB therapy:

- 1) Lack of effect and Underdose
- 2) Baclofen withdrawal
- 3) Overdose
- 4) Medication Errors
- 5) Product Defects
 - a. Device failure and malfunction
- 6) CNS Infections (meningitis)

Of the 2,578 AE Reports, only 12 referenced intrathecal granuloma. Nevertheless the small number of cases and their relative importance prompted the DPV review conducted independently of this NDA and discussed below.

The following table from the submission displays the MedDRA Preferred Terms and their incidence in the database examined:

Table 2: MedDRA Terms for ITB Complications With Incidence >1%

MedDRA Preferred Term	Intrathecal Baclofen (N=2,578)
Drug Ineffective	39.6% (N=1,022)
Hypertonia	32.4% (N=835)
Pain	8.4% (N=217)
Overdose	7.4% (N=191)
Hypotonia	7.3% (N=188)
Drug Withdrawal Syndrome	6.6% (N=171)
Muscle Spasticity	6.4% (N=166)
Pyrexia	6.3% (N=162)
Withdrawal Syndrome	6.0% (N=155)
Somnolence	5.5% (N=141)
Pruritus	5.4% (N=140)
Nausea	4.0% (N=102)
Convulsion	3.9% (N=100)
Headache	3.3% (N=85)
Vomiting	3.1% (N=79)
Hyperhidrosis	2.9% (N=74)
Catheter Related Complication	2.9% (N=74)
Paraesthesia	2.7% (N=70)
Hypotension	2.4% (N=62)
Muscle Spasms	2.4% (N=62)
Device Failure	2.2% (N=57)
Death	2.1% (N=55)
Meningitis	2.1% (N=54)
Gait Disturbance	2.0% (N=51)
Tachycardia	1.9% (N=48)
Tremor	1.8% (N=47)
Medical Device Complication	1.7% (N=45)
Coma	1.7% (N=43)
Pneumonia	1.7% (N=43)
Condition Aggravated	1.6% (N=41)
Confusional State	1.6% (N=41)
Agitation	1.6% (N=41)
Dyspnoea	1.4% (N=37)
Respiratory Disorder	1.4% (N=36)
Urinary Retention	1.4% (N=36)
Insomnia	1.4% (N=35)
Lethargy	1.4% (N=35)
Hypertension	1.3% (N=34)
Urinary Tract Infection	1.3% (N=34)
Hallucination	1.3% (N=33)
Asthenia	1.3% (N=33)
Dizziness	1.2% (N=32)

As can be seen, the most commonly reported AE term ('Drug Ineffective; 39.6%; N=1,022) referred to lack of effect. Other groups of commonly reported terms of interest

(i.e., terms of note with a reporting prevalence $\geq 2.0\%$) pertained to underlying conditions being treated by intrathecal baclofen:

- 'Hypertonia' [32.4%, N=835],
- 'Muscle Spasticity' [6.4%; N=166],
- 'Muscle Spasms' [2.4%; N=62],
- to the syndrome associated with baclofen withdrawal ('Drug Withdrawal Syndrome' [6.6%; N=171],
- 'Withdrawal Syndrome' [6.0%; N=155]),
- to overdose/medication errors ('Overdose' [7.4%; N=191],
- to product defects ('Device Failure' [2.2%; N=57]),
- to complications of instrumentation ('Catheter Related Complication' [2.9%; N=74]), and
- To central nervous system infections ('Meningitis' [2.1%; N=54]).

For the intrathecal granuloma condition of interest, the only term suggesting a potential excessive tissue reaction was "granuloma." The 12 cases in the report collection constitute 0.5% of the AEs in the database. No terms suggested fibrosis or fibrous overgrowth at the site of intrathecal infusion. The reports were all considered "serious," but none mentioned "disability," as a consequence.

Bottom Line: No new, previously unknown safety signals were found in the AERs database searches conducted by CNS (summarized above), Medtronic, or FDA (discussed below). Further details can be found in Appendices 9.1.1 and 9.1.2. The FDA DPV review and the Medtronic review of the AERS database describe similar findings as those of the sponsor.

7.1.1.2 Sponsor's Literature Review

(b) (4) performed a targeted literature review on the safety of ITB for CNS Therapeutics, again from 1 January 2002 to 2009 using both electronic and manual components. The objective of the sponsor's literature search, as well as our corroborative FDA search, was to identify new adverse events relating to ITB Rx which might influence drug safety or efficacy. It was appropriately conducted and returned 57 literature reports which I read and corroborated independently.

MEDLINE (via PubMed) and EMBASE were both searched for citations. Their study selection, exclusion criteria and inclusion criteria were appropriate. However one critical paper does not appear to have been cited nor discussed in the submission: *Solubility and Stability of Intrathecal Baclofen Solutions at High Concentrations: Implications for Chronic Use in the SynchroMed Infusion System*, by Juergen Sigg, PhD (Novartis), Jean-Claude Sonntag (Novartis), Jianwei Li (Medtronic). This was published by Medtronic in 2006 and critically addresses high-dose solubility issues from the perspectives of Medtronic and Novartis. Please see the CDER CMC (Review Section

4.1 above) and CDRH review for details. CDER CMC found concerns with this White Paper's studies which limits any dose concentration conclusions as introduced in Review Section 4.1.

The omitted citation describes the solubility and physical stability of 3 and 4 mg/mL aqueous baclofen solutions. The evaluation, undertaken by Novartis Pharmaceuticals Corporation, manufacturer of Lioresal® Intrathecal (baclofen injection), sought to determine if a formulation of baclofen at concentrations higher than those commercially available is a safe, viable option for further development. No independent confirmation of these findings was offered.

Their 2006 study demonstrated precipitation occurs in concentrations above 2 mg/mL, independent of the several variables they evaluated. They concluded there are numerous unsubstantiated risks associated with formulation of intrathecal baclofen above the commercially available 2 mg/mL concentration. They particularly note the unknown risks associated with inaccurate dosing due to an altered concentration of the drug solution in the pump or potential clogging of the pump filter by precipitate. Given the unknown nature of these risks, Novartis/Medtronic warn, use of intrathecal baclofen solution with SynchroMed® Programmable Drug Infusion Systems at concentrations higher than the commercially available 2 mg/mL is inadvisable. (b) (4)

(b) (4)

Their summary otherwise includes reports from pediatric to geriatric patients (age 4 years to 70 years) and a range of intrathecal doses (80 mcg/day to 2000 mcg/day). AEs / events focus on withdrawal, overdose, mechanical complications, infection and other events such as intrathecal mass formation. But possible complications within the delivery system, as outlined in the Novartis/Medtronic white paper, are not specifically addressed in the original NDA submission. These two troublesome conditions, intrathecal mass formation and high dose precipitation are not yet fully defined.

There is considerable clinical experience based on the studies since 1984. This experience has provided the current recommendations for drug use and is reflected in the current package insert for Lioresal® Intrathecal. The CNS review of 57 recent articles and case reports (Submission sections 2.5.7 [listing] and 5.4 [articles]) revealed drug side effects and AEs similar to those previously reported.

There was one exception: the new possible association of chronic intrathecal baclofen therapy with the formation of granulomas or masses at the tip of the intrathecal catheter reported by Murphy and Deer. These two reports, plus a reinterpretation of these cases by one of the original authors', were considered in detail, not only by CNS in this review, but by FDA and Medtronic as well. At the pre-NDA meeting, the firm was requested to

evaluate this phenomenon in their search and relate the potential for mass formation to their product.

