

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-462/S-008

Trade Name: Gablofen

Generic Name: baclofen

Sponsor: Piramal Critical Care LTD

Approval Date: February 11, 2015

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APPLICATION NUMBER:
NDA 22-462/S-008

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APPLICATION NUMBER:
NDA 22-462/S-008

APPROVAL LETTER



NDA 22462/S-008

SUPPLEMENT APPROVAL

Mallinckrodt Inc.
Attention: Bill Kirkpatrick, PhD
Regulatory Coordinator
675 McDonnell Blvd., Bldg. 30-2
Saint Louis, MO 63042

Dear Dr. Kirkpatrick:

Please refer to your Supplemental New Drug Application (sNDA) dated May 15, 2014, received May 15, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Gablofen (baclofen) injection 50 mcg/mL, 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL.

We acknowledge receipt of your amendments dated September 26, 2014, December 17, 2014, February 3, 2015, February 4, 2015, and February 5, 2015.

The December 17, 2014, submission constituted a complete response to our December 1, 2014, action letter.

We also refer to our letter dated December 1, 2014, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Gablofen. This information pertains to the risk of the potential for contamination and consequent adverse events due to the external surface of the prefilled syringe not being sterile, based on new safety information about this risk identified since the product was approved.

This supplemental new drug application provides for revisions to the labeling for Gablofen, consistent with our December 1, 2014, Complete Response and Safety Labeling Change Notification letter.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on February 5, 2015 (attached), as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22462/S-008.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Taura Holmes, RPh, Regulatory Project Manager, via email or telephone at Taura.Holmes@fda.hhs.gov or (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Alice Hughes, MD
Deputy Director for Safety
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

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

/s/

ALICE HUGHES
02/11/2015

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
NDA 22-462/S-008

OTHER ACTION LETTER(S)



NDA 22462/S-008

**COMPLETE RESPONSE
SAFETY LABELING CHANGE NOTIFICATION**

Mallinckrodt Pharmaceuticals, Inc.
c/o Pacific-Link Consulting
Attention: Richard Lowenthal, MS, MBA
8195 Run of the Knolls Court
San Diego, CA 92127

Dear Mr. Lowenthal:

Please refer to your Supplemental New Drug Application (sNDA) dated May 15, 2014, received May 15, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Gablofen (baclofen) injection 50 mcg/mL, 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL.

This “Prior Approval” labeling supplemental new drug application proposes the addition of a statement to the final package labeling to [REDACTED] (b) (4)

We have completed the review of your application and have determined that we cannot approve this application in its present form.

The statement on the final package labeling, “For Maintenance Dosing with Intrathecal Pump,” [REDACTED] (b) (4) does not adequately inform prescribers about the potential for contamination of a sterile field or the modifications to the filling and refilling procedures that would mitigate the risk for contamination. Prescribers should be warned that the external surface of all strengths of the Gablofen prefilled syringe, including the 50 mcg/mL strength, is not sterile. Prescribers should be instructed not to use Gablofen prefilled syringes to fill sterile intrathecal infusion pumps in the operating room prior to implanting intrathecal pumps into patients. Providers who use Gablofen prefilled syringes to refill implantable intrathecal pumps in the outpatient setting should be warned to employ procedures that avoid contamination of sterile surfaces through contact with the unsterile exterior of the Gablofen prefilled syringe.

SAFETY LABELING CHANGE NOTIFICATION

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety-related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Gablofen (baclofen) injection in the 50 mcg/mL (prefilled syringe), the 500 mcg/mL (vial), and the 2000 mcg/mL (vial), was approved on November 19, 2010, and Gablofen (baclofen) injection 1000 mcg/ml (vial) was approved on June 22, 2012. The Gablofen (baclofen) prefilled syringe in 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL strengths was approved on January 17, 2013. Since the approval of the Gablofen (baclofen) prefilled syringe, we have become aware of information from postmarketing reports that indicates the potential for contamination and consequent adverse events. Labeling supplement S-008, which reported use of the Gablofen (baclofen) prefilled syringe in the operating room to fill intrathecal pumps before implantation, proposes [REDACTED] (b) (4)

The prefilled syringe carton is a plastic tray with a peel-back top, giving the appearance that the exterior surface of the syringe is sterile; however, the final packaging is [REDACTED] (b) (4) and the exterior of the syringe is unsterile. Operators may unknowingly violate aseptic technique during pump implantation surgery by placing the syringe on the sterile operating room field. We have received a postmarketing report that described contamination of the sterile surgical field during a pump implantation procedure. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and discussed with you during a teleconference on September 2, 2014, we believe that the new safety information should be included in the labeling for Gablofen (baclofen) injection 50 mcg/mL, 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL as follows:

- Add a subsection to Section 5, Warnings and Precautions, to warn prescribers that the external surface of all strengths of the Gablofen (baclofen) prefilled syringe, including the 50mcg/mL strength, is not sterile. The language should instruct prescribers not to use Gablofen (baclofen) prefilled syringes to fill sterile intrathecal infusion pumps in the operating room prior to implanting intrathecal pumps into patients. The language should also warn providers who use Gablofen (baclofen) prefilled syringes to refill implantable intrathecal pumps in the outpatient setting to employ procedures that avoid contamination of sterile surfaces through contact with the unsterile exterior of the Gablofen (baclofen) prefilled syringe.
- Revise the package labeling as follows:
 - Relocate the proposed statement “Drug and drug pathway sterile, syringe exterior not sterile” to the left side of the packaging labeling, as this is where the health care practitioner will first look to examine the labeling prior to use.
 - Increase the prominence of the cautionary statement by enlarging the font size, using bold lettering, and/or using colored text to minimize the risk of this important information being overlooked.
 - Ensure that the proposed statement “Drug and drug pathway sterile, syringe exterior not sterile” is in the same orientation with the rest of the text on the packaging labeling in order to improve readability.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).”

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>

SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you do not submit electronically, please send 5 copies of the submission.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, “Formal Meetings Between the FDA and Sponsors or Applicants,” May 2009 at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, contact Taura Holmes, PharmD, Regulatory Project Manager, via email or telephone at Taura.Holmes@fda.hhs.gov or (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

ERIC P BASTINGS
12/01/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-462/S-008

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GABLOFEN® safely and effectively. See full prescribing information for GABLOFEN.

**GABLOFEN (baclofen injection), for intrathecal use
Initial U.S. Approval: 1992**

WARNING: DO NOT DISCONTINUE ABRUPTLY
See full prescribing information for complete boxed warning

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 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 post-implant clinician and patient information. (5.4)

- **Maintenance Therapy:** Titrate patients individually; Lowest dose with an optimal response should be used, generally 300 mcg/day to 800 mcg/day for spasticity of spinal cord origin and 90 mcg/day to 700 mcg/day for spasticity of cerebral origin; Titrate GABLOFEN to maintain some degree of muscle tone and allow occasional spasms. (2.6)

----- **DOSAGE FORMS AND STRENGTHS** -----
Injection: 50 mcg/mL, 500 mcg/mL, 1,000 mcg/mL, and 2,000 mcg/mL (3)

----- **CONTRAINDICATIONS** -----

- Hypersensitivity to baclofen (4)
- Do not use GABLOFEN for intravenous, intramuscular, subcutaneous or epidural administration. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Do not directly inject GABLOFEN into the pump catheter access port, as this may cause a life-threatening overdose (5.1)
- Potential for contamination due to non-sterile external surface of prefilled syringe (5.2)
- Potentially life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure; Resuscitative equipment and trained staff must be available during screening, dose titration, and refills (5.3)
- Overdose may cause drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia and loss of consciousness progressing to coma (5.4)
- Possible exacerbation of psychotic disorders, schizophrenia or confusional states (5.6)

----- **RECENT MAJOR CHANGES** -----
Warnings and Precautions, Potential for Contamination due to Non-sterile External Surface of Prefilled Syringe (5.2) 2/2015

----- **ADVERSE REACTIONS** -----

- The most common adverse reactions in patients with spasticity of spinal origin were somnolence, dizziness, nausea, hypotension, headache, convulsions and hypotonia (6.1)
- The most common adverse reactions in patients with spasticity of cerebral origin were agitation, constipation, somnolence, leukocytosis, chills, urinary retention and hypotonia (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt Brand Pharmaceuticals, Inc. at 1-800-778-7898 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----
Combined use with morphine: hypotension and dyspnea (7)

----- **USE IN SPECIFIC POPULATIONS** -----

- **Pregnancy:** Based on animal data, may cause fetal harm (8.1)
- **Pediatric use:** Safety and effectiveness in pediatric patients below the age of 4 years have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: DO NOT DISCONTINUE ABRUPTLY

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2 DOSAGE AND ADMINISTRATION

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DO NOT DISCONTINUE ABRUPTLY

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 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 post-implant clinician and patient information [see *Warnings and Precautions (5.4)*].

1 INDICATIONS AND USAGE

GABLOFEN is indicated for use in the management of severe spasticity in adult and pediatric patients age 4 years and above. Patients should first respond to a screening dose of intrathecal baclofen prior to consideration for long term infusion via an implantable pump. For spasticity of spinal cord origin, chronic infusion of GABLOFEN 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. Patients with spasticity due to traumatic brain injury should wait at least one year after the injury before consideration of long term intrathecal baclofen therapy. GABLOFEN is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only with the Medtronic SynchroMed[®] II Programmable Pump or other pumps labeled for intrathecal administration of GABLOFEN [see *Clinical Studies (14)*].

Prior to implantation of a device for chronic intrathecal infusion of GABLOFEN, patients must show a response to GABLOFEN in a screening trial [see *Dosage and Administration (2.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Use Only with Medtronic SynchroMed[®] II Programmable Pump (or other pumps labeled for intrathecal administration of GABLOFEN)

GABLOFEN is approved only for use with the Medtronic SynchroMed[®] II Programmable Pump or other pumps labeled for intrathecal administration of GABLOFEN. Refer to the manufacturer's manual for specific instructions and precautions for programming the pump and/or refilling the reservoir. It is important to select the appropriate refill kit for the pump used to administer GABLOFEN. GABLOFEN is not to be compounded with other medications.

2.2 Screening Phase

Prior to pump implantation and initiation of chronic infusion of GABLOFEN, patients must demonstrate a positive clinical response to a GABLOFEN bolus dose administered intrathecally in a screening trial. The screening trial employs GABLOFEN at a concentration of 50 mcg/mL. A 1 mL syringe (50 mcg/mL) is available for use in the screening trial. The screening procedure is as follows. An initial bolus containing 50 micrograms in a volume of 1 milliliter is administered into the intrathecal space by barbotage over a period of not less than one minute. The patient is observed over the ensuing 4 to 8 hours. A positive response consists of a significant decrease in muscle tone and/or frequency and/or severity of spasms. If the initial response is less than desired, a second bolus injection may be administered 24 hours after the first. The second screening bolus dose consists of 75 micrograms in 1.5 milliliters. Again, the patient should be observed for an interval of 4 to 8 hours. If the response is still inadequate, a final bolus screening dose of 100 micrograms in 2 milliliters may be administered 24 hours later.

