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

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Lioresal Intrathecal Package Insert

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Summary

Solubility and physical stability of 3 and 4mg/mL aqueous baclofen solutions were evaluated in a study undertaken by Novartis Pharmaceuticals Corporation, manufacturer of Lioresal® Intrathecal (baclofen injection), to determine if a formulation of baclofen at concentrations higher than those commercially available is a safe, viable option for further development. The results of the study demonstrate that precipitation occurs in concentrations above 2mg/mL, independent of several variables evaluated in the study. Consequently, there are numerous unsubstantiated risks associated with formulation of intrathecal baclofen above the commercially available 2mg/mL concentration. Of particular concern are the unknown risks associated with inaccurate dosing due to an altered concentration of the drug solution in the pump or potential clogging of the pump filter by precipitate. Given the unknown nature of these risks, use of intrathecal baclofen solution with SynchroMed® Programmable Drug Infusion Systems at concentrations higher than the commercially available 2mg/mL is inadvisable.

Introduction

With the FDA approved formulations of Lioresal Intrathecal available in concentrations of 0.5mg/mL and 2mg/mL, most patients are able to achieve a period of 60-90 days between refills.¹ The SynchroMed II System has enabled some patients to benefit from an increase in this refill interval; stability data in the SynchroMed II System supports refill intervals up to 180 days. However, certain populations of patients require higher daily doses of baclofen, and obtaining a desirable length of time between refills for these patients becomes difficult.²

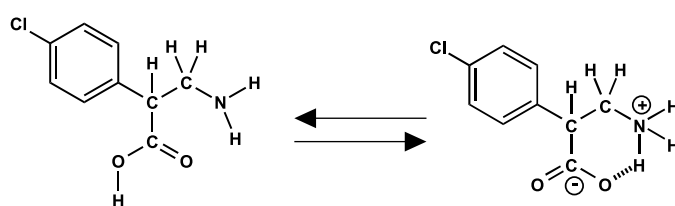
In the interest of extending refill intervals and providing clinicians and patients with the option to use higher concentrations of intrathecal baclofen than are currently commercially available, the feasibility of formulations containing more than 2mg/mL of baclofen in aqueous solution was investigated by Novartis Pharma AG, Basel, Switzerland.³

Methods and Materials

Baclofen, (RS)- β -(4-Chlorophenyl)- γ -aminobutyric acid, was obtained from Novartis Chemical Production in a quality for parenteral use. To comply with the specific requirements for parenteral and intrathecal injections, the last purification step is performed with water for injection as a solvent. The content of pyrogenic substances and the microbial count is tightly limited and monitored. All further quality parameters comply at

least with the requirements as stipulated by the current Pharmacopoeias (Ph. Eur., USP).

The drug substance is a derivative of gamma-amino butyric acid, and is used in its racemic mixture. Due to an amino as well as a carboxylic group it is able to form a zwitterionic structure in neutral solutions (close to physiological pH-values). Based on the vicinity of both groups, a hydrogen bond between both of these groups can be formed, thus stabilizing the zwitterionic structure. It is noted that the ionization constants (pKa) of the amino and carboxylic functional groups of baclofen are 9.62 and 3.87, respectively.⁴ The two functional groups remain charged in the pH range of 5.0 to 8.5, resulting in a low state of solubility. Moreover, it is possible for anhydrous baclofen to form hydrates, further decreasing the solubility.⁵



The saturation solubility of baclofen in aqueous media is still controversially discussed in the literature, data range from 2.09mg/mL⁶ to 7.5mg/mL.⁷ Therefore the feasibility of a higher-than-commercially-available strength cannot directly be derived from existing literature data.

Requirements for baclofen solution for intrathecal infusion

The current formulation was optimized to allow for best possible intrathecal tolerability and to ensure highest possible safety. To comply with these requirements, the specifications for the formulation trials described in this paper were set as follows:

- A purely aqueous solution with a pH-value between 5.5 and 7.0.
- Solutions to be isotonic to the cerebrospinal fluid which has an osmolality of approximately 300 mOsmol/kg (range 279 - 324).^{8,9} The requirement for osmolality was therefore set to be between 285 and 315 mOsmol/kg.
- Due to the very limited information on cerebrospinal tolerability of ionic and nonionic additives frequently used in formulation of parenteral drug products¹⁰, only sodium chloride was used for adjustment of the solution tonicity. For the same reasons it was decided not to add any buffer.

Preparation of baclofen solutions

Sterile baclofen solution is prepared by dissolving baclofen drug substance and sodium chloride in water for injection, filtered (0.2 μ m), and filled into particulate-free ampoules. The ampoules are sealed and terminally sterilized by moist heat. The finished drug conforms to the requirements for particulate matter in Ph. Eur 2.9.20.

Results

Saturation solubility of baclofen in isotonic sodium chloride solution

To determine the saturation solubility of baclofen in isotonic sodium chloride solution, a suspension of 0.5g of drug substance powder in 25 mL isotonic (0.9%) sodium chloride solution was prepared. The suspension was kept at 25.0 \pm 0.2°C, and was continuously stirred with a magnetic rod for 120 hours. Aliquots were periodically analyzed by HPLC for their content in dissolved baclofen drug substance.