Hard copies of all articles were submitted and reviewed manually by me and I agree with the sponsor's conclusions. The list of the articles is reproduced at the conclusion of this review section. As noted, fifty-seven literature reports and case series (Submission Section 5.4) which included AEs were found. Table 3 in Review Section 9.1, displays the sponsor's literature review extracted case reports from the literature and provides details on selected summaries from CNS's search. The cases were representative of the findings in the literature. As the table shows, these descriptive summaries present pediatric to geriatric patients (age 4 years to 70 years) and a range of intrathecal doses (80 mcg/day to 2000 mcg/day). AEs / events focus on withdrawal, overdose, mechanical complications, infection and other events.

Not unexpected and consistent with the AERS findings, the most common finding in these articles was *withdrawal reaction* (Colachis 2003, Saveika 2007, Santiago-Palma 2004, Hansen 2007, Rigoli 2004, Mohammed 2004, Alden 2002, D'Aleo 2007, Pizon 2007, Greenberg 2003, Douglas 2005, Zuckerbraun 2004 and Shirley 2006). The common effect of under dosing is a return of spasticity. While it is rare, baclofen withdrawal syndrome can result in exaggerated rebound spasticity, muscle rigidity possibly evolving into rhabdomyolysis and multiple organ system failure. This was reported prior to 2002 and is included in the drug labeling. Since 2002 the literature has continued to document the occurrence of withdrawal symptomatology. Abrupt withdrawals of baclofen or significant reductions in dose are complications most frequently associated with delivery system failures.

Drug overdoses also were reported and the effect of baclofen overdose has been well recognized and described in the pre-2002 literature. Most often they occur due to technical errors during surgery or incorrect programming of the infusion system. Catheter complications were reported in these articles on overdose (Lyew 2003, Dalton 2008, Lew 2005, Anderson 2002, Shirley 2006). While each was determined to be accidental, a clear understanding of filling of the pump and techniques with placing the intrathecal catheter are carefully noted in the current labeling.

Catheter migration (Ross 2005 and Pasquier 2003) and *catheter leak* (Dickerman 2002, Bardutzky 2003 and Dawes 2003) were primary reports. Once again, these mechanical issues have been previously noted and consistent with the AERS dataset. *Surgery related complications* such as infection or poor placement of the catheter or pump were also reported.

Infection accounted for several reports of AEs associated with intrathecal baclofen treatment. Three reports of meningitis (Kallweit 2007, Aliabadi 2008 and Bensmail 2006) and two reports of pump pocket infections (Boviatsis 2004 and Atiyeh 2006) were discussed in the case reports. Infections, both local (implant site) and central (catheter)

were risks with any surgical procedure utilizing intrathecal pump application. The recent literature reflects a low incidence of these complications, presumably due to improved techniques, surgical experience, and a keen awareness for infectious complications.

The area of special focus in the CNS literature review as well as mine and Medtronic's, is the formation of intrathecal masses/granuloma when baclofen is the *sole* therapeutic agent. Intrathecal masses are well-known and documented with opioid use and also with other drugs administered chronically intrathecally. Some of these drugs are concurrently given with baclofen. Unfortunately, intrathecal mass occurring with only baclofen administration alone remains unresolved as pointed out in this CNS review and those conducted by FDA and Medtronic.

In 2006, when Murphy reported the first case of intrathecal baclofen as the sole agent producing an intrathecal mass, it labeled a "granuloma," though no histology was ever obtained. A 57-year-old quadriplegic patient had been treated successfully for 38 months with intrathecal baclofen when her lower limb spasms dramatically increased. Increasing the dose of baclofen did not help. A catheter myelogram showed filling of the thecal sac. An MRI "suggesting the presence of a tip associated granuloma" was reported. The catheter was removed and reimplanted and her spasticity was again well controlled. It is important to note that no open surgery was performed, simply a catheter removal and reimplantation. Therefore no granuloma was ever seen, biopsied or excised. The MRI image of an abnormal mass at the catheter tip which was small and did not impinge upon the spinal cord or nerve roots was the sole diagnostic test.

Next, Deer 2007 reported two other patients with "granulomas" associated with baclofen. The first was a 70-year-old stroke patient treated successfully for 30 months with 150 mcg/day of baclofen. His spasticity increased and in spite of a dose increase to 215 mcg/day he remained spastic. An MRI using a T2 image demonstrated a space occupying inflammatory mass at the catheter tip. The catheter was replaced and the spasticity was controlled. No pathological mass examination was made and there were no neurological signs or symptoms. The second case reported by Deer was a 39-year-old woman who had MS and was receiving compounded baclofen 4000 mcg/mL at a rate of 2000 mcg/day. She underwent an evaluation after 50 months of treatment because her spasticity dramatically worsened. An MRI showed an "oval lesion" consistent with an inflammatory mass. The catheter was revised and her spasticity was controlled. The mass was diagnosed only by MRI, it did not cause neurological findings, and it was not confirmed pathologically.

Late last year (2008) Deer et al. (2008) recently reconsidered his and Murphy's diagnosis of granuloma in an article in Pain Medicine. Co-authors of this paper were employees at Medtronic. At the outset they sought to clarify "*why the same inflammatory process observed in pain patients and animals exposed to intrathecal opioids are highly unlikely to occur during ITB therapy*". They importantly pointed out that the diagnosis of granuloma was not made on clinical, surgical or pathological

grounds but only on interpretations of MRI images. Reinterpretation of the MRI scans revealed the “masses” on MRI could also represent arachnoidal cysts or (in the case of 4000 mcg/mL compounded baclofen) a localized precipitate. They were not convinced, in hindsight, that these three reported granulomas had been proven to be true granuloma similar to the fully documented reports with opioids.

In effect, Deer retracted the previous conclusions now that they were aware of other explanations for the MRI findings. I corroborated this and, in my own literature review, was unable to find a single biopsy-proven intrathecal granuloma. In the 3 cases, the loss of anti-spastic effect that prompted the initial MRI’s ameliorated with the interventions described above, indicating the pump system was once again intact. No MRI’s were done to determine if the “masses” disappeared with simple catheter revision or reinsertion.

As described in Review Section 7.1.3, Medtronic, Inc. sent a Dear Health Professional letter concerning reported inflammatory mass formation at the catheter tip during intrathecal drug administration in January 2008 (Section 5.4, ref 59). This communication focused primarily on the use of opioids, but also briefly mentioned pharmacy-compounded baclofen and other admixtures. They noted the highest reported rate of these inflammatory masses occurred with opioids. They also noted this complication was supported by pre-clinical findings with opioids. While other contributing factors were described (i.e., infusates, catheter design, foreign material, etc.) baclofen was only meaningfully noted in the summary and always linked with opioids and/or pharmacy-compounded admixtures. Baclofen, as the sole agent given intrathecally, was not referenced or described as producing an intrathecal mass in the Dear Health Professional letter. And, as described previously, the authors of the original paper have withdrawn their original conclusions regarding baclofen’s role in intrathecal mass formation when it is used as the sole agent.