Pediatric Patients

The starting screening dose for pediatric patients is the same as in adult patients, i.e., 50 mcg. However, for very small patients, a screening dose of 25 mcg may be tried first.

Patients who do not respond to a 100 mcg intrathecal bolus should not be considered candidates for an implanted pump for chronic infusion.

2.3 Preparation Information

Screening

Use the 1 mL screening syringe only (50 mcg/mL) for bolus injection into the subarachnoid space. For a 50 mcg bolus dose, use 1 mL of the screening syringe. Use 1.5 mL of 50 mcg/mL baclofen injection for a 75 mcg bolus dose. For the maximum screening dose of 100 mcg, use 2 mL of 50 mcg/mL baclofen injection (2 screening syringes).

Maintenance

The specific concentration that should be used depends upon the total daily dose required as well as the delivery rate of the pump. For patients who require concentrations other than 500 mcg/mL, 1,000 mcg/mL or 2,000 mcg/mL, GABLOFEN must be diluted with sterile preservative free Sodium Chloride for Injection, USP.

2.4 Administration Information

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

The external surface of GABLOFEN prefilled syringes (all strengths, including the 50 mcg/mL strength) are non-sterile. The use of GABLOFEN prefilled syringe in an aseptic setting (i.e., operating room) to fill sterile intrathecal pumps prior to implantation in patients is not recommended. For outpatient use, modify aseptic procedures to avoid contamination of sterile surfaces through contact with the non-sterile exterior of the GABLOFEN prefilled syringe when filling the pump reservoir [*see Warnings and Precautions (5.2)*].

Delivery Regimen

GABLOFEN is most often administered in a continuous infusion mode immediately following implant. For those patients implanted with programmable pumps who have achieved relatively satisfactory control on continuous infusion, further benefit may be attained using more complex schedules of GABLOFEN delivery. For example, patients who have increased spasms at night may require a 20% increase in their hourly infusion rate. Changes in flow rate should be programmed to start two hours before the time of desired clinical effect.

2.5 Dose Titration

Post-Implant Dose Titration Period

To determine the initial total daily dose of GABLOFEN following implant, the screening dose that gave a positive effect should be doubled and administered over a 24-hour period, unless the efficacy of the bolus dose was maintained for more than 8 hours, in which case the starting daily dose should be the screening dose delivered over a 24-hour period. No dose increases should be given in the first 24 hours (i.e., until the steady state is achieved). In most patients, it will be necessary to increase the dose gradually over time to maintain effectiveness; a sudden requirement for substantial dose escalation typically indicates a catheter complication (i.e., catheter kink or dislodgement).

Adult Patients with Spasticity of Spinal Cord Origin

After the first 24 hours, for adult patients, the daily dosage should be increased slowly by 10% to 30% increments and only once every 24 hours, until the desired clinical effect is achieved.

Adult Patients with Spasticity of Cerebral Origin

After the first 24 hours, the daily dose should be increased slowly by 5% to 15% only once every 24 hours, until the desired clinical effect is achieved.

Pediatric Patients

After the first 24 hours, the daily dose should be increased slowly by 5% to 15% only once every 24 hours, until the desired clinical effect is achieved. If there is not a substantive clinical response to increases in the daily dose, check for proper pump function and catheter patency. Patients must be monitored closely in a fully equipped and staffed environment during the screening phase and dose-titration period immediately following implant. Resuscitative equipment should be immediately available for use in case of life-threatening or intolerable side effects.

Additional Considerations Pertaining to Dosage Adjustment

Careful dose titration of GABLOFEN is needed when spasticity is necessary to sustain upright posture and balance in locomotion or whenever spasticity is used to obtain optimal function and care. It may be important to titrate the dose to maintain some degree of muscle tone and allow occasional spasms to: 1) help support circulatory function, 2) possibly prevent the formation of deep vein thrombosis, 3) optimize activities of daily living and ease of care.

Except in overdose related emergencies, the dose of GABLOFEN should ordinarily be reduced slowly if the drug is discontinued for any reason.

An attempt should be made to discontinue concomitant oral antispasticity medication to avoid possible overdose or adverse drug interactions, either prior to screening or following implant and initiation of chronic GABLOFEN infusion. Reduction and discontinuation of oral anti-spasmodics should be done slowly and with careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispastics should be avoided.

2.6 Maintenance Therapy

Spasticity of Spinal Cord Origin Patients

The clinical goal is to maintain muscle tone as close to normal as possible, and to minimize the frequency and severity of spasms to the extent possible, without inducing intolerable side effects. Very often, the maintenance dose needs to be adjusted during the first few months of therapy while patients adjust to changes in lifestyle due to the alleviation of spasticity. During periodic refills of the pump, the daily dose may be increased by 10% to 40%, but no more than 40%, to maintain adequate symptom control. The daily dose may be reduced by 10% to 20% if patients experience side effects. Most patients require gradual increases in dose over time to maintain optimal response during chronic therapy. A sudden large requirement for dose escalation suggests a catheter complication (i.e., catheter kink or dislodgement).

Maintenance dosage for long term continuous infusion of intrathecal baclofen has ranged from 12 mcg/day to 2,003 mcg/day, with most patients adequately maintained on 300 micrograms to 800 micrograms per day. There is limited experience with daily doses greater than 1,000 mcg/day. Determination of the optimal GABLOFEN dose requires individual titration. The lowest dose with an optimal response should be used.

Spasticity of Cerebral Origin Patients

The clinical goal is to maintain muscle tone as close to normal as possible and to minimize the frequency and severity of spasms to the extent possible, without inducing intolerable side effects, or to titrate the dose to the desired degree of muscle tone for optimal functions. Very often the maintenance dose needs to be adjusted during the first few months of therapy while patients adjust to changes in lifestyle due to the alleviation of spasticity.

During periodic refills of the pump, the daily dose may be increased by 5% to 20%, but no more than 20%, to maintain adequate symptom control. The daily dose may be reduced by 10% to 20% if patients experience side effects. Many patients require gradual increases in dose over time to maintain optimal response during chronic therapy. A sudden large requirement for dose escalation suggests a catheter complication (i.e., catheter kink or dislodgement).

Maintenance dosage for long term continuous infusion of intrathecal baclofen has ranged from 22 mcg/day to 1,400 mcg/day, with most patients adequately maintained on 90 micrograms to 703 micrograms per day. In clinical trials, only 3 of 150 patients required daily doses greater than 1,000 mcg/day.

Pediatric Patients

Use same dosing recommendations for patients with spasticity of cerebral origin. Pediatric patients under 12 years seemed to require a lower daily dose in clinical trials. Average daily dose for patients under 12 years was 274 mcg/day, with a range of 24 mcg/day to 1,199 mcg/day.

Dosage requirement for pediatric patients over 12 years does not seem to be different from that of adult patients. Determination of the optimal GABLOFEN dose requires individual titration. The lowest dose with an optimal response should be used.

Potential Need for Dose Adjustments in Chronic Use

During long term treatment, approximately 5% (28/627) of patients become refractory to increasing doses. There is not sufficient experience to make firm recommendations for tolerance treatment; however, this “tolerance” has been treated on occasion, in hospital, by a “drug holiday” consisting of the gradual reduction of intrathecal baclofen over a 2 to 4 week period and switching to alternative methods of spasticity management. After the “drug holiday,” intrathecal baclofen may be restarted at the initial continuous infusion dose.

3 DOSAGE FORMS AND STRENGTHS

GABLOFEN is a sterile, pyrogen-free, isotonic solution free of antioxidants, preservatives or other potentially neurotoxic additives indicated only for intrathecal administration. The drug is stable in solution at 37°C and compatible with CSF. Each milliliter of GABLOFEN contains baclofen USP 50 mcg, 500 mcg, 1,000 mcg or 2,000 mcg and sodium chloride 9 mg in Water for Injection; pH range is 5.5 to 7.5. Each vial or syringe is intended for single use only. Discard any unused portion. Do not autoclave.

4 CONTRAINDICATIONS

GABLOFEN is contraindicated in patients with a hypersensitivity to baclofen. Do not use GABLOFEN for intravenous, intramuscular, subcutaneous or epidural administration.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Life-Threatening Overdose During Pump Refills

Use extreme caution when filling the Medtronic SynchroMed® II Programmable Pump which is equipped with an injection port that allows direct access to the intrathecal catheter. Direct injection into the catheter through the catheter access port may cause a life-threatening overdose.

Reservoir refilling must be performed by fully trained and qualified personnel following the directions provided by the pump manufacturer. Carefully calculate refill intervals to prevent depletion of the reservoir, as this would result in the return of severe spasticity and possibly symptoms of withdrawal.

Strict aseptic technique in filling is required to avoid bacterial contamination and serious infection. A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir.

5.2 Potential for Contamination due to Non-sterile External Surface of Prefilled Syringe

Although the drug solution and pathway in the GABLOFEN prefilled syringes are sterile, the external surface of the prefilled syringes (all strengths, including the 50 mcg/mL strength) are non-sterile. This has the potential to lead to contamination and consequent adverse reactions.

The use of GABLOFEN prefilled syringe in an aseptic setting (e.g., operating room) to fill sterile intrathecal pumps prior to implantation in patients is not recommended, unless the external surface of the prefilled syringe is treated to ensure sterility. GABLOFEN supplied in vials may be used with conventional aseptic technique to fill intrathecal pumps prior to implantation. Procedures should also be put in place while refilling implantable intrathecal pumps in an outpatient setting to avoid contamination of sterile surfaces through contact with the non-sterile exterior of the GABLOFEN prefilled syringe.

5.3 Prescriber, Caregiver and Patient Training and Screening Procedure/Post-Implantation Environment

GABLOFEN is for use in single bolus intrathecal injections (via a catheter placed in the lumbar intrathecal space or injection by lumbar puncture) and in the implantable Medtronic SynchroMed® II Programmable Pump or other pumps labeled for intrathecal administration of GABLOFEN. Because of the possibility of potentially life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure, physicians must be adequately trained and educated in chronic intrathecal infusion therapy.

The pump system should not be implanted until the patient's response to bolus GABLOFEN injection is adequately evaluated. Evaluation (consisting of a screening procedure) requires that GABLOFEN be administered into the intrathecal space via a catheter or lumbar puncture [*see Dosage and Administration (2.2)*]. Because of the risks associated with the screening procedure and the adjustment of dosage following pump implantation, these phases must be conducted in a medically supervised and adequately equipped environment following the instructions outlined in the Dosage and Administration section [*see Dosage and Administration (2.2 and 2.5)*].

Resuscitative equipment should be available.

Following surgical implantation of the pump, particularly during the initial phases of pump use, the patient should be monitored closely until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

On each occasion that the dosing rate of the pump and/or the concentration of GABLOFEN in the reservoir is adjusted, close medical monitoring is required until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

It is mandatory that the patient, all patient caregivers, and the physicians responsible for the patient receive adequate information regarding the risks of this mode of treatment. All medical personnel and caregivers should be instructed in 1) the signs and symptoms of overdose, 2) procedures to be followed in the event of overdose and 3) proper home care of the pump and insertion site.

