

| Parameters                   | Remarks  | Parameters                | Remarks                                 |
|------------------------------|--|---------------------------|---|
| Product name/Generic name    | Gablofen PI  | Market/Country            | USA                                     |
| Strength                     | N/A  | Barcode                   | N/A                                     |
| Component                    | Insert leaflet   | Material Code             | 750-0543-1M1-03                         |
| Dimensions                   | 17" x 11"  | Superseded Material Code  | 750-0543-1M1-02                         |
| Specification                | N/A  | Artwork Number            | N/A                                     |
| Font size & type             | 6pt. Helvetica LT Std  | Superseded Artwork Number | N/A                                     |
| Pantone number               | Process Black <span style="background-color: black; color: black;">█</span> DieLine - no print | MAH                       | N/A                                     |
| Cut Margins/Peel off Margins | N/A  | GTIN                      | N/A                                     |
| Unvarnished Zone             | N/A  | Special Instructions      | N/A                                     |
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## 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)

### INDICATIONS AND USAGE

GABLOFEN is a gamma-aminobutyric acid (GABA) ergic agonist indicated for use in the management of severe spasticity of cerebral or spinal origin in adult and pediatric patients age 4 years and above. (1)

GABLOFEN should be reserved for patients unresponsive to oral baclofen therapy, or those who experience intolerable central nervous system side effects at effective doses. (1)

Patients should first respond to a screening dose of intrathecal baclofen prior to consideration for long term infusion via an implantable pump. (1)

Spasticity due to traumatic brain injury: wait at least one year after injury before considering GABLOFEN therapy. (1)

### DOSSAGE AND ADMINISTRATION

GABLOFEN is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use in the Medtronic SynchroMed® II Programmable Pump or other pumps labeled for intrathecal administration of GABLOFEN. Refer to the pump manufacturer's manual and follow the specific instructions and precautions for programming the pump and/or refilling the reservoir. (2.1)

Screening: Patients who do not respond to a 100 mcg intrathecal bolus should not be considered for an implanted pump for chronic infusion. (2.2)

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## 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

Dose Titration: Spasticity may be necessary to sustain upright posture and balance in locomotion or may be useful to obtain optimal function and care. (2.5)

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)

### DOSSAGE 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)

### 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 Piramal Critical Care, Inc. at 1-888-822-8431 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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)

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Revised: 10/2020

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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)*].

### 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)*].

### DOSSAGE AND ADMINISTRATION

#### 2.1 Use Only in 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 antispasitics 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 DOSSAGE FORMS AND STRENGTHS

GABLOFEN (baclofen injection) is available, for intrathecal use only, in:

- Single-dose syringe of 1 mL containing 50 mcg (50 mcg/mL)
- Single-dose syringes and vials of 10,000 mcg per 20 mL (500 mcg/mL)
- Single-dose syringes and vials of 20,000 mcg per 20 mL (1,000 mcg/mL)
- Single-dose syringes and vials of 40,000 mcg per 20 mL (2,000 mcg/mL)

### 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.

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



### 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, sequelae. 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 (≥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                        |
| Amylopia             | 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, arrhythmic 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 (≥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 (≥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

#### Risk Summary

There are no adequate data on the developmental risk associated with the use of GABLOFEN in pregnant women.

In animal studies, oral administration of baclofen to pregnant rats produced an increase in fetal malformations (*see Data*). There are no animal data on developmental risk associated with baclofen administered via continuous intrathecal infusion.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### Data

#### Animal Data

Baclofen given orally to pregnant rats has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses at a dose associated with maternal toxicity. This abnormality was not seen in mice or rabbits.

### 8.2 Lactation

#### Risk Summary

There is insufficient information regarding levels of baclofen in milk of nursing mothers receiving GABLOFEN. There are no adequate data on the effects of GABLOFEN on the breastfed infant or on milk production. At recommended oral doses, baclofen is present in human milk and withdrawal symptoms can occur in breastfed infants when maternal administration of baclofen is stopped or when breastfeeding is stopped.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GABLOFEN and any potential adverse effects on the breastfed infant from GABLOFEN or from the underlying maternal condition.

### 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 overdosage, 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:

- Residual intrathecal baclofen solution should be removed from the pump as soon as possible.
- 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

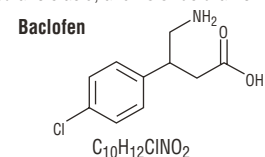
Administer 0.02 mg/kg physostigmine intramuscularly or intravenously, do not give more than 0.5 mg per minute. The dosage may be repeated at 5 to 10 minute intervals until a therapeutic effect is obtained or a maximum dose of 2 mg is attained.

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 is a white to off-white powder, with a molecular weight of 213.66. It is slightly soluble in water, very slightly soluble in methanol and ethanol, practically insoluble in acetone and ether, soluble in 0.1N hydrochloric acid, 0.1N sodium hydroxide, and insoluble in chloroform. 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 mL 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.

## 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<sub>B</sub> 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 are 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

Carcinogenesis: No increase in tumors was seen in rats receiving baclofen orally for two years.

#### Mutagenesis

Mutagenicity assays with baclofen have not been performed.

#### Impairment of Fertility