When the Division met with CNS in April 2008 for a pre-NDA meeting, we discussed the issue raised in the Medtronic, Inc. letter i.e., inflammatory masses / granuloma occurring at or near the distal tip of the intrathecal catheters (see above) (b) (4)

[REDACTED]

The sponsor has no clinical data to definitively address this issue in this NDA. Instead CNS made the following observations and descriptions to support the appropriate position for this product. They acknowledge that both concentration and flow rate could be factors and suggest an appropriate and effective post-marketing surveillance

program would be key in monitoring for this event following approval. Upon review,

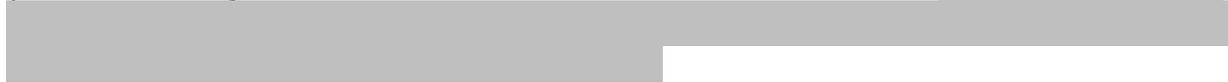
(b) (4) this appears inadequate. (b) (4)

The response to the Division request considered concentration and flow rate from both a clinical and pre-clinical perspective. They did not consider the evidence from the Novartis/Medtronic White Paper referenced above. Their conclusions, nevertheless summarized, are:

(b) (4)



The sponsor concludes from their review of the clinical literature since 2002, there is no identification of any AE (rate or severity) that would suggest that the current labeling for intrathecal baclofen be revised. They ascribe the MRI lesions in the baclofen only patients as likely due to the catheters or the catheters themselves.



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59. Medtronic January 2008 Letter: “Urgent: Medical Device Correction – Updated Information – Inflammatory Mass (granuloma) At or Near the Distal Tip of Intrathecal Catheters”

7.1.2 FDA Literature Searches

Please see Appendix Review Section 9.1 for a detailed review of the FDA literature search. The FDA various database search for additional articles on the use of high dose intrathecal baclofen in spastic patients did not return any new information, with the

exception of the White Paper, which was not addressed by the sponsor. Other than this single omission, we essentially confirmed the material from CNS and Medtronic. The White Paper is discussed further in the appendix.

7.1.3 NDA Consult Performed by CDRH

Please see Appendix Review Section 9.3 for details as well as for the definitive consult. CDRH discusses specific significant safety and efficacy issues in their pending review section of the NDA (Section 4.5, above) CDRH reached the following conclusions in their consultative review. CNS Therapeutics has not adequately demonstrated their formulation of baclofen can be used safely and effectively through the life of the pump (approximately 7 years). This is true for both the Medtronic SynchroMed Pump and the associated catheters required for product delivery into the theca. (b) (4)

Because CNS Baclofen is only compatible with the Medtronic Synchromed pump, serious risks are incurred should Medtronic become the pump manufacturer when CNS baclofen comes to market.

7.2 Adequacy of Safety Assessments

No new data was acquired for this 505(b)2 application; the sponsor relies on the Baclofen Intrathecal RLD and the published literature as above for their product. (b) (4)

8 Postmarket Experience

No new data was specifically acquired for this 505(b)2 application; the sponsor relies on the Baclofen Intrathecal RLD for their product as well as their AERS database and literature searches for presentation of the post-marketing experience.

(b) (4)

- (b) (4)
- (b) (4)

This experience is addressed in the various literature searches already described and in the consults discussed below.

9 Appendices

9.1 Literature Review/References

9.1.1 Search and Review Strategy

I used two sources for the literature review with available FDA references seeking further details regarding complications of ITB therapy and high dose baclofen use. I concluded the consequences of high dose ITB, including the recently described complication of ITB therapy - intrathecal masses at the IT catheter tip, are not yet fully defined. There was not a single case of a histologically-proven intrathecal mass in the literature, in contrast to intrathecal masses using opioid products, where this phenomenon is well-known.

The sources were:

- The *CNS literature review*, discussed above, which we corroborated and verified
- *Our own independent FDA literature search* which essentially corroborated all the literature searches

CNS Therapeutics, the sponsor, searched both MEDLINE and EMBASE and assembled a detailed list of references, and provided hard copies for review as discussed above in Section 7.1. They reviewed the literature from January 1, 2002 to the present to identify new adverse events (AEs) related to the use intrathecal baclofen of importance for drug safety and efficacy. The sponsor's literature search was performed using both electronic and manual components. I performed a confirmatory overall PubMed Search for "Intrathecal Baclofen" verifying the sponsor's search results.

Additionally, we developed our own search strategy and asked Joanne Berger, the FDA Biosciences reference librarian, to further search the databases, PubMed and EMBASE, again to ascertain reporting accuracy from the sponsor. We then searched other databases that the sponsor did not use, including:

- Web of Science,
- TOXLINE, and
- International Pharmaceutical Abstracts

Our FDA search for additional articles on the use of high dose intrathecal baclofen in spastic patients did not return any new information and essentially confirmed the material from the other 3 sources. I concluded the literature review by then reviewing every article submitted by the sponsor for corroboration in our own search.

FDA Biosciences Library searches involved two in-person consultations, first discussing the background for the NDA, and then performing detailed PubMed searches related to baclofen dose increases, drug concentration, and effects of prolonged treatment. Ms. Berger also obtained the full text of some articles referenced by the sponsor in their supplied reference list while the sponsor responded to our request for same.

The sponsor found, and we corroborated, 57 literature reports and case series which included AEs. They prepared a summary Table representative of the findings in the literature. These articles summarized the experience in pediatric to geriatric patients (age 4 years to 70 years) with a range of intrathecal doses (80 mcg/day to 2000 mcg/day). AEs / events focus on withdrawal, overdose, mechanical complications, infection and other events.

9.1.2 Overview of ITB Complications Literature

ITB treatment has been in use for over 20 years and the indications for and the complications of continuous ITB treatment are many and detailed. Upon review of these articles and reports, complications, simply put, reflect the Drug Delivery System. These are:

- Drug-related
 - Constipation
 - Muscular Hypotonia
 - Urinary Retention
 - Erectile Dysfunction
 - Nausea
 - Dizziness
 - Drowsiness
 - Hypotension
 - Bradycardia
 - Baclofen Tolerance
- Device-(Pump) related
 - Infection
 - Pump Malfunction with Consequent Overdose or Underdose
 - Pump or Valve Failure
 - Wound Complications and Infections
 - Pump Dislodgements or Flipping in-situ
 - Programming Errors
- Catheter-related
 - Occlusions
 - Fractures
 - Meningitis
 - CSF Leaks and Hypotensive HA

Brennan, et. al, delineated theoretical risk factors for granuloma formation in Br. J. Neurosurgery Aug 2008. They suggest these might include catheter tip design, catheter placement associated trauma, final catheter tip position, and altered CSF flow dynamics secondary to CSF shunts or syringomyelia all influencing local drug concentrations. Local inflammatory response in arachnoiditis occurring secondary to repeated spinal surgery or catheter revision, may also contribute. Chronic infection is generally not implicated in their review of the issue.

The sponsor prepared a summary table of illustrative complications of IT Baclofen from their search shown below. It displays the typical reports detailed in articles throughout the literature.