5.4 Overdose

Signs of overdose may appear suddenly or insidiously. Acute massive overdose may present as coma. Less sudden and/or less severe forms of overdose may present with signs of drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia and loss of consciousness progressing to coma. Should overdose appear likely, the

patient should be taken immediately to a hospital for assessment and emptying of the pump reservoir. In cases reported to date, overdose has generally been related to pump malfunction or dosing error [*see Overdosage (10)*].

Extreme caution must be used when filling the implantable pump.

The Medtronic SynchroMed® II Programmable Pump should only be refilled through the reservoir refill septum. The Medtronic SynchroMed® II Programmable Pump is also equipped with a catheter access port that allows direct access to the intrathecal catheter. Direct injection into this catheter access port may cause a life-threatening overdose.

5.5 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. Cases of intrathecal mass at the tip of the implanted catheter leading to withdrawal symptoms have also been reported, most of them involving pharmacy compounded analgesic admixtures [*see Warnings and Precautions (5.10)*].

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 intrathecal baclofen as well as in patients maintained on therapeutic doses of intrathecal baclofen.

5.6 Possible Exacerbation of Psychotic Disorders, Schizophrenia, or Confusional States

Patients suffering from psychotic disorders, schizophrenia, or confusional states should be treated cautiously with GABLOFEN and kept under careful surveillance, because exacerbations of these conditions have been observed with oral administration.

5.7 Fatalities

Spasticity of Spinal Cord Origin

There were 16 deaths reported among the 576 U.S. patients treated with intrathecal baclofen in pre- and post-marketing studies evaluated as of December 1992. Because these patients were treated under uncontrolled clinical settings, it is impossible to determine definitively what role, if any, intrathecal baclofen played in their deaths. As a group, the patients who died were relatively young (mean age was 47 with a range from 25 to 63), but the majority suffered from severe spasticity of many years duration, were nonambulatory, had various medical complications such as pneumonia, urinary tract infections, and decubiti, and/or had received multiple concomitant medications. A case-by-case review of the clinical course of the 16 patients who died failed to reveal any unique signs, symptoms, or laboratory results that would suggest that treatment with intrathecal baclofen caused their deaths. Two patients, however, did suffer sudden and unexpected death within 2 weeks of pump implantation and one patient died unexpectedly after screening.

One patient, a 44 year-old male with Multiple Sclerosis, died in hospital on the second day following pump implantation. An autopsy demonstrated severe fibrosis of the coronary conduction system. A second patient, a 52 year-old woman with MS and a history of an inferior wall myocardial infarction, was found dead in bed 12 days after pump implantation, 2 hours after having had documented normal vital signs. An autopsy revealed pulmonary congestion and bilateral pleural effusions. It is impossible to determine whether intrathecal baclofen contributed to these deaths. The third patient underwent three baclofen screening trials. His medical history included spinal cord injury, aspiration pneumonia, septic shock, disseminated intravascular coagulopathy, severe metabolic acidosis, hepatic toxicity, and status epilepticus. Twelve days after screening (he was not implanted), he again experienced status epilepticus with subsequent significant neurological deterioration. Based upon prior instruction, extraordinary resuscitative measures were not pursued and the patient died.

Spasticity of Cerebral Origin

There were three deaths occurring among the 211 patients treated with intrathecal baclofen in pre-marketing studies as of March 1996. These deaths were not attributed to the therapy.

5.8 Use with Caution in Patients with a History of Autonomic Dysreflexia

GABLOFEN should be used with caution in patients with a history of autonomic dysreflexia. The presence of nociceptive stimuli or abrupt withdrawal of GABLOFEN may cause an autonomic dysreflexic episode.

5.9 Infections

Patients should be infection-free prior to the screening trial with GABLOFEN because the presence of a systemic infection may interfere with an assessment of the patient's response to bolus GABLOFEN. Patients should be infection-free prior to implantation of the pump because the presence of infection may increase the risk of surgical complications. Moreover, a systemic infection may complicate dosing.

5.10 Drowsiness

Drowsiness has been reported in patients on intrathecal baclofen. Patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system depressant effects of intrathecal baclofen may be additive to those of alcohol and other CNS depressants.

5.11 Intrathecal Mass Formation

Cases of intrathecal mass at the tip of the implanted catheter have been reported, most of them involving pharmacy compounded analgesic admixtures. The most frequent symptoms associated with intrathecal mass are: 1) 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), 2) pain, 3) neurological deficit/dysfunction. Clinicians should monitor patients on intraspinal therapy carefully for any new neurological signs or symptoms. In patients with new neurological signs or symptoms suggestive of an intrathecal mass, consider a neurosurgical consultation, since many of the symptoms of inflammatory mass are not unlike the symptoms experienced by patients with severe spasticity from their disease. In some cases, performance of an imaging procedure may be appropriate to confirm or rule-out the diagnosis of an intrathecal mass.

5.12 Ovarian Cysts

A dose-related increase in incidence of ovarian cysts was observed in female rats treated chronically with oral baclofen. Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients who were treated with oral baclofen for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population.

6 ADVERSE REACTIONS

6.1 Spasticity of Spinal Cord Origin

Most Common Adverse Reactions in Patients with Spasticity of Spinal Origin

In pre- and post-marketing clinical trials, the most common adverse reactions associated with use of intrathecal baclofen which were not seen at an equivalent incidence among placebo-treated patients were: somnolence, dizziness, nausea, hypotension, headache, convulsions and hypotonia.

Adverse Reactions Associated with Discontinuation of Treatment

8/474 patients with spasticity of spinal cord origin receiving long term infusion of intrathecal baclofen in pre- and post-marketing clinical studies in the U.S. discontinued treatment due to adverse reactions. These include: pump pocket infections (3), meningitis (2), wound dehiscence (1), gynecological fibroids (1) and pump overpressurization (1) with unknown, if any, sequela. Eleven patients who developed coma secondary to overdose had their treatment temporarily suspended, but all were subsequently re-started and were not, therefore, considered to be true discontinuations.

Fatalities - [*see Warnings and Precautions (5.6)*].

Incidence in Controlled Trials

Experience with intrathecal baclofen obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimating the incidence of adverse reactions because the studies were of very brief duration (up to three days of infusion) and involved only a total of 63 patients. The following events occurred among the 31 patients receiving intrathecal baclofen in two randomized, placebo-controlled trials: hypotension (2), dizziness (2), headache (2), dyspnea (1). No adverse reactions were reported among the 32 patients receiving placebo in these studies.

Events Observed during the Pre- and Post-marketing Evaluation of Intrathecal Baclofen

Adverse events associated with the use of intrathecal baclofen reflect experience gained with 576 patients followed prospectively in the United States. They received intrathecal baclofen for periods of one day (screening) (N=576) to over eight years (maintenance) (N=10). The usual screening bolus dose administered prior to pump implantation in these studies was typically 50 mcg. The maintenance dose ranged from 12 mcg to 2,003 mcg per day. Because of the open, uncontrolled nature of the experience, a causal linkage between events observed and the administration of intrathecal baclofen cannot be reliably assessed in many cases and many of the adverse reactions reported are known to occur in association with the underlying conditions being treated. Nonetheless, many of the more commonly reported reactions — hypotonia, somnolence, dizziness, paresthesia, nausea/vomiting and headache — appear clearly drug-related.

Adverse experiences reported during all U.S. studies (both controlled and uncontrolled) are shown in Table 1. Eight of 474 patients who received chronic infusion via implanted pumps had adverse experiences which led to a discontinuation of long term treatment in the pre- and post-marketing studies.

Table 1: Most Common ($\geq 1\%$) Adverse Reactions in Patients with Spasticity of Spinal Origin in Prospectively Monitored Clinical Trials

Adverse Reaction	Percent N=576 Screening*	Percent N=474 Titration[†]	Percent N=430 Maintenance[‡]
Hypotonia	5.4	13.5	25.3
Somnolence	5.7	5.9	20.9
Dizziness	1.7	1.9	7.9

Paresthesia	2.4	2.1	6.7
Nausea and Vomiting	1.6	2.3	5.6
Headache	1.6	2.5	5.1
Constipation	0.2	1.5	5.1
Convulsion	0.5	1.3	4.7
Urinary Retention	0.7	1.7	1.9
Dry Mouth	0.2	0.4	3.3
Accidental Injury	0.0	0.2	3.5
Asthenia	0.7	1.3	1.4
Confusion	0.5	0.6	2.3
Death	0.2	0.4	3.0
Pain	0.0	0.6	3.0
Speech Disorder	0.0	0.2	3.5
Hypotension	1.0	0.2	1.9
Ambyopia	0.5	0.2	2.3
Diarrhea	0.0	0.8	2.3
Hypoventilation	0.2	0.8	2.1
Coma	0.0	1.5	0.9
Impotence	0.2	0.4	1.6
Peripheral Edema	0.0	0.0	2.3
Urinary Incontinence	0.0	0.8	1.4
Insomnia	0.0	0.4	1.6
Anxiety	0.2	0.4	0.9
Depression	0.0	0.0	1.6
Dyspnea	0.3	0.0	1.2
Fever	0.5	0.2	0.7
Pneumonia	0.2	0.2	1.2
Urinary Frequency	0.0	0.6	0.9
Urticaria	0.2	0.2	1.2
Anorexia	0.0	0.4	0.9
Diplopia	0.0	0.4	0.9
Dysautonomia	0.2	0.2	0.9
Hallucinations	0.3	0.4	0.5
Hypertension	0.2	0.6	0.5

* Following administration of test bolus

† Two month period following implant

‡ Beyond two months following implant

N=Total number of patients entering each period

%=% of patients evaluated

In addition to the more common (1% or more) adverse reactions reported in the prospectively followed 576 domestic patients in pre- and post-marketing studies, experience from an additional 194 patients exposed to intrathecal baclofen from foreign studies has been reported. The

following adverse reactions, not described in the table, and arranged in decreasing order of frequency, and classified by body system, were reported:

Nervous System: Abnormal gait, thinking abnormal, tremor, amnesia, twitching, vasodilatation, cerebrovascular accident, nystagmus, personality disorder, psychotic depression, cerebral ischemia, emotional lability, euphoria, hypertonia, ileus, drug dependence, incoordination, paranoid reaction and ptosis.

Digestive System: Flatulence, dysphagia, dyspepsia and gastroenteritis.

Cardiovascular: Postural hypotension, bradycardia, palpitations, syncope, arrhythmia ventricular, deep thrombophlebitis, pallor and tachycardia.

Respiratory: Respiratory disorder, aspiration pneumonia, hyperventilation, pulmonary embolus and rhinitis.

Urogenital: Hematuria and kidney failure.

Skin and Appendages: Alopecia and sweating.

Metabolic and Nutritional Disorders: Weight loss, albuminuria, dehydration and hyperglycemia.

Special Senses: Abnormal vision, abnormality of accommodation, photophobia, taste loss and tinnitus.