At the beginning of the experiment, the anhydrous drug substance dissolved rapidly, such that dissolved baclofen concentrations up to 6.5mg/mL were obtained. Typically, upon contact with water, the less soluble hydrate modification of baclofen is formed in the suspension. This transformation showed to be quite slow and was not completed within 24 hours at 25°C. Even after 118 hours, the equilibrium was not reached, the saturation value achieved at that time was 4.6mg/mL (Figure 1).

Feasibility of baclofen injections with 3 or 4mg/mL

As no equilibrium could be obtained by determination of the saturation solubility in a reasonable time frame, solubilization experiments were made with the most desired concentrations of 3 and 4mg/mL.

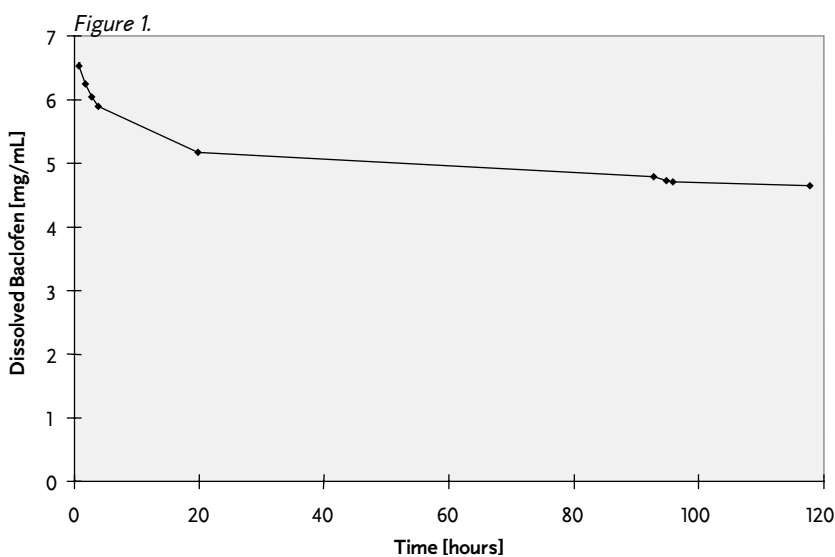
Dissolution of the 4mg/mL baclofen proved to be particularly difficult, resulting in a slightly opalescent solution showing that even at this concentration the saturation solubility of the baclofen hydrate was surpassed. The solution was filtered to remove the insoluble or precipitated portion. In contrast to the 4mg/mL strength the lower strengths could be prepared without problems and initially yielded clear particle-free solutions.

After filtration and filling into ampoules, all solutions were clear and free from particles. A portion of the ampoules were sterilized by moist heat, whereas others were kept without sterilization. After 24 hours storage at room temperature and at 8°C, both the 3 and 4mg/mL concentrations started to form a small part of insoluble particulate matter, whereas a 2mg/mL control formulation manufactured in the same manner remained clear and free of particulate matter.

Correlation of particulate matter generation with content of poorly soluble degradation products

During long-term storage, and upon heating, baclofen forms a poorly soluble degradation product with a lactamic structure, (4RS)-4-(4-chlorophenyl)pyrrolidin-2-one.¹¹ To investigate any correlation between content of this degradation product and particulate formation, samples of baclofen solution were prepared and sterilized by moist heat for up to 45 minutes. By this additional heat intake, up to 1.4% of the lactam degradation product was formed, which is far above the allowed level for the marketed drug product.

All solutions were clear and free of particulate matter at the control immediately after sterilization. After



storage for one month at 25°C as well as at an elevated temperature of 35°C, the reference solution with 2mg/mL strength remained free of particulate matter, whereas in all samples of the 3 and 4mg/mL formulation precipitates were observed. The amount of particles detected was independent of the assay value of the degradation product. The heat stressed 2mg/mL strength with a content of 0.028mg/mL of the lactam degradation product stayed particle-free whereas a sample of the 4mg/mL strength with a content of the degradation product of only 0.004mg/mL developed particulate matter contamination. This result confirms that the likelihood of particulate formation is not related to the amount of degradation product present in the formulation.

Characterization of the precipitate

To further investigate the nature of the precipitate observed after storage of initially clear and particle-free baclofen solutions, a 4mg/mL strength batch was prepared, and was filtered to yield in a particle-free clear solution. This solution was allowed to stand for one week, when a faint precipitate started to form. This precipitate was removed by filtration and was subsequently re-dissolved and analyzed by HPLC. The resulting chromatogram showed only one peak, which occurred at the same retention time as that of baclofen, indicating the precipitate is baclofen. This confirms that the precipitation observed in higher-concentration baclofen solutions consists of poorly soluble modifications of baclofen, which are slowly formed during the storage of initially clear and particle-free solutions.