Table 3: Illustrative Overall Summary of ITB Complications

CITATION	SUBJECT AGE/GENDER	DIAGNOSIS	IT BACLOFEN TREATMENT	AE EVENT	OUTCOME	COMMENTS
Carda, 2008	65/F	Primary lateral sclerosis	100 µg IT bolus*	@10 hours; BP 90/60, @48 hours symptoms reappear; BP 60/40 Dx: DT and PE	Recovered; suggest hypotonia led to pooling, stasis and clots; direct action of baclofen on vasomotor tone	NB: This was a bolus dose
Dalton, 2008	45/F	Severe lower limb spasticity	Approximately 140µg/day	Drowsy; nausea; vomiting; respiratory depression	Recovered	baclofen concentration was reduced to 1000µg/ml but the 2000µg/ml volume in the "dead space" resulting in an overdose
Lad, 2008	62/F	Spasticity secondary to CVA	Unknown	Headaches; somnolence-intracranial hypertension	Recovered S/P epidural blood patch	ICA secondary to CSF leak around catheter
Grande, 2008	39/F	Dystonia	1330µg/day decreased to 555µg/day	Dissociative spells; anterograde memory loss; transient global amnesia	Treated with nitroglycerin and fludrocortisone; condition continues but was improved	Speculate that TGA caused by baclofen combined with decreased NO resulting in amnesic outcomes
Saval, 2008	41/M	C6 spinal injury; MVA	81µg/day	Difficulty ejaculating; difficult orgasm	Recovered	Sexual dysfunction abated with reduction in dose
	42/F	Diplegic, spastic cerebral palsy	400-600µg/day	Difficult orgasm	Recovered	Difficulties abated after dose reduction
Deer, 2007	70/M	Spasticity following CVA	50µg IT bolus 150µg/day for 30	"space-occupying inflammatory mass"	Catheter replacement; no significant	NB: The opinion that these findings were

Clinical Review
 Rob Harris, M.D., Ph.D., FACS
 22-462, 505 (b) (2) NDA
 Baclofen Intrathecal

	39/F	Progressive MS	mo. 215µg/day [conc 2000µg/ml] 235µg/day – 100 bolus q6h 2000µg/day for 56 mo “compounded” drug to 4000µg/ml	“oval lesion consistent with inflammatory mass”	complications Catheter revision patient developed a seizure post cath removal... Recovered	related to granuloma were reversed in a paper by Deer, et al 2008
Hansen, 2007	11/F	Spastic cerebral palsy secondary to congenital CMV infection	408µg/day	Fever; erythema, spasticity agitation; tachycardia; hypertension	Recovered after 78 hospital days	Problems started after pump removal and disappeared when the pump was replaced
Morant, 2006	52/M	Spastic tetraplegia; brainstem stroke	100µg/day	Paralytic ileus	Baclofen dose reduced until normal GI function	ITB dose was increased after this incident with no recurrence
Tunali, 2006	33/M	Head injury post MVA	500µg/ml/20ml then 250µg/ml/20ml	2 months later hypotonicity, bradycardia, hypertension, seizures	Possible overdose of 10mg of baclofen Pump malfunction leading to overdose	
Murphy, 2006	57/F	Quadriplegic	80mg/day oral; IT placed due to oral side effects IT bolus test to 200µg/day over 3 mo. To daily dose of 400µg at 35 mo dose increased to 500µg/day	Therapeutic failure; MRI suggested catheter tip granuloma	Displaced catheter migrating into epidural space; mass did not cause compression and catheter was re-implanted	
Atiyeh, 2006	37/M	Astrocytoma with diffuse	Unknown	Purulent discharge from drainage around	The pump pocket was revised; antibiotic	Pump removal not required if central

Clinical Review
 Rob Harris, M.D., Ph.D., FACS
 22-462, 505 (b) (2) NDA
 Baclofen Intrathecal

		spasticity		the pump; <i>Proteus mirabilis</i>		infection not involved
Lew, 2005	15/F	Cerebral palsy; dystonia; spasticity	570µg/day	Hypotonia; hypotension; hypoventilation	Recovered	Inadvertent subdural placement followed by a bolus from the sequestered space
Rigoli, 2004	30s/M 20s/M	Severe brain injury C6 burst fracture	80-100µg/day 200-300µg/day	High fever; tachycardia; hypertonia Fever; hypertonia; hypotension; hemorrhage; respiratory failure	Symptoms disappeared after pump refill Recovered after ICU	Withdrawal symptoms secondary to low residual volume in the pump Withdrawal symptoms secondary to low residual volume in the pump
Mohammed, 2004	24/M	Cerebral palsy; spastic quadriplegia	260µg/day	Seizures; respiratory distress; fever; hypotension; tachycardia; multisystem organ failure	Recovered over 6 months	Pump stopped due to programming error
Vaidyanathan, 2003	44/M	C5/6 fracture; severe lower limb spasticity	300µg/day to 1200µg/day	Bladder calculi; increased spasticity	Catheter repositioned; patent recovered	Bladder stones masked the signs of a catheter extrusion
Dickerman, 2002	4/M	Cerebral palsy	750µg/day	Respiratory distress; flaccidity; lethargy; increased spasticity	Recovered after catheter replacement	Catheter with a small "nick" near the pump; no pump defects
Murphy, 2002	17/M	Spastic diplegic cerebral palsy	350µg/day	Deep venous thrombosis	Recovered with anticoagulant therapy	Possible post-op complication following pump catheter repair

9.1.3 ITB and IT Inflammatory Masses

Over the last several years, FDA has received reports of intrathecal masses attendant to use of intrathecal drug products, including the RLD when admixed with other compounds. These have been reviewed and evaluated by CDRH and DPV under the Medtronic Lioresal NDA 20-075 and are not discussed here.

9.2 Medtronic Public Information

The following attachments represent the material Medtronic has provided the public to date describing certain safety information for the RLD. These are copied directly from the Medtronic public documents.

Appendix B

Dear Healthcare Provider Letter Issued by Medtronic Regarding Baclofen Withdrawal



**The FDA Safety Information and
Adverse Event Reporting Program**

This is the retyped text of a letter from Medtronic. Contact the company for a copy of any referenced enclosures.

IMPORTANT DRUG WARNING

April 2002

Dear Healthcare Provider:

We have updated the prescribing information for Lioresal® Intrathecal (baclofen injection) to include a warning about rare cases of intrathecal baclofen withdrawal that can lead to life threatening sequelae and/or death in patients who abruptly discontinue therapy.

Lioresal Intrathecal is indicated for use in the management of severe spasticity of cerebral and spinal origin.

The following BOX WARNING has been added to the Lioresal Intrathecal prescribing information:

Abrupt discontinuation of intrathecal baclofen, regardless of the cause, has resulted in sequelae that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure and death.

Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to proper programming and monitoring of the infusion system, refill scheduling and procedures,

and pump alarms. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of baclofen withdrawal. Special attention should be given to patients at apparent risk (e.g. spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or intrathecal baclofen). Consult the technical manual of the implantable infusion system for additional postimplant clinician and patient information. (see WARNINGS).

Additional details regarding the risk of baclofen withdrawal associated with Lioresal Intrathecal are included in the WARNINGS section of the prescribing information:

Withdrawal: Abrupt withdrawal of intrathecal baclofen, regardless of the cause, has resulted in sequelae that included high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity that in rare cases progressed to rhabdomyolysis, multiple organ-system failure, and death. In the first 9 years of post-marketing experience, 27 cases of withdrawal temporally related to the cessation of baclofen therapy were reported; six patients died. In most cases, symptoms of withdrawal appeared within hours to a few days following interruption of baclofen therapy. Common reasons for abrupt interruption of intrathecal baclofen therapy included malfunction of the catheter (especially disconnection), low volume in the pump reservoir, and end of pump battery life; human error may have played a causal or contributing role in some cases. Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of baclofen withdrawal.