Body as a Whole: Suicide, lack of drug effect, abdominal pain, hypothermia, neck rigidity, chest pain, chills, face edema, flu syndrome and overdose.

Hemic and Lymphatic System: Anemia.

6.2 Spasticity of Cerebral Origin

Most Common Adverse Reactions

In pre-marketing clinical trials, the most common adverse reactions associated with use of intrathecal baclofen which were not seen at an equivalent incidence among placebo-treated patients included: agitation, constipation, somnolence, leukocytosis, chills, urinary retention and hypotonia.

Adverse Reactions Associated with Discontinuation of Treatment

Nine of 211 patients receiving intrathecal baclofen in pre-marketing clinical studies in the U.S. discontinued long-term infusion due to adverse reactions associated with intrathecal therapy.

The nine adverse reactions leading to discontinuation were: infection (3), CSF leaks (2), meningitis (2), drainage (1), and unmanageable trunk control (1).

Fatalities

Three deaths, none of which were attributed to intrathecal baclofen, were reported in patients in clinical trials involving patients with spasticity of cerebral origin. See Warnings on other deaths reported in spinal spasticity patients.

Incidence in Controlled Trials

Experience with intrathecal baclofen obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimating the incidence of adverse reactions because the studies involved a total of 62 patients exposed to a single 50 mcg intrathecal bolus. The following adverse reactions occurred among the 62 patients receiving intrathecal baclofen in two randomized, placebo-controlled trials involving cerebral palsy and head injury patients, respectively: agitation, constipation, somnolence, leukocytosis, nausea, vomiting, nystagmus, chills, urinary retention, and hypotonia.

Events Observed during the Pre-marketing Evaluation of Intrathecal Baclofen

Adverse events associated with the use of intrathecal baclofen reflect experience gained with a total of 211 U.S. patients with spasticity of cerebral origin, of whom 112 were pediatric patients (under age 16 at enrollment). They received intrathecal baclofen for periods of one day (screening) (N=211) to 84 months (maintenance) (N=1). The usual screening bolus dose administered prior to pump implantation in these studies was 50 mcg to 75 mcg. The maintenance dose ranged from 22 mcg to 1,400 mcg per day. Doses used in this patient population for long-term infusion are generally lower than those required for patients with spasticity of spinal cord origin.

Because of the open, uncontrolled nature of the experience, a causal linkage between events observed and the administration of intrathecal baclofen cannot be reliably assessed in many cases. Nonetheless, many of the more commonly reported reactions — somnolence, dizziness, headache, nausea, hypotension, hypotonia and coma — appear clearly drug-related.

The most frequent ($\geq 1\%$) adverse reactions reported during all clinical trials are shown in Table 2. Nine patients discontinued long term treatment due to adverse reactions.

Table 2: Most Common ($\geq 1\%$) Adverse Reactions in Patients with Spasticity of Cerebral Origin

Adverse Reaction	Percent N=211 Screening*	Percent N=153 Titration[†]	Percent N=150 Maintenance[‡]
Hypotonia	2.4	14.4	34.7
Somnolence	7.6	10.5	18.7
Headache	6.6	7.8	10.7
Nausea and Vomiting	6.6	10.5	4.0
Vomiting	6.2	8.5	4.0
Urinary Retention	0.9	6.5	8.0
Convulsion	0.9	3.3	10.0

Dizziness	2.4	2.6	8.0
Nausea	1.4	3.3	7.3
Hypoventilation	1.4	1.3	4.0
Hypertonia	0.0	0.7	6.0
Paresthesia	1.9	0.7	3.3
Hypotension	1.9	0.7	2.0
Increased Salivation	0.0	2.6	2.7
Back Pain	0.9	0.7	2.0
Constipation	0.5	1.3	2.0
Pain	0.0	0.0	4.0
Pruritus	0.0	0.0	4.0
Diarrhea	0.5	0.7	2.0
Peripheral Edema	0.0	0.0	3.3
Thinking Abnormal	0.5	1.3	0.7
Agitation	0.5	0.0	1.3
Asthenia	0.0	0.0	2.0
Chills	0.5	0.0	1.3
Coma	0.5	0.0	1.3
Dry Mouth	0.5	0.0	1.3
Pneumonia	0.0	0.0	2.0
Speech Disorder	0.5	0.7	0.7
Tremor	0.5	0.0	1.3
Urinary Incontinence	0.0	0.0	2.0
Urination Impaired	0.0	0.0	2.0

* Following administration of test bolus

† Two month period following implant

‡ Beyond two months following implant

N=Total number of patients entering each period. 211 patients received drug; (1 of 212) received placebo only

The more common (1% or more) adverse reactions reported in the prospectively followed 211 patients exposed to intrathecal baclofen have been reported. In the total cohort, the following adverse reactions, not described in Table 2, and arranged in decreasing order of frequency, and classified by body system, were reported:

Nervous System: Akathisia, ataxia, confusion, depression, opisthotonos, amnesia, anxiety, hallucinations, hysteria, insomnia, nystagmus, personality disorder, reflexes decreased, and vasodilatation.

Digestive System: Dysphagia, fecal incontinence, gastrointestinal hemorrhage and tongue disorder.

Cardiovascular: Bradycardia.

Respiratory: Apnea, dyspnea and hyperventilation.

Urogenital: Abnormal ejaculation, kidney calculus, oliguria and vaginitis.

Skin and Appendages: Rash, sweating, alopecia, contact dermatitis and skin ulcer.

Special Senses: Abnormality of accommodation.

Body as a Whole: Death, fever, abdominal pain, carcinoma, malaise and hypothermia.

Hemic and Lymphatic System: Leukocytosis and petechial rash.

7 DRUG INTERACTIONS

There is inadequate systematic experience with the use of intrathecal baclofen in combination with other medications to predict specific drug-drug interactions. Interactions attributed to the combined use of GABLOFEN and epidural morphine include hypotension and dyspnea.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. GABLOFEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Baclofen given orally has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times on a mg/kg basis, or 3 times on a mg/m² basis, the maximum oral dose recommended for human use; this dose also caused reductions in food intake and weight gain in the dams. This abnormality was not seen in mice or rabbits.

8.2 Labor and Delivery

The effect of baclofen on labor and delivery is unknown.

8.3 Nursing Mothers

At therapeutic oral doses, baclofen is excreted in human milk. It is not known whether detectable levels of drug are present in milk of nursing mothers receiving GABLOFEN. Because of the potential for serious adverse reactions in nursing infants from GABLOFEN, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Please consult pump manufacturer's manual for specific recommendations.

Safety and effectiveness in pediatric patients below the age of 4 have not been established.

10 OVERDOSAGE

Special attention must be given to recognizing the signs and symptoms of overdose, especially during the initial screening and dose-titration phase of treatment, but also during re-introduction of GABLOFEN after a period of interruption in therapy.

Symptoms of Intrathecal Baclofen Overdose

Drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia and loss of consciousness progressing to coma of up to 72 hours duration. In most cases reported, coma was reversible without sequelae after drug was discontinued. Symptoms of intrathecal baclofen overdose were reported in a sensitive adult patient after receiving a 25 mcg intrathecal bolus.

Treatment Suggestions for Overdose

There is no specific antidote for treating overdoses of GABLOFEN; however, the following steps should ordinarily be undertaken:

- 1) Residual intrathecal baclofen solution should be removed from the pump as soon as possible.
- 2) Patients with respiratory depression should be intubated if necessary, until the drug is eliminated.

Anecdotal reports suggest that intravenous physostigmine may reverse central side effects, notably drowsiness and respiratory depression. Caution in administering physostigmine is advised, however, because its use has been associated with the induction of seizures and bradycardia.

Physostigmine Doses for Adult Patients

Administer 2 mg of physostigmine intramuscularly or intravenously at a slow controlled rate of no more than 1 mg per minute. Dosage may be repeated if life-threatening signs, such as arrhythmia, convulsions or coma occur.

Physostigmine Doses for Pediatric Patients

Administer 0.02 mg/kg physostigmine intramuscularly or intravenously, do not give more than 0.5 mg per minute. The dosage may be repeated at 5 to 10 minute intervals until a therapeutic effect is obtained or a maximum dose of 2 mg is attained.

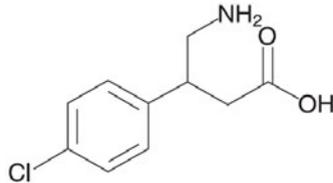
Physostigmine may not be effective in reversing large overdoses and patients may need to be maintained with respiratory support.

If lumbar puncture is not contraindicated, consideration should be given to withdrawing 30 to 40 mL of CSF to reduce CSF baclofen concentration.

11 DESCRIPTION

GABLOFEN (baclofen injection) is a muscle relaxant and antispastic. Baclofen's pharmacological class is a gamma-aminobutyric acid (GABA) ergic agonist. Baclofen's chemical name is 4-amino- 3-(4-chlorophenyl) butanoic acid, and its structural formula is:

Baclofen



Baclofen is a white to off-white, odorless or practically odorless crystalline powder, with a molecular weight of 213.66. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of action of baclofen as a muscle relaxant and antispasticity agent is not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Baclofen is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and may exert its effects by stimulation of the GABA_B receptor subtype.

Baclofen when introduced directly into the intrathecal space permits effective CSF concentrations to be achieved with resultant plasma concentrations 100 times less than those occurring with oral administration. In people, as well as in animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

12.2 Pharmacodynamics

Intrathecal Bolus

Adult Patients

The onset of action is generally one-half hour to one hour after an intrathecal bolus. Peak spasmolytic effect is seen at approximately four hours after dosing and effects may last four to eight hours. Onset, peak response, and duration of action may vary with individual patients depending on the dose and severity of symptoms.

Pediatric Patients

The onset, peak response and duration of action is similar to those seen in adult patients.

Continuous Infusion

Adult Patients

Intrathecal baclofen's antispastic action is first seen at 6 to 8 hours after initiation of continuous infusion. Maximum activity is observed in 24 to 48 hours.

Pediatric Patients

No additional information on continuous infusions is available for pediatric patients.

12.3 Pharmacokinetics

The pharmacokinetics of cerebrospinal fluid (CSF) clearance of intrathecal baclofen calculated from intrathecal bolus or continuous infusion studies approximates CSF turnover, suggesting elimination is by bulk-flow removal of CSF.

Intrathecal Bolus

After a bolus lumbar injection of 50 mcg or 100 mcg intrathecal baclofen in seven patients, the average CSF elimination half-life was 1.51 hours over the first four hours and the average CSF clearance was approximately 30 mL/hour.