Removal of particulate matter by re-processing of solutions after short-term storage to complete precipitation

The target of this trial was to investigate whether a clear and particle-free solution is obtained after the additional precipitation has occurred in the experiment above, or whether filtration of the solution prior to loading in the infusion pump could yield in a stable, particulate-free solution. The 4mg/mL baclofen solution obtained in the experiment described above was again sterile filtered and filled into ampoules. These solutions started to form a faint particulate precipitation after 5 days additional storage time in the ampoules at room temperature. Based on these results, manufacturing highly concentrated baclofen solutions by such re-processing is not feasible. The data also suggest that a filtration prior to loading of infusion pumps may not ensure a particulate-free solution during the time of application.

Influence of ionic strength

Addition of salts can influence aqueous solubility of drug substances by modulation of the water structure. Ionic salts often lead to a increase of the cluster size of water and therefore lead to salting-out effects for other compounds.¹² In order to assess whether such effects also play a role in the formation of baclofen precipitates, baclofen solutions in pure water for injection without addition of isotonicizing agents were investigated. However, no difference in formation and amount of precipitates was observed in comparison with the sodium chloride containing solutions. Formulations containing 3 and 4mg/mL baclofen formed precipitates after storage of 4 weeks with and without addition of sodium chloride.

Optimization of the pH-value

By variation of the pH-value of the solution, the amino as well as the carboxylic group can be protonated or deprotonated and therefore the molecule can be transformed into species with a net charge, which should allow for an increased solubility. Limitations however are given by the application route of the drug product to the cerebrospinal fluid which permits only for moderate variations. A pH-range of 5.5 to 7.5 of the unbuffered solution was considered to be acceptable and was, therefore, investigated.

Baclofen 4mg/mL solutions, made isotonic with sodium chloride, were adjusted with hydrochloric acid or sodium hydroxide solution to pH-values of 5.7, 6.7 and 7.5. After 1 week of storage, particulate matter was formed. A significant trend to higher particulate matter counts was observed at the pH-value of 7.5.

Based on these results it can be concluded that by variation of the pH-value in a physiologically acceptable range, no improvement on the solubility properties of baclofen can be obtained.

An overall summary of the results is presented in Table 1. Results showed that precipitation occurs in 3 and 4mg/mL solutions regardless of the various conditions to which the samples are subjected. No precipitation occurred in any of the 2mg/mL solutions studied.

Discussion

While there are perceived benefits associated with using 3 and 4mg/mL baclofen solutions, the unknown risks cannot be overlooked. The data presented in this study demonstrate a physical, long-term stability issue as a result of baclofen precipitation observed at 3mg and 4mg/mL.

In addition, it is unknown if precipitation in the pump may partially or fully clog the filter between the pump reservoir and catheter. Clogging of the filter could potentially decrease or completely stop the flow rate of the intrathecal baclofen solution, thereby decreasing the dose

Table 1. Summary of results of high concentration baclofen feasibility studies.

Study	Result
Feasibility with identical formulation to marketed product	Initially clear, particles in 3 and 4mg/mL solutions after 24 hours regardless of storage temperature; no particles in 2mg/mL solutions
Influence of degradation products	Precipitation does not correlate to amount of degradation products; 2mg/mL strength remains particle free even with substantially increased degradation product levels
Nature of particulate matter	Particulate matter consists of baclofen; no other products could be detected
Influence of ions	No influence of neutral salts could be detected; also baclofen solutions in water, not isotonized, show precipitation at concentrations above 2mg/mL
pH-range	Increased precipitation at pH 7.5, particulate matter is formed at all tested pH-values if the concentration is increased above 2mg/mL
Reprocessing	Particulate matter formation with higher concentrated baclofen solutions cannot be avoided by intermediate storage of a concentrated bulk solution to complete precipitation

received by the patient. Since it is likely that precipitation continues to take place after injection into the pump, potential blockage cannot be avoided by additional filtration prior to loading of the pump.

These risks bring into question the safety of formulating intrathecal baclofen solutions at concentrations higher than 2mg/mL. Of particular concern is the risk of baclofen withdrawal. Inaccurate baclofen dosing can have severe and potentially life-threatening complications for the patient.¹³ The use of 3 and 4mg/mL intrathecal baclofen solutions may increase the risk of baclofen withdrawal due to clogging of the pump filter and/or inaccurate concentration of the drug product either initially or during the course of treatment.

Conclusion

Although higher concentrations of intrathecal baclofen are desirable for increasing refill intervals, this study raises concern about the presence of particulates in solutions and the potency of the intrathecal drug delivered. The safety and efficacy of intrathecal baclofen therapy may be compromised by the use of concentrations of baclofen solution higher than 2mg/mL. Given the results obtained from this study, it is recommended that formulations of baclofen above the highest commercially available formulation of 2mg/mL not be used with the Medtronic SynchroMed Pump in order to ensure safe and effective drug therapy for the patient.

Lioresal® is a registered trademark of Novartis Pharmaceuticals Corporation.

SynchroMed® is a registered trademark of Medtronic, Inc.

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SynchroMed® II Drug Infusion System Brief Summary:

Product technical manuals and the appropriate drug labeling must be reviewed prior to use for detailed disclosure.

Indications:

US: Chronic intraspinal (epidural and intrathecal) infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain, chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain, and chronic intrathecal infusion of Lioresal® Intrathecal (baclofen injection) for the management of severe spasticity; chronic