All patients receiving intrathecal baclofen therapy are potentially at risk for withdrawal. Early symptoms of baclofen withdrawal may include return of baseline spasticity, pruritus, hypotension, and paresthesias. Some clinical characteristics of the advanced intrathecal baclofen withdrawal syndrome may resemble autonomic dysreflexia, infection (sepsis), malignant hyperthermia, neuroleptic-malignant syndrome, or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis.

Rapid, accurate diagnosis and treatment in an emergency-room or intensive-care setting are important in order to prevent the potentially life-threatening central nervous system and systemic effects of intrathecal baclofen withdrawal. The suggested treatment for intrathecal baclofen withdrawal is the restoration of intrathecal baclofen at or near the same dosage as before therapy was interrupted. However, if restoration of intrathecal delivery is delayed, treatment with GABA-ergic agonist drugs such as oral or enteral baclofen, or oral, enteral, or intravenous benzodiazepines may prevent potentially fatal sequelae. Oral or enteral baclofen alone should not be relied upon to halt the progression of intrathecal baclofen withdrawal.

Seizures have been reported during overdose and with withdrawal from LIORESAL INTRATHECAL as well as in patients maintained on therapeutic doses of LIORESAL INTRATHECAL.

Clinical Review
Rob Harris, M.D., Ph.D., FACS
22-462, 505 (b) (2) NDA
Baclofen Intrathecal

In addition, we have enclosed a copy of the updated Emergency Procedure Card for both intrathecal baclofen underdose/withdrawal and for intrathecal baclofen overdose.

Please refer to the enclosed Lioresal Intrathecal (baclofen injection) Package Insert for full prescribing information.

Healthcare professionals are strongly encouraged to report any serious adverse events that occur with the use of Lioresal Intrathecal to Medtronic at 1.800.328.0810 or to the FDA's MedWatch program by phone (1-800-FDA-1088), fax (1-800-FDA-0178), via the MedWatch website at www.fda.gov/medwatch, or by mail (using postage-paid form) to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20857-9787.

If you have any questions regarding Lioresal Intrathecal, please contact Medtronic Neurological Technical Services at 1.800.707.0933

Sincerely,

Robert J. Coffey, M.D.
Medical Director
Medtronic Drug Delivery

Lioresal[®] is a registered trademark of Novartis Pharmaceuticals Corporation.

Appendix C

Excerpts from the January 2008 Dear Healthcare Professional Letter



January 2008

Urgent: Medical Device Correction

Updated Information -Inflammatory Mass (granuloma) At or Near the Distal Tip of Intrathecal Catheters

Dear Healthcare Professional,

This letter is an update to two previous communications¹ issued by Medtronic in 2001 and 2003, and is intended to provide the medical community with the current post-market incidence of reported inflammatory mass and **information that may facilitate patient management**.

Inflammatory mass presents as a chronic inflammatory or granulomatous mass at or near the distal tip of intrathecal catheters and has been reported with the intrathecal infusion of opioids, baclofen, pharmacy-compounded drugs, and other pharmacological admixtures. The precise etiology of inflammatory mass is unknown. Clinical evaluation with MRI or histology shows an association of inflammatory mass with morphine sulfate, other opioids, and analgesic admixtures. The highest reported rate of inflammatory mass formation has been associated with the use of opioids. The most plausible etiology for inflammatory mass formation with the use of opioids, as supported by preclinical studies, relates inflammatory mass to the administration of relatively high dose and/or high concentration morphine sulfate and/or other opioids. Current available information does not definitively exclude other possible contributing factors such as other infusates, catheter design or material.

Incidence of Opioid-Related Inflammatory Mass

One study that prospectively evaluated 208 patients reported a 3% incidence of inflammatory mass². Through September 2007, there has been an estimated 0.49% incidence of inflammatory mass reported to Medtronic for patients ever implanted with a drug infusion system for treatment of pain. The actual incidence is likely to be higher due to under reporting, but the extent of under reporting is currently unknown.

Based on current Medtronic analysis, the reported incidence of patients who have developed inflammatory mass (0.49%) is approximately five times higher than was reported in 2001 (0.1%). The rate of occurrence of inflammatory mass is expected to continue to increase. This may be at least partially due to the longer average duration of time that the product is implanted. Some reported cases occurred within six months, while others occurred as long as ten or more years after starting opioid therapy. Reported cases of inflammatory mass are from reports submitted to Medtronic by patients and/or health care providers, Medtronic personnel, or from scientific literature.

- Table 1.0 presents a summary of the frequency of symptoms associated with 448 reports of inflammatory mass from October 1990 through September 2007. These reported patient symptoms are currently identified in the professional labeling (Appendix C). A patient may have reported more than one symptom. The most frequently reported symptoms associated with inflammatory mass are:
 - decreased therapeutic response/inadequate pain relief (reported in 33.5% of patients),
 - pain (reported in 32.6% of patients),

Table 1.0 Summary of Symptoms Reported for Cases of Inflammatory Mass

Symptoms [a]	Number of Reports of Symptom	Percent of Cases with Symptom (n = 448)
Decreased therapeutic response/inadequate pain relief	150	33.5%
Pain	146	32.6%
Neurological deficit/dysfunction	78	17.4%
Unknown (reports did not provide the patient's condition)	74	16.5%
Paralysis/paraplegia/paresis	67	15.0%
Weakness/muscle weakness	62	13.8%
Numbness	43	9.6%
Incontinence	32	7.1%
Ambulation difficulties	12	2.7%
Urinary retention	8	1.8%
Tingling	8	1.8%
Headache	7	1.6%
Muscle spasm(s)	7	1.6%
Burning sensation	6	1.3%
Other [b]	68	15.2%

- neurological deficit/dysfunction (reported in 17.4% of patients).

[a] There may be more than one symptom per report of inflammatory mass

[b] Multiple symptoms, each reported in less than 1% of cases of inflammatory mass

Inflammatory mass has been associated with a wide range of doses and concentrations of opioids. No dose and/or concentration of morphine sulfate can be considered completely free of risk from

inflammatory mass³. The risk of inflammatory mass occurrence appears to be cumulative over time and increases with higher concentrations of opioids.

The following product information is an excerpt from the Infumorph[®] Drug Package Insert (Baxter)⁴.

The recommended initial lumbar intrathecal dose range in patients with no tolerance to opioids is 0.2 to 1 mg/day. The published range of doses for individuals who have some degree of opioid tolerance varies from 1 to 10 mg/day. The upper daily dosage limit for each patient must be individualized.

Doses above 20 mg/day should be employed with caution since they may be associated with a higher likelihood of serious side effects.

Preclinical^{5,6,7,8,9} and clinical^{10,11,12,13,14,15,16} studies with intrathecal infusion have suggested that high doses and/or high concentrations of opioids increase the risk of inflammatory mass. Additionally, Medtronic data analysis indicates the risk of developing inflammatory mass in the next six months increases at least through the first thirty-six months of opioid therapy. Therefore, intrathecal opioids should be administered to achieve adequate analgesia for as long as possible at the lowest effective dose and concentration.