Continuous Infusion

The mean CSF clearance for intrathecal baclofen was approximately 30 mL/hour in a study involving ten patients on continuous intrathecal infusion. Concurrent plasma concentrations of baclofen during intrathecal administration are expected to be low (0 to 5 ng/mL). Limited pharmacokinetic data suggest that a lumbar-cisternal concentration gradient of about 4:1 is established along the neuroaxis during baclofen infusion. This is based upon simultaneous CSF sampling via cisternal and lumbar tap in 5 patients receiving continuous baclofen infusion at the lumbar level at doses associated with therapeutic efficacy; the interpatient variability was great. The gradient was not altered by position. Six pediatric patients (age 8 to 18 years) receiving continuous intrathecal baclofen infusion at doses of 77 to 400 mcg/day had plasma baclofen levels near or below 10 ng/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No increase in tumors was seen in rats receiving baclofen orally for two years at approximately 30 to 60 times on a mg/kg basis, or 10 to 20 times on a mg/m² basis, the maximum oral dose recommended for human use. Mutagenicity assays with baclofen have not been performed.

14 CLINICAL STUDIES

Spasticity of Spinal Cord Origin

Evidence supporting the efficacy of intrathecal baclofen was obtained in randomized, controlled investigations that compared the effects of either a single intrathecal dose or a three day intrathecal infusion of intrathecal baclofen to placebo in patients with severe spasticity and spasms due to either spinal cord trauma or multiple sclerosis. Intrathecal baclofen was superior to placebo on both principal outcome measures employed: change from baseline in the Ashworth rating of spasticity and the frequency of spasms.

Spasticity of Cerebral Origin

The efficacy of intrathecal baclofen was investigated in three controlled clinical trials; two enrolled patients with cerebral palsy and one enrolled patients with spasticity due to previous brain injury. The first study, a randomized controlled cross-over trial of 51 patients with cerebral palsy, provided strong, statistically significant results; intrathecal baclofen was superior to placebo in reducing spasticity as measured by the Ashworth Scale. A second cross-over study was conducted in 11 patients with spasticity arising from brain injury. Despite the small sample size, the study yielded a nearly significant test statistic ($p=0.066$) and provided directionally favorable results. The last study, however, did not provide data that could be reliably analyzed.

16 HOW SUPPLIED/STORAGE AND HANDLING

GABLOFEN (baclofen injection) is available in a single use syringe of 1 mL containing 50 mcg (50 mcg/mL) and in single use syringes and vials of 10,000 mcg per 20 mL (500 mcg/mL), 20,000 mcg per 20 mL (1,000 mcg/mL), and 40,000 mcg per 20 mL (2,000 mcg/mL) for intrathecal administration only.

50 mcg per mL

NDC 45945-151-01: 1 mL Syringe – 50 mcg per 1 mL

500 mcg per mL

NDC 45945-155-01: 20 mL Syringe – 10,000 mcg per 20 mL

NDC 45945-155-02: 20 mL Vial – 10,000 mcg per 20 mL

1,000 mcg per mL

NDC 45945-156-01: 20 mL Syringe – 20,000 mcg per 20 mL

NDC 45945-156-02: 20 mL Vial – 20,000 mcg per 20 mL

2,000 mcg per mL

NDC 45945-157-01: 20 mL Syringe – 40,000 mcg per 20 mL

NDC 45945-157-02: 20 mL Vial – 40,000 mcg per 20 mL

Does not require refrigeration.

Do not store above 86°F (30°C).

Do not freeze.

Do not heat sterilize.

17 PATIENT COUNSELING INFORMATION

Risks Related to Sudden Withdrawal of GABLOFEN

Advise patients and caregivers that sudden withdrawal of GABLOFEN, regardless of the cause, can result in serious complications that include high fever, confusion, muscle stiffness, multiple organ-system failure, and death. Inform patients that early symptoms of GABLOFEN withdrawal may include increased spasticity, itching, and tingling of extremities. If GABLOFEN

withdrawal or a pump malfunction is suspected, patients should be brought immediately to a hospital for assessment and treatment.

Inform patients and caregivers that sudden withdrawal occurs most frequently due to a delivery problem with the catheter or the pump, or failure to refill the pump on schedule. Advise patients and their caregivers to pay careful attention to infusion system alarms. Instruct patients and caregivers that if they miss their scheduled pump refill, they should immediately contact their physician to reschedule the refill before the pump runs out of drug.

GABLOFEN Overdose

Inform patients and their caregivers that GABLOFEN overdose may occur suddenly or insidiously, and that symptoms may include confusion, drowsiness, lightheadedness, dizziness, slow or shallow breathing, seizures, loss of muscle tone, loss of consciousness, and coma. If an overdose appears likely, patients should be brought immediately to a hospital for assessment and possible emptying of the pump.

Operation of Automobiles and Other Dangerous Machinery

Advise patients that GABLOFEN may cause drowsiness, and that they should exercise caution regarding the operation of automobiles or other dangerous machinery, or activities made hazardous by decreased alertness.

Increased Risk of Drowsiness with Alcohol and Other CNS Depressants

Inform patients and their caregivers that the drowsiness associated with GABLOFEN use can be worsened by alcohol and other CNS depressants. Advise patients to read all medicine labels carefully, and to tell their physician about all prescription and nonprescription drugs they may use.

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Distributed by:
Mallinckrodt Brand Pharmaceuticals, Inc.
Hazelwood, MO 63042 USA

Issued 02/2015

P/N: 750-0543



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-462/S-008

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	NDA 22,462 (Supp#008)
Sponsor:	Mallinckrodt Pharmaceuticals
Drug:	Gablofen (Baclofen solution) Prefilled Syringes for Intrathecal administration
Proposed Indication:	Sever Spasticity
Material Submitted:	Prior Approval Supplement
Correspondence Date:	May 14, 2014
Date Received / Agency:	May 15, 2014
Date Review Completed	November 10, 2014
Reviewer:	Gerald D. Podskalny, DO, MPHS Medical Reviewer, DNDP, ODE I

1. Introduction

Gablofen (baclofen injection) is administered through an implanted intrathecal pump manufactured by separate device manufactures (Medtronic (b) (4)) for the treatment of severe spasticity in adults and children (age 4 and above). Gablofen (baclofen injection) was approved as a 50 mcg/mL prefilled syringe and as a 500 mcg/mL, 2000 mcg/mL, (b) (4) vial, on November 19, 2010. Supplement 4 that added Gablofen packaged in prefilled syringes for the 500mcg/mL, 1000 mcg/mL and 2000 mcg/mL strengths, was approved on January 17, 2013.

Mallinckrodt submitted a (b) (4)
The PAS was submitted on May 14, 2014, (b) (4)

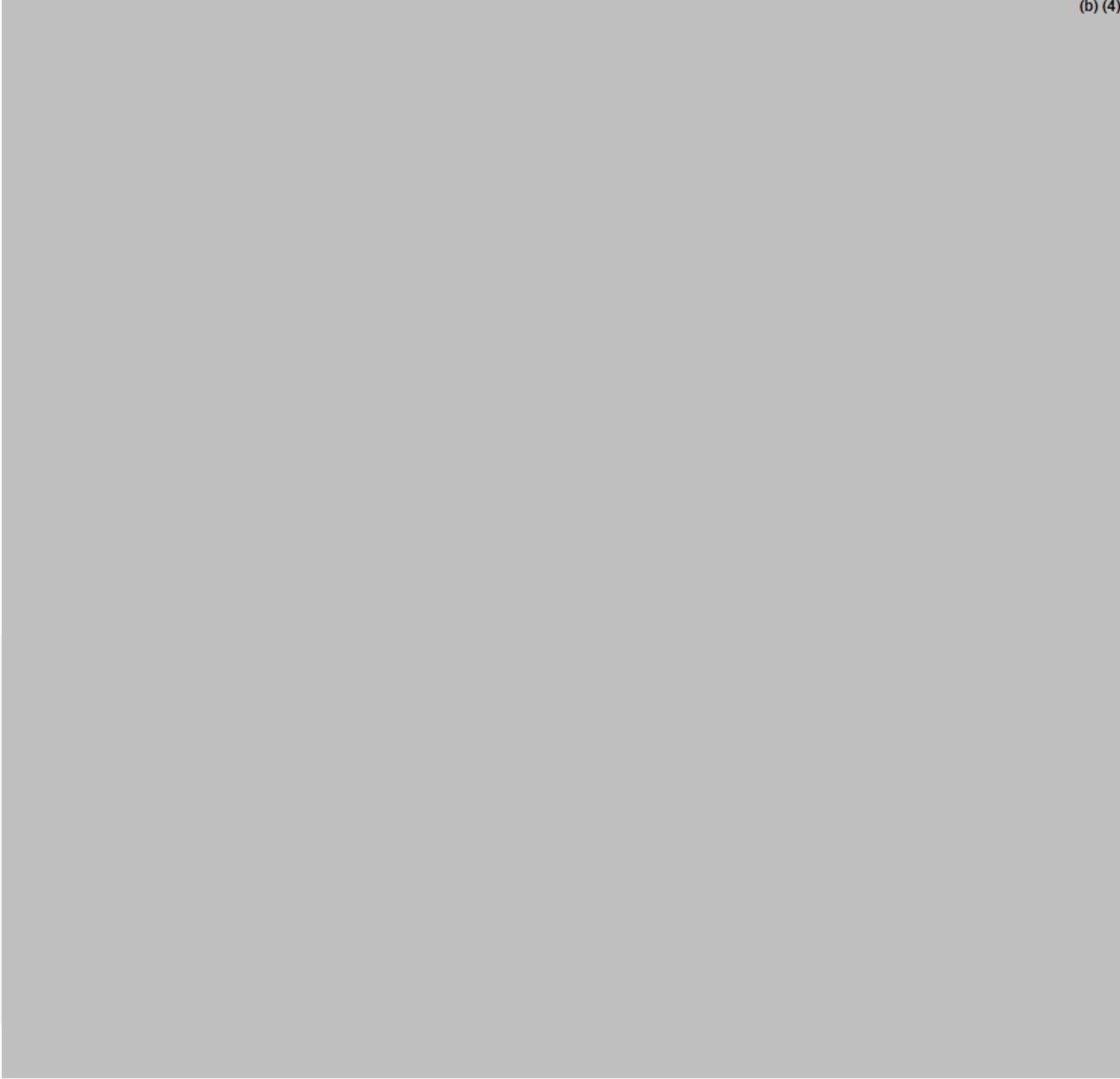
The cover letter that accompanied the PAS explained that: “The Gablofen 500 mcg/mL, 1000 mcg/mL and 2000 mcg/mL drug product and pathway in 20 mL pre-filled syringes are sterile; however, field use has shown the desire by care providers to bring the 20 mL pre-filled syringe into an environment that requires sterility”. The external surface of the Gablofen PFS is not sterile. However, the packaging in a sterile peel back container gives the appearance that the exterior of the syringe is sterile. The Sponsor is ware of cases where the Gablofen PFS was presumed to have a sterile exterior and it was used in the operating room where it was placed in the sterile field contaminating the aseptic environment (Mallinckrodt DHPC November 15, 2013).