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- see http://www.fda.gov/medwatch/safety/2008/Medtronic_Neuromod_DHCP.pdf for complete DHCP letter.
-

Information Regarding Intrathecal Baclofen Infusion

Medtronic has also reviewed its reports database and the medical literature to evaluate inflammatory mass in patients receiving intrathecal baclofen. There are cases of inflammatory mass reported with intrathecal baclofen as the sole agent.^{17,18,19,20} The estimated risk of developing inflammatory mass is lower for patients treated for spasticity (presumably with intrathecal baclofen) than for patients treated for pain (see Figure 1). A common symptom associated with decreased baclofen therapy is the return of spasticity in patients. Physicians managing patients on ITB TherapySM (Intrathecal Baclofen Therapy) should use their medical judgment regarding the most appropriate monitoring specific to their patients' medical needs to identify prodromal clinical signs and symptoms for inflammatory mass, especially if using pharmacy-compounded drugs or baclofen admixtures that include opioids.

Recommendations for Patient Management

Individual patient susceptibility to inflammatory mass cannot be predicted. Diligent patient management and increased awareness of inflammatory mass symptoms may reduce the incidence of inflammatory mass or its sequelae. For pain therapy, the patient management recommendations for inflammatory mass as provided in the professional labeling (see Appendix A) have not changed.

In patients with new neurological signs or symptoms, consider neurosurgical consultation and the prompt performance of an imaging procedure (for example, MRI with and without contrast or CT myelogram) to confirm or rule-out the diagnosis of an inflammatory mass.

Medtronic is aware that pharmacy-compounded drugs and other pharmacological drug mixtures may be administered to patients through drug infusion systems. Medtronic strongly advises physicians to be familiar with the approved intrathecal indications for these devices; including preservative-free morphine sulfate sterile solution; Lioresal® Intrathecal (baclofen injection); and preservative-free ziconotide sterile solution. The effect of administering other drugs intrathecally through these devices has not been assessed.

Summary

In summary, healthcare professionals are encouraged to consider the following recommendations:

- When administering intrathecal opioids, the lowest effective dose and concentration should be administered.
- In patients treated with Intrathecal Baclofen Therapy, physicians should closely monitor their patients in order to identify the prodromal clinical signs and symptoms of inflammatory mass, especially if using pharmacy-compounded drugs or baclofen admixtures that include opioids.
- In patients with new neurological signs or symptoms, consider neurosurgical consultation and the prompt performance of an imaging procedure to confirm or rule-out the diagnosis of an inflammatory mass.

The US Food and Drug Administration (FDA) has knowledge of this communication being sent to Healthcare Professionals.

Please report any new and/or previously unreported inflammatory mass in a patient with a Medtronic device to Medtronic Neuromodulation Product Performance at 1-800-328-0810, and to the FDA's MedWatch Program by phone at 1-800-FDA-1088, by Fax at 1-800-FDA-0178, by mail at MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or on the MedWatch web site at www.fda.gov/medwatch.

For Assistance

Contact Medtronic Neuromodulation Technical Services at 1-800-707-0933, Monday - Friday, 7:00 a.m. - 6:00 p.m. (Central Time), or your local Medtronic field representative. This information including links to the references or abstracts can be found on our web site at www.medtronicconnect.com.

Sincerely,



George Aram

Vice President Quality

Medtronic Neuromodulation

- 1 Medtronic January 2001 letter “Important Message Regarding the Occurrence of Inflammatory Masses at the Tip of Intraspinal Catheters,” and Medtronic July 2003 Educational Brief “Information about Inflammatory Mass, Intrathecal Drug Infusion”
- 2 Deer, TR. A prospective analysis of intrathecal granuloma in chronic pain patients: a review of the literature and report of a surveillance study. *Pain Physician*. 2004;7:225-228.
- 3 Yaksh TL, Hassenbusch S, Burchiel K, Hildebrand KR, Page LM, Coffey RJ. Inflammatory masses associated with intrathecal drug infusion, a review of preclinical evidence and human data. *Pain Med* 2002;3:300-312.
- 4 Product Information Infumorph Baxter Healthcare Corp. Deerfield Illinois October 2003.
- 5 *ibid* endnote 3
- 6 Yaksh TL, Horais KA, Tozier NA, et al. Chronically infused intrathecal morphine in dogs. *Anesthesiology*. 2003;99:174-187.
- 7 Gradert TL, Baze WB, Satterfield WC, Hildebrand KR, Johansen MJ, Hassenbusch SJ. Safety of chronic intrathecal morphine infusion in a sheep model. *Anesthesiology*. 2003;99:188-198.
- 8 Allen JW, Horais KA, Tozier NA, et al. Time course and role of morphine dose and concentration in intrathecal granuloma formation in dogs: a combined magnetic resonance imaging and histopathology investigation. *Anesthesiology*. 2006;105:581-589.
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- 10 McMillan MR, Doud T, Nugent W. Catheter-associated masses in patients receiving intrathecal analgesic therapy. *Anesth Analg*. 2003;96:186-190.
- 11 *ibid* endnote 2
- 12 *ibid* endnote 3
- 13 Hassenbusch S, Burchiel K, Coffey RJ, et al. Management of intrathecal catheter-tip inflammatory masses: a consensus statement. *Pain Med*. 2002;3:313-323.
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- 16 Schuchard M, Lanning R, North R, et al. Neurologic sequelae of intraspinal drug delivery systems: Results of a survey of American implanters of implantable drug delivery systems. *Neuromodulation*. 1998;1:137-148.
- 17 Murphy PM, Skouvaklis DE, Amadeo RJ, Haberman C, Brazier DH, Cousins MJ. Intrathecal catheter granuloma associated with isolated baclofen infusion. *Anesth Analg*. 2006; 102:848–852.
- 18 Narouze SN, Mekhail NA. Intrathecal catheter granuloma with baclofen infusion. *Anesth Analg*. 2007; 104:209–210.
- 19 Coffey RJ, Allen JW. Not all intrathecal catheter tip MRI findings are inflammatory mass. *Anesth Analg*. 2007; 104:1600–1602.

20 Deer TR, Raso LJ, Garten TG. Inflammatory mass of an intrathecal catheter in patients receiving baclofen as a sole agent: a report of two cases and a review of the identification and treatment of the complication. Pain Med 2007; 8:259-262.

Appendix D

Excerpts from the Approved Medtronic (Device) Professional Labeling (baclofen-specific sections highlighted)

Warnings

Inflammatory mass at the catheter tip (symptoms) –

An inflammatory mass that can result in serious neurological impairment, including paralysis, could occur at the tip of the implanted catheter. Patients on intraspinal opioid therapy should be monitored carefully at each visit for any new neurological signs or symptoms.

Physicians should routinely monitor patients receiving opioids for the following prodromal clinical signs or symptoms of inflammatory mass:

- Change in the character, quality, or intensity of pain
- Reports of new radicular pain, especially at or near the dermatomal level of the catheter tip
- Frequent or large escalations of the daily drug dose are required to maintain the analgesic effect
- Dose escalations alleviate increasing pain only temporarily

To prevent possible permanent neurological injury, physicians should immediately evaluate patients who develop the following signs or symptoms:

- New or different sensory symptoms (eg, numbness, tingling, burning, hyperesthesia, hyperalgesia)
- New, occasional, or intermittent bowel or bladder sphincter dysfunction
- New motor weakness, change in gait, or difficulty walking
- Any neurological symptoms or signs that differ from baseline (eg, reflex changes)

Physicians should routinely monitor patients receiving **intrathecal baclofen** as a sole agent for the following prodromal clinical signs or symptoms of inflammatory mass:

- Change in the character, quality, or intensity of spasticity
- Frequent or large escalations of the daily drug dose are required to maintain the antispastic effect
- Rapid dose escalations alleviate the increasing spasticity only temporarily

Refer to “Adverse events summary” for more information on recognition, treatment, and mitigation of inflammatory mass.