The Division held a teleconference with the Sponsor on September 2, 2014. The sponsor was asked by the Division to explore the timeline needed to implement a change in the (b) (4) Gablofen PFS. The sponsor agreed to provide a response within two weeks. Instead, the sponsor replied in writing, on September 26, 2014, informing the Agency that they will not to pursue

(b) (4) of the Gablofen PFS. The sponsor proposed (b) (4)
(b) (4)
The proposal included (b) (4)
(b) (4)

2. Clinical Safety Information

Mallinckrodt's (b) (4) Warning Statement (b) (4)



Mallinckrodt's Final Printed Package Label



(b) (4)

Excerpt from Mallinckrodt's Response Letter

- *There have been no reports of any product contamination or infections that are possibly related to the outside of the syringe not being sterilized. There are no safety reports and no quality complaints on this topic.*
- *Historically, Lioresal ampoules are not sterile on the outside and have been used for over 40 years without significant safety concern. Further, the Gablofen vials are also not sterile on the outside of the vial.*
- *Even without sterilization, given these are glass syringes and there is no moisture present on the outside of the syringe, the bioburden is extremely low.*
- *The drug contents, syringe tip and drug pathway are all completely sterile. Further, to help reduce any potential of infection caused by poor handling technique, the infusion line has a 0.2 μm filter that would remove any possible contamination. Finally, the SynchroMed II pump itself has a 0.2 μm filter from the pump reservoir to the intrathecal catheter. These precautions are mainly implemented in the event of mishandling of the product during the assembly of the infusion system.*

(b) (4)

Mallinckrodt suggests that the most prudent action to address the Agency concern is to ensure (b) (4)

Therefore, (b) (4) *Mallinckrodt is proposing the following actions:*

(b) (4)

Mallinckrodt believes that the concern raised by the Agency is best managed by these (b) (4)

Reviewer Comment:

Mallinckrodt response dated September 26, 2014, does not address the important safety issues communicated to the company during the September 2, 2014, teleconference. The sponsor agrees that it is unacceptable to use an unsterile Gablofen PFS in the operating room to fill an intrathecal baclofen pump for the first time as suggested by their statement in the DHCP letter. The potential still exists for the surgeon to unknowingly contaminate (through contact with the Gablofen PFS) and implant an intrathecal pump in the patient. Gablofen is used primarily to fill the Medtronic SynchroMed II Implantable Intrathecal Pumps.

Instructions for Use Medtronic SynchroMed II Implant Manual September 2011, Page 15

Preparing for pump implant

1. Assemble equipment and supplies.

Sterile items

- The pump package containing the pump, 22-gauge noncoring needle (for filling the pump), and 24-gauge noncoring needle (for flushing the catheter access port)
- Empty 20-mL syringes (for emptying the pump)
- 0.22- μ m (micron) filter
- Syringe containing prescribed fluid (volume not to exceed the reservoir volume of the pump)
- 10-mL syringe with 1–2 mL of sterile, preservative-free saline (for flushing the catheter access port)

Nonsterile items

- Medtronic clinician programmer

The intrathecal pump manufacture's (Medtronic) pump fill Instruction for Use describe the use of all sterile component for the pump filling procedure in the operation room. The CDC considers all implanted devices as critical components that should be sterilized using the most effective means of sterilization and handling with strict adherence to aseptic technique.

The Sponsor's rationale that the risk for infection is mitigated by the pumps internal filtration system does not effectively protect against contamination of the exterior of the pump immediately before implantation. The comment that there is "low bioburden" on the exterior of the PFS, affirms the risk for contamination. The current Instructions for Use are insufficient for maintaining aseptic surgical technique or mitigate the risk for infection caused by implantation of a contaminated intrathecal baclofen pump.

Adverse event reporting has shown that implanted pumps delivering intrathecal medication have had a background infection rate since their inception. Implantation of a contaminated intrathecal baclofen pump would be reported as a postoperative infection (wound infection or meningitis), making it difficult to identify these events and attribute them to the Gablofen PFS. In addition, postmarketing reports frequently do not identify the specific product as being the PFS versus Gablofen from a vial or Lioresal also making it difficult to attribute infections to the use of the PFS.

The Centers for Disease Control recently proposed changes to the ICD-19 codes to attempt to capture information regarding mechanical failure and infections related to intrathecal pumps. These changes to the ICD-10 codes are specifically meant to address the difficulty in tracking the frequency of these events.

Centers for Disease Control and Prevention ICD-10 Coordination and Maintenance Committee Meeting, March 19-20, 2014

Diagnosis Agenda

“Mechanical Complications of Neurostimulators”

“Mechanical Complications of Other Nervous System Devices ICD-10-CM has no codes specifically defined for mechanical complications of any nervous system devices beyond ventricular shunts and neurostimulators. For example, no specific codes exist for mechanical complication of implanted intrathecal infusion pump. Also, while there are existing codes for mechanical complications of epidural and subdural infusion catheter, implanted intrathecal infusion catheters are subarachnoid. It should also be clarified that these codes can be applied to both cranial and spinal catheters in the epidural, subdural and subarachnoid spaces.”
(Centers for Disease Control and Prevention , 2014)

“Infection and Inflammatory Reaction”

“Infections of the nervous system, particularly of the brain and spinal cord, can be very serious. However, ICD-10-CM currently has no specific code for infection and inflammatory reaction due to nervous system devices, either as a general subcategory or for specific nervous system devices. This detail is currently present in ICD-9-CM, at code 996.63, Infection and inflammatory reaction due to nervous system device, implant and graft. In the current draft of ICD-10-CM, this is indexed to code T85.79, Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts. There is no specificity for nervous system devices in this code. It is proposed to create codes to restore this detail as well as further specify these devices similar to codes for mechanical complications for these found in subcategories T85.0, T85.1, and T85.6.”
(Centers for Disease Control and Prevention , 2014)

Although with adequate warning and careful attention to maintaining aseptic technique, the PFS may be used safely to refill an implanted baclofen pump in outpatients. The PFS remains the only unsterile component used in the refill procedure and providers will have to modify the refill procedure to prevent contamination of the sterile field.

Medtronic Refill Kit for use with Medtronic Implantable Programmable Infusion Pumps February 2014, Page 11.

Instructions for use

Become thoroughly familiar with all product literature before using this refill kit.

Sterilization

All components of the kit are sterile. Do not resterilize. Should sterility of the kit be in question, discard and use a new kit.

Preliminary procedures

1. Gather the following sterile equipment:

From the refill kit:

- Extension set with a clamp
- 0.22-micron filter
- 22-gauge noncoring needle
- 20-mL empty syringe
- Fenestrated drape
- Template

Locally supplied:

- Syringe(s) containing prescribed fluid
- Cleansing agent
- Sterile gloves (not made with natural rubber latex)
- Alcohol pads or swabs
- Adhesive bandage, optional

The Sponsor reported sending a Dear Health Care Provider (DHCP) letter dated November 15, 2013, to “potential Gablofen users”. The Sponsor claimed they sent the DHCP letter “in response to inquiries from health care professionals and not due to any known or suspected safety risk”.

Excerpt from the Gablofen DHCP Letter (November 15, 2013)

“While Gablofen is a sterile solution intended for intrathecal administration, the external surfaces of the prefilled syringes are NOT pre-sterilized. The syringe is packaged within a peel-back blister pack. When the top of the packaging is peeled back, the exposed components of the syringe and packaging are NOT sterilized. Only the syringe tip, which is covered by a screw off cap, and the Gablofen solution are sterile.”

The letter does not instruct providers not to use the Gablofen prefilled syringe in the operating room because of the risk of contamination. It also does not does not instruct providers to modify aseptic technique to prevent contamination of sterile components used to refill intrathecal pumps. The letter remained silent about the sterility of the 50mcg/mL prefilled syringe used to administer the test dose of Gablofen.

CDRH Inter-center Consult Recommendation:

“The proposed statement “Drug and drug pathway sterile, syringe exterior not sterile” addition to the labeling is acceptable. The location of the statement on the labeling is not ideal. When a health care provider examines a drug label package, they will primarily look at the drug name, dosage, route of administration and expiration date. The current location of the statement is located on the far right of the package label. The label addition statement regarding sterility is recommended to be located on the left side of the

package label close to the drug name and dosage or under the statement “Sterile solution for intrathecal use only.”

CDRH also recommends that you consult DMEPA regarding the proposed addition to the drug labeling.”

DMEPA consultant’s comments to the Sponsor regarding the proposed

(b) (4)

(b) (4)

3. Conclusions

(b) (4)

The SynchroMed II Pump Insertion Manual, Instruction for Use section, states the pump filling is accomplished using all sterile components. Mallinckrodt cannot include a warning about the Gablofen prefilled Syringe in the Pump Insertion Manual because the manual is proprietary to the pump manufacturer (Medtronic). The changes proposed by the sponsor to

(b) (4)

There are baclofen injection products that are available and comply with the Instructions for Use for pump filling prior to implantation. Although baclofen solution (Gablofen and Lioresal) is packaged in ampules or vials that are not sterile, they do not give the appearance that they are sterile. Drug from a vial or ampule is transferred from the unsterile vial or ampule into a sterile syringe that has a sterile drug pathway and exterior surface, before it is used to fill the pump.

Recommendation:

I recommend a **Complete Response** action for this Prior Approval Supplement. We should request the sponsor submit a new Prior Approval Supplement to add a new entry to Section 5 of the product label, Warnings and Precautions, pursuant to Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA). The new language should warn

prescribers that the external surface of all strengths of the Gablofen prefilled syringe, including the 50mcg/mL strength is not sterile. Instruct prescribers not to use Gablofen prefilled syringes to fill sterile intrathecal infusion pump in the operating room, prior to implanting an intrathecal pump into patients. Warn providers who use Gablofen prefilled syringe to refill implantable intrathecal pumps in the outpatient setting to modify their procedure to avoid contamination of sterile surfaces through contact with the unsterile exterior of the Gablofen prefilled syringe.

The Sponsor's proposal to (b) (4) stating "Drug and drug pathway sterile, syringe exterior not sterile" on the exterior of the packaging labeling is acceptable with the modification described in DMEPA's labeling comments. The sponsor also needs to submit the (b) (4) permanent revisions to the printed package label with the supplement that adds a statement describing this issue in the Warnings and Precautions section of the product label

4. Bibliography

- Alicia J. Mangram, M., Teresa C. Horan, M. C., Michele L. Pearson, M., Leah Christine Silver, B., & William R. Jarvis, M. (1999). *Guideline for Prevention of Surgical Site Infection 1999*. Atlanta: Infectious Diseases Centers for Disease Control and Prevention Public Health Service US Department of Health and Human Services.
- Centers for Disease Control and Prevention I. (2014). *ICD-10 Coordination and Maintenance Committee Meeting March 19-20, 2014 Diagnosis Agenda*. Atlanta: Centers for Disease Control and Prevention ICD-10 Coordination and Maintenance Committee Meeting.
- Medtronic Inc. (2011, September). *SYNCHROMED® II Programmable Pumps Implant Manual*. Medtronic Inc.
- Medtronic Inc. (2014, February). *Medtronic Refill Kit for use with Medtronic Implantable Programmable Infusion Pumps*. Medtronic Inc.