Intraspinal therapy –

For intraspinal therapy, use ONLY a preservative-free sterile solution indicated for intraspinal use. Nonindicated fluids containing preservatives or endotoxins can be neurotoxic in intraspinal applications. Using nonindicated fluids can result in adverse events including, but not limited to, extreme pain, cramps, seizures, and death.

Adverse events summary

Drug-related complications

- Local or systemic drug toxicity and related side effects
- Inflammatory mass formation at the tip of the implanted catheter particularly in patients who receive intraspinal morphine or other opioid drugs

Recognition of inflammatory mass

For patients receiving intrathecal opioids, the following **prodromal**, or **warning** signs or symptoms may occur before the onset of more severe neurological impairment:

- Change in the character, quality, or intensity of pain
- New radicular pain, especially at or near the dermatomal level of the catheter tip
- Frequent or large escalations of the daily drug dose are required to maintain the analgesic effect
- Dose escalations alleviate the increasing pain only temporarily

For patients receiving intrathecal baclofen as a sole agent, the following **prodromal**, or **warning** signs or symptoms may occur before the onset of more severe neurological impairment ¹:

- Change in the character, quality, or intensity of spasticity
- Frequent or large escalations of the daily drug dose are required to maintain the antispastic effect
- Rapid dose escalations alleviate the increasing spasticity only temporarily

All patients on intraspinal opioid therapy should be monitored carefully at each visit for any new neurological signs or symptoms, including:

- New or different sensory symptoms (eg, numbness, tingling, burning, hyperesthesia, hyperalgesia)
- New, occasional, or intermittent bowel or bladder sphincter dysfunction
- New motor weakness, change in gait, or difficulty walking
- Any neurological symptom or sign that differs from baseline (eg, reflex changes)

In patients with new neurological signs or symptoms, consider neurosurgical consultation and the prompt performance of an imaging procedure (eg, MRI with and without contrast or CT myelogram) to confirm or rule-out the diagnosis of an inflammatory mass.

Treatment of inflammatory mass

Timely treatment may minimize, or help to avert permanent neurological injury.

If an inflammatory mass is detected early in its clinical course, a decrease or discontinuation of opioid delivery into the mass may cause it to shrink or disappear without the need for surgical removal.

Note: Refer to Emergency Procedures included in the technical manual packaged with the refill kit for information on emptying the pump. Stopping the pump for more than a few days can cause the rotor to stall permanently. If therapy is to be discontinued for an extended period of time, the pump should be filled with preservative-free saline and programmed to run at the minimum rate of 0.048 mL/day.

Depending upon an individual patient's clinical condition, intraspinal therapy may be continued after one of the following interventions:

- Withdraw the catheter to a level below the inflammatory mass.
- Remove the involved catheter and replace it with a new catheter positioned below the inflammatory mass.
- Disconnect the involved catheter from the connector (two-piece catheter), or transect the involved catheter above the level of the lumbo-dorsal fascia (one-piece catheter) leaving the intraspinal catheter segment undisturbed. Ligate the exposed end of involved catheter to prevent CSF loss. Implant a new catheter with its tip below the inflammatory mass, and connect the new catheter to the proximal (pump) catheter segment.

Prompt open surgical removal of the mass or decompression of the spinal canal should be considered in patients who have a significant or progressive neurological deficit.

Mitigation of inflammatory mass

Intraspinal therapy should be administered to achieve adequate clinical response for as long as possible at the lowest effective dose and concentration.

For the treatment of pain patients, whenever medically possible, the tip of the intraspinal catheter should be placed in the lumbar thecal sac, below the conus medullaris. Lumbar placement may lessen the neurological consequences if an inflammatory mass develops.

Patients who receive intraspinal opioid therapy should be monitored carefully at each visit for any new clinical and neurological signs or symptoms.

¹ Based on three case reports of patients from Murphy and Deer, respectively - Murphy PM, Skouvaklis DE, Amadeo RJJ et al. Intrathecal Catheter Granuloma Associated with Isolated Baclofen Infusion, *Anesthesia Analgesia* 2007; 102:848-852. Deer TR, Raso LJ, Garten TG. Inflammatory Mass of an Intrathecal Catheter in Patients Receiving Baclofen as a Sole Agent: A Report of Two Cases and a Review of the Identification and Treatment of the Complication. *Pain Medicine* 2007; 8(3):259-262.

9.3 CDRH Consult

The Division-requested CDRH Consult for this NDA is reproduced below. Dr. Lana Shiu's evaluation and conclusion details the CDRH history of the baclofen pump and lists the concerns with the proposed CNS product. As can be seen, she believes, ultimately, CNS Therapeutics has not adequately demonstrated that their formulation of baclofen can be used safely and effectively with the Medtronic SynchroMed Pump and the

various catheters through the life of the pump (approximately 7 years). (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Because CNS Baclofen is only compatible with the Medtronic Synchronomed pump, serious risks are incurred should Medtronic become the pump manufacturer when CNS baclofen comes to market.

Her proposed remedy is for CNS to contact Medtronic and allow CNS baclofen to be indicated for use with the SynchroMed pump. Currently FDA does not have any new data that compel Medtronic to change its labeling. In fact Medtronic's labeling is very accurate in terms of Lioresal's concentration limits when used together with this pump. To ensure safe Synchronomed use of the new Baclofen drug product, the drug sponsor and the device manufacturer must work together and resolve labeling discrepancies. The new baclofen ought to be cross-labeled with SynchroMed. A clear warning should be added indicating CNS baclofen may not be used with the Codman intrathecal pump due to drug instability.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug
Administration
Office of Device
Evaluation
9200 Corporate Avenue
Rockville, MD 20850

Date: September 29, 2009
From: Medical Officer
DAGID/GHD
Subject: NDA 22-462—CNS Intrathecal Baclofen
To: Eric Bastings, M.D. of CDER/OND/DNP
Thru: Branch Chief, Anthony Watson

BACKGROUND:

On March 27, 2009, CNS Therapeutics (CNS) filed a 505(b)(2) application for Baclofen Intrathecal Injection, 0.05 mg/mL, 0.5 mg/mL, 2 mg/mL (b) (4). CNS' NDA provides for three concentrations of Intrathecal Baclofen that have previously been approved under the Medtronic NDA. (b) (4)

Presently, there is only a single approved application for Baclofen Intrathecal Injection. The NDA for intrathecal Baclofen (NDA 020075) is owned by Medtronic, Inc. Medtronic distributes the product under the trade name, Lioresal®. Medtronic, Inc. also manufactures and distributes the SynchroMed II and the SynchroMed EL delivery systems that are used for chronic delivery of Baclofen into the intrathecal space.

It has been CNS' intention to seek approval of its Baclofen Intrathecal Injection as a drug product, and not a drug-device combination product. CNS is not seeking to co-package its product with a pump, nor is it seeking to qualify its product for use with any pump that is not already approved for the Intrathecal delivery of Baclofen at this time.