Gerald D. Podskalny, DO, MPHS
Medical Reviewer – DNDP ODE I

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HFD-120
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/s/

GERALD D PODSKALNY
11/14/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-462/S-008

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 6, 2015
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 022462/S-008
Product Name and Strength: Gablofen (Baclofen Injection),
5 mcg/mL, 500 mcg/mL, 1000 mcg/mL, 2000 mcg/mL
Submission Date: February 5, 2014
Applicant/Sponsor Name: Mallinckrodt
OSE RCM #: 2015-62-1
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised carton and container labels and labeling and prescribing information (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised carton and container labels and labeling and prescribing information are acceptable from a medication error perspective.

¹ Harris, J. Label and Labeling Review for Gablofen (NDA 022462/S-008). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 DEC 17. 8 p. OSE RCM No.: 2014-1154.

APPENDIX A. LABEL AND LABELING

APPENDIX A.1 TRAY LABELS (SUBMITTED FEBRUARY 5, 2015)

NDC 45945-151-01 Contains one x 1 mL

Gablofen[®]
(baclofen injection)

50 mcg/mL

For intrathecal use only
**Drug and drug pathway sterile,
syringe exterior not sterile**
Single Use Syringe—
Discard Unused Portion

Rx only **LATEX FREE**

 **Mallinckrodt[™]**
Pharmaceuticals


780-05890-2 Rev 02/2015




NDC 45945-155-01 Contains one x 20 mL syringe

Gablofen[®]
(baclofen injection)

**10,000 mcg/20 mL
(500 mcg/mL)**

Sterile solution for intrathecal use only
Drug and drug pathway sterile, syringe exterior not sterile
Rx only
For Maintenance Dosing with Intrathecal Pump.
Single Use Syringe—Discard Unused Portion

 **Mallinckrodt[™]**
Pharmaceuticals

Distributed by: Mallinckrodt Brand Pharmaceuticals, Inc.
Hazelwood, MO 63042 USA


780-05807-1 Rev 02/2015




NDC 45945-156-01 Contains one x 20 mL syringe

Gablofen[®]
(baclofen injection)

**20,000 mcg/20 mL
(1,000 mcg/mL)**

Sterile solution for intrathecal use only
Drug and drug pathway sterile, syringe exterior not sterile
Rx only
For Maintenance Dosing with Intrathecal Pump.
Single Use Syringe—Discard Unused Portion

 **Mallinckrodt[™]**
Pharmaceuticals

Distributed by: Mallinckrodt Brand Pharmaceuticals, Inc.
Hazelwood, MO 63042 USA


780-05812-1 Rev 02/2015






APPENDIX A.2 CARTON LABELS (SUBMITTED FEBRUARY 5, 2015)



Do not use if syringe contains precipitate.
Dosage: See package insert for complete prescribing information.
 Does not require refrigeration. Do not store above 86°F (30°C).
 Do not freeze. Do not heat-sterilize.



NDC 45945-155-01

Gablofen[®]
(baclofen injection)

10,000 mcg/20 mL
(500 mcg/mL)

For intrathecal use only
Drug and drug pathway sterile, syringe exterior not sterile

Rx only
 Single Use Syringe- Discard Unused Portion

Contains one x 20 mL syringe

Gablofen[®]
(baclofen injection)
10,000 mcg/20 mL
(500 mcg/mL)
 For intrathecal use only



800-654420 Rev 02/2015

Hazelwood, MO 63042 USA
 Distributed by:
 Mallinckrodt Brand Pharmaceuticals, Inc.

Syringe contains baclofen USP 10 mg, sodium chloride USP 180 mg
 in Water for Injection USP to equal 20 mL.

NDC 45945-155-01

Gablofen[®]
(baclofen injection)

10,000 mcg/20 mL
(500 mcg/mL)

For intrathecal use only
Drug and drug pathway sterile, syringe exterior not sterile

Rx only
 Single Use Syringe-Discard Unused Portion

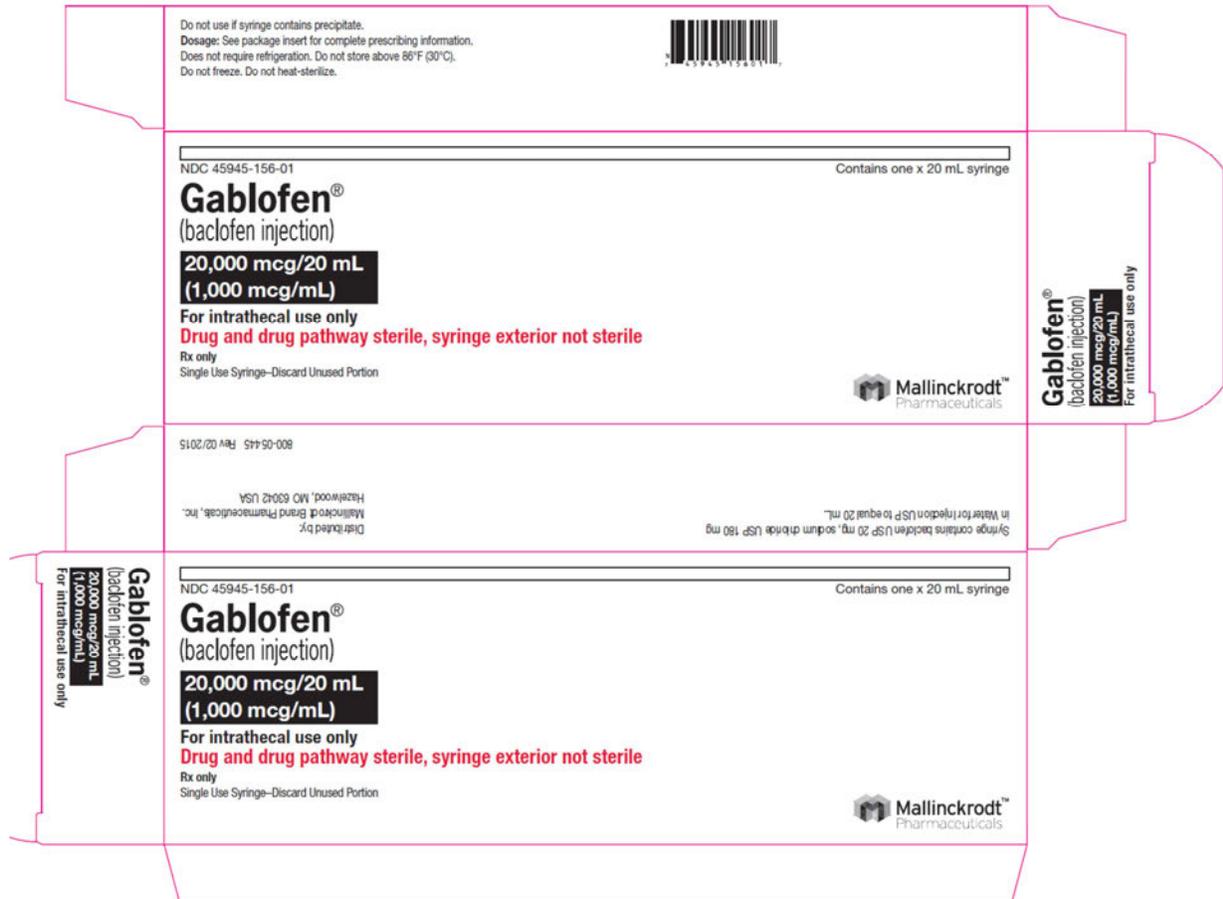
Contains one x 20 mL syringe

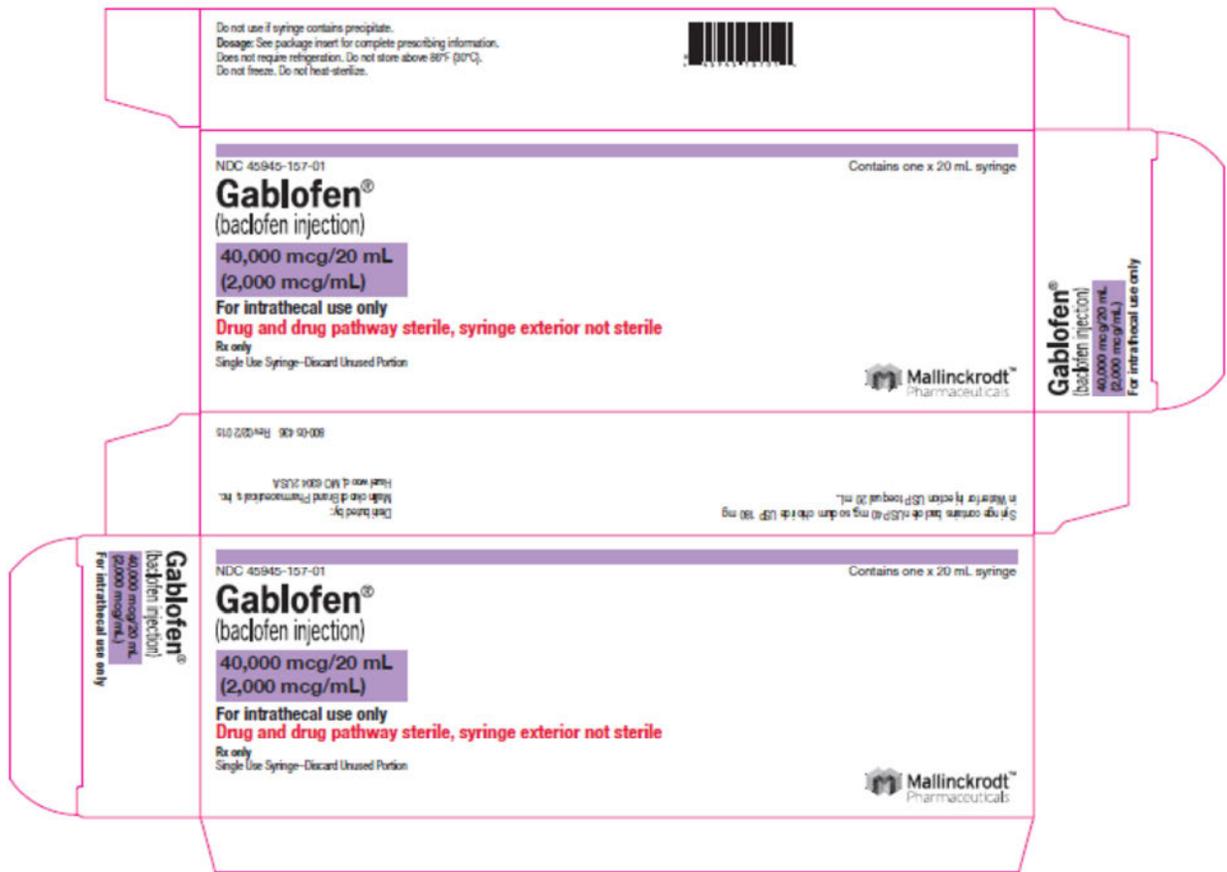


Gablofen[®]
(baclofen injection)
10,000 mcg/20 mL
(500 mcg/mL)
 For intrathecal use only

4

Reference ID: 3698515





A. 3 PRESCRIBING INFORMATION (SUBMITTED FEBRUARY 4, 2015): NO IMAGE

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/s/

JUSTINE HARRIS
02/06/2015

IRENE Z CHAN
02/06/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 12, 2015
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 022462/S-008
Product Name and Strength: Gablofen (Baclofen Injection),
50 mcg/mL, 500 mcg/mL, 1000 mcg/mL, 2000 mcg/mL
Submission Date: December 17, 2014
Applicant/Sponsor Name: Mallinckrodt
OSE RCM #: 2015-62
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Team Leader: Irene Z. Chan, PharmD, BCPS

1 PURPOSE OF MEMO

Division of Neurology Products (DNP) requested that we review the revised tray labels, carton labeling, and Prescribing Information (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container label, carton labeling, and Prescribing Information (PI) is unacceptable from a medication error perspective. The language of the cautionary statement “Drug and drug pathway sterile, syringe exterior not sterile” on the container label is acceptable; however, the statement should be made more prominent to prevent healthcare professionals (HCP) from

¹ Harris, J. Label and Labeling Review for PRODUCT NAME (NDA 022462/S-008). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 AUG 01. 11 p. OSE RCM No.: 2014-1154.

missing this important information. In addition, although we did not review the carton labeling in our prior review nor were they submitted this review cycle under this supplement, we determined that adding the sterility warning on the carton labeling is also needed.