Currently, there are only 2 types of intrathecal pumps legally marketed in the U.S. (Codman 3000 and Medtronic SynchroMed). From the pump compatibility study, 1 month data (Day 17) showed that CNS Baclofen was not stable with Codman Pump (b) (4) but stable in the SynchroMed reservoir(6 month supporting

data measured at 1mo, 3mo, 5 mo and 6mo). However, the label does not have any warning for the CNS Baclofen not to use the Codman pump. Furthermore, it was found that the reference product (Lioresal) was also unstable with Codman Pump during testing by CNS.

June 12, 2009 Filing Communication from CDER to the Sponsor designated this product as a “combination product” where CDER requested that the CNS Baclofen drug labeling needs to specifically reference an intrathecal pump by the brand name, that the approved device should change its labeling, or CNS should obtain authorization for the device manufacturer to reference its PMA.

CDER to CDRH Consult: Recent discussions between CDER, CDRH and OCP are suggesting that intrathecal baclofen products should be approved as combination products (drug/pump) with mutually conforming labeling. However, the specific case of a generic drug identical in all aspects to the reference listed drug is less clear. Please comment as to whether you believe that some or all of the strengths of this product must be approved as a combination product, and discuss other device-related issues with baclofen.

DEVICE DESCRIPTION:

There is not formulation difference between CNS's Baclofen and the reference product, Lioresal, for the lower strengths (0.5mg/ml and 2mg/ml). (b) (4)



CNS' Baclofen had a wide range osmolality of (b) (4) when compared to Lioresal's tighter range of osmolality (b) (4) Solutions for intrathecal infusion are supposed to be isotonic to the CSF which has an osmolality of approximately 300mOsmol/kg.

INTENDED USE

The management of severe spasticity.

- Spasticity of spinal cord origin, chronic infusion of Baclofen Injection (Intrathecal) via an implantable pump should be reserved for patients unresponsive to oral baclofen therapy, or those who experience intolerable CNS side effects at effective doses.
- Spasticity due to traumatic brain injury should wait at least one year after the injury before consideration of long term intrathecal baclofen therapy.
- Baclofen Injection (Intrathecal) is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only in implantable pumps approved by the FDA specifically for the administration of Baclofen Injection (Intrathecal) into the intrathecal space.

REVIEW:

Medtronic SynchroMed Intrathecal Pumps can stay implanted in the body up to 7 years if the battery and other components do not have early failure. There are also multiple catheters that can be used with the SynchroMed pump for intrathecal infusion. The stability data collected so far delineated only the medication filled into the reservoir but no compatibility data over a certain duration using catheters and thus the whole entire fluid path's compatibility is not complete.

Current literature did cite cases of intrathecal baclofen patients reportedly present with MRI findings of intrathecal masses. Medtronic's own animal data using Lioresal could not reproduce the intrathecal mass associated with Baclofen use. However, Dr. Deer and Dr. Coffey co-authored an article in Pain Medicine (volume 9. Number 4. 2008) where further radiological evaluation of the MRI images indicates the appearance of the masses may be consistent with drug masses from highly concentrated baclofen unable to adequately mix with CSF flow leading to precipitation/drug mass at the catheter tip.

Novartis Pharmaceuticals Corporation (the manufacturer of Lioresal) did explain in their white paper that higher concentrations of Baclofen at 3mg/ml and 4mg/ml formed precipitates over time which translated to concerns of unknown risks associated with inaccurate dosing due to an altered concentration of the drug solution in the pump or potential clogging of the pump filter by precipitate.

DISCUSSION:

Lioresal is a baclofen formulated specifically for the Medtronic SynchroMed Intrathecal Pump and the maximum concentration that can be safely used is 2mg/ml. This recommendation is current and true for this particular formulation of baclofen and for the Medtronic SynchroMed Pump.

(b) (4)

(b) (4)

In 2008, CDRH conducted a Class I recall of Medtronic SynchroMed Pump regarding granuloma formation at the catheter tip resulting from intrathecal infusion of mostly opiates and some from baclofen. Medtronic came to meet with FDA/CDRH to defended its position with clinical data and animal data to show that Lioresal does not cause Inflammatory Mass but the use of highly concentrated compounded baclofen into the lower thoracic or lumbar spine does not mix well with CSF because the of relatively stagnant flow in this area which can result in drug precipitate/drug mass at the catheter tip. MRI findings for the baclofen cases showed subtle different from the granuloma formation secondary to opiate infusion in that the mass is non-enhanced on T-2 fat saturated slices and proton density-weighted MR images.

(b) (4)

At this current time, Medtronic's pump labeling specifies Lioresal as the safe and effective drug to be used and it further defined the maximum concentration of baclofen to be used is 2mg/ml.

(b) (4)

RECOMMENDATION:

(b) (4)

Consequently, given the foreseeable clinical confusion the potential new baclofen label will create with the use of SynchroMed pump label as well as the serious risks that Medtronic would be taking on as the pump manufacturer if CNS' baclofen comes to market (since it is only compatible with the SynchroMed pump) then CNS should contact Medtronic to allow CNS baclofen to be indicated for use with the SynchroMed pump. At this current time, FDA does not have any new data that can be used to compel Medtronic to change its labeling when in fact Medtronic's labeling is very accurate in terms Lioresal's limitations when used together with this pump.

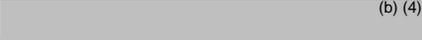
Finally, in order to ensure the safe use of the new Baclofen drug product with the SynchroMed intrathecal pump then the drug sponsor and the device manufacturer will have to work together to resolve labeling discrepancies so that the new baclofen can be cross-labeled with

Clinical Review
Rob Harris, M.D., Ph.D., FACS
22-462, 505 (b) (2) NDA
Baclofen Intrathecal

SynchroMed with a clear warning not to be used with Codman intrathecal pump due to drug instability.

Lana Shiu, M.D.
Medical Officer

9.4 Labeling Recommendations

The CDTL and I reviewed the labeling from the sponsor,  (b) (4)

During the review cycle, the sponsor addressed DNP and OCP concerns regarding the Gablofen and Synchromed pump labeling contradictions for concentrations above 2 mg/ml. At issue:

- *The Synchromed pump labeling* states that it is approved for “The chronic intrathecal infusion of Lioresal Intrathecal (baclofen injection) in the management of severe spasticity. The maximum approved concentration is 2 mg/mL”.
- *The Medtronic white paper* described above adds “use of intrathecal baclofen solution with SynchroMed® Programmable Drug Infusion Systems at concentrations higher than the commercially available 2mg/mL is unadvisable”.

➤



(b) (4)

(b) (4)

The CNS proposed labeling is not acceptable as described by Dr. Bastings, the CDTL. The sponsor refers to future Synchromed labeling changes which may never come. (b) (4)

(b) (4) For approval, the confusion presented by the contradictory language of the Synchromed pump and the Medtronic papers may need harmonization with the Gablofen product.

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Clinical Review
Rob Harris, M.D., Ph.D., FACS
22-462, 505 (b) (2) NDA
Baclofen Intrathecal

9.4 Advisory Committee Meeting

None needed or required.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT D HARRIS
07/08/2010

ERIC P BASTINGS
07/16/2010

Please see my CDTL memo, which describes my conclusions and recommendations for this application (and may differ from the clinical review).