Furthermore, we recommend that information be added to the Dosage and Administration section of the PI, which will alert HCPs that the external surface of the prefilled syringes is non-sterile. We have the following recommendations

2.1 RECOMMENDATIONS FOR THE DIVISION:

A. Prescribing Information

1. Include cautionary statements to Section 2. Dosage and Administration section of the PI informing HCPs that the external surface of the prefilled syringes is non-sterile.
2. Consider adding a statement regarding sterility to the *Highlights of the Prescribing Information*.

2.2 RECOMMENDATIONS FOR MALLINCKRODT

A. Tray labels:

Increase the prominence of the cautionary statement “Drug and drug pathway sterile, syringe exterior not sterile” by enlarging the font size and using colored text to minimize the risk of this important information being overlooked.

B. Carton labeling:

For consistency and to alert HCPs initially when interfacing with the product, add the cautionary statement “Drug and drug pathway sterile, syringe exterior not sterile” to the carton labeling.

APPENDIX A. LABEL AND LABELING

A.1 Tray Labels (submitted December 17, 1014)

(b) (4)



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/s/

JUSTINE HARRIS
01/12/2015

LUBNA A MERCHANT on behalf of IRENE Z CHAN
01/12/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: August 1, 2014
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 022462/S-008
Product Name and Strength: Gablofen (Baclofen Injection),
5 mcg/mL, 500 mcg/mL, 1000 mcg/mL, 2000 mcg/mL
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Mallinckrodt
Submission Date: May 14, 2014
OSE RCM #: 2014-1154
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Acting Team Leader: Tingting Gao, PharmD

1 REASON FOR REVIEW

Mallinckrodt submitted a Prior Approval Labeling Supplement (NDA 022462/S-008) to propose the addition of a statement, “Drug and drug pathway sterile, syringe exterior not sterile” to the final packaging labeling to communicate to the end users that the exterior part of the packaged syringe is not sterile. Thus, the Division of Neurology Products (DNP) requested that we review the submitted Gablofen (Baclofen) Injection packaging labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D – N/A
ISMP Newsletters	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified one case of potential medication error from FAERS search describing a potential source of contamination with Gablofen syringe because the packaging gives the appearance that the syringe is ready for a sterile field. The reporter stated the syringe packaging has been opened and the Gablofen syringe has been dropped onto a sterile field when used in the Operating Room setting, and could be an infection risk. However, no infections have been traced back to this source of potential contamination.

After evaluation of the packaging labeling (b) (4) for packaging, we determined that the proposed cautionary statement addition to the packaging labeling is acceptable but could be improved to improve readability. Specifically, we recommend that the cautionary statement “Drug and drug pathway sterile, syringe exterior not sterile” be placed in the same orientation with the rest of the text on the packaging labeling and relocated to the left side of the packaging labeling as this is where the health care practitioner will first look to examine the

labeling prior to use. In addition, we recommend that the cautionary statement be made more prominent by enlarging the font size, using bold lettering, and/or colored text to minimize the risk of this important information being overlooked.

4 CONCLUSION & RECOMMENDATIONS

The packaging labeling (b) (4) for the packaging for Gablofen may be improved to communicate important use information and to improve prominence of the cautionary statement. We recommend the following revisions be implemented at the next scheduled printing of packaging labeling.

4.1 RECOMMENDATIONS FOR MALLINCKRODT

A. Packaging labeling

Relocate the proposed statement “Drug and drug pathway sterile, syringe exterior not sterile” to the left side of the packaging labeling as this is where the health care practitioner will first look to examine the labeling prior to use. In addition, we recommend that you increase the prominence of the cautionary statement by enlarging the font size, using bold lettering, and/or colored text to minimize the risk of this important information being overlooked. Ensure that the proposed statement “Drug and drug pathway sterile, syringe exterior not sterile” is in the same orientation with the rest of the text on the packaging labeling to improve readability.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gablofen that Mallinckrodt submitted on July 13, 2012 (in NDA 022462/S-004 since Mallinckrodt did not provide a prescribing information labeling with supplement 008).

Table 2. Relevant Product Information for Gablofen	
Initial Approval Date	November 19, 2010
Active Ingredient	Baclofen
Indication	Management of severe spasticity of cerebral or spinal origin in adult and pediatric patients age 4 years and above
Route of Administration	Intrathecal
Dosage Form	Solution for Injection
Strength	5 mcg/mL, 500 mcg/mL, 1000 mcg/mL, 2000 mcg/mL
Dose and Frequency	<p>Screening dose:</p> <ul style="list-style-type: none"> • 50 mcg to 100 mcg intrathecal bolus; if patient responds to screening dose, Gablofen should be titrated to maintain some degree of muscle tone and allow occasional spasms. <p>Maintenance Dose:</p> <ul style="list-style-type: none"> • For Spasticity of Spinal Cord Origin Patients: Maintenance dosage for long term continuous infusion of intrathecal baclofen has ranged from 12 mcg/day to 2,003 mcg/day, with most patients adequately maintained on 300 mcg/day to 800 mcg/day. • For Spasticity of Cerebral Origin Patients: Maintenance dosage for long term continuous infusion of intrathecal baclofen has ranged from 22 mcg/day to 1,400 mcg/day, with most patients adequately maintained on 90 mcg/day to 703 mcg/day.
How Supplied	<p>Single use pre-filled syringe:</p> <ul style="list-style-type: none"> • 50 mcg/mL – 1 mL pre-filled syringe • 10,000 mcg/20 mL (500 mcg/mL) • 20,000 mcg/20 mL (1,000 mcg/mL) • 40,000 mcg/20 mL (2,000 mcg/mL)

	Single use vials: <ul style="list-style-type: none">• 10,000 mcg/20 mL (500 mcg/mL)• 20,000 mcg/20 mL (1,000 mcg/mL)• 40,000 mcg/20 mL (2,000 mcg/mL)
Storage	Does not require refrigeration. Do not store above 86°F (30°C). Do not freeze. Do not heat sterilize.
Container Closure	(b) (4)

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on June 12, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Table 3: FAERS Search Strategy	
Date Range	June 5, 2012* to June 12, 2014 *Date of last FAERS search in OSE Review # 2012-1114, NDA 022462
Product	baclofen [active ingredient] Gablofen [product name]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 59 cases; of which 1 case describe errors relevant for this review.

Potential contamination (n=1)

One case described that the Gablofen syringe packaging gives the appearance that the syringe is ready for a sterile field. The reporter stated that the syringe packaging has been opened and the Gablofen syringe has been dropped onto a sterile field when used in the Operating Room setting, and could be an infection risk. However, the reporter stated that no infections have been traced back to this source of potential contamination.

We excluded 58 cases because they described adverse drug reaction not related to medication error (n=5), Lioresal (n=2), events involved in pump or catheter issues (n=33), and medication errors not relevant to the subject of this review (n=18).

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case Number	Version	Manufacturer Control Number
9625065	1	Not provided

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on June 12, 2014 using the terms, baclofen to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified two previous reviews following reviews^{1,2} and we confirmed that our previous recommendations were implemented.

¹ Neshiewat, J. Label and Labeling Review for Gablofen (Baclofen Injection) (NDA 022462/S-004). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 July 24. 16 p. RCM 2012-1114.

² Neshiewat, J. Final label, labeling, and packaging review of Gablofen (Baclofen Injection) (NDA 022462/S-004). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 December 18. 7 p. RCM 2012-2250.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on June 12, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing
Search Strategy and Terms	Match Exact Word or Phrase: baclofen

E.2 Results

The search did not retrieve any relevant articles for this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Gablofen labels and labeling submitted by Mallinckrodt on May 14, 2014.

(b) (4)

- Packaging labeling

G.2 Label and Labeling Images



³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE HARRIS
08/04/2014

TINGTING N GAO
08/04/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-462/S-008

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MANDATORY: Send a copy of the consult request form to the

Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: OMPT/CDRH/DAGRID/GHDB

Division:

Mail Code: HF

Consulting Reviewer Name:

Building/Room #:

Phone #:

Fax #:

Email Address: GHDBCPConsults@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER/OND

Division: Neurology Products

Mail Code: HF 120

Requesting Reviewer Name: Dave Podskalny, DO, Team Lead

Building/Room #: Bldg 22 Room 4205

Phone#: 301-796-2778 (RPM: 6-1932)

Fax #:

Email Address: RPM: Taura.Holmes@fda.hhs.gov

RPM/CSO Name and Mail Code: Taura Holmes, PharmD

Requesting Reviewer's Concurring

Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 06/11/14

Requested Completion Date: 07/11/14

Submission/Application Number: 22462/S-008
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: 05/15/14

Official Submission Due Date: 11/15/14

Name of Product: Baclofen

Name of Firm: Mallinckrodt Pharmaceuticals

Intended Use: Treatment of Spasticity

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

(b) (4)

(b) (4)

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

This request is for the collaborative review of the supplement to determine if the proposed addition is approvable. The meeting invite for this supplement will be provided upon reviewer assignment.

Of note, the previous reviewer assigned to this application was Ryan McGowan.

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/s/

TAURA N HOLMES
06/11/2014



NDA 22462/S-008

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Mallinckrodt Inc.
Attention: Bunny Bierman
Manager, Regulatory Affairs
675 McDonnell Boulevard
Hazelwood, MO 63042

Dear Ms. Bierman:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 22462
SUPPLEMENT NUMBER: 008
PRODUCT NAME: Gablofen (baclofen) injection 50 mcg/mL, 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL
DATE OF SUBMISSION: May 15, 2014
DATE OF RECEIPT: May 15, 2014

This supplemental application proposes the following change: addition of a statement to the final package labeling to [REDACTED] (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 14, 2014, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be November 15, 2014.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, contact me via email or telephone at Taura.Holmes@fda.hhs.gov or (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Taura Holmes, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

TAURA N HOLMES
06/03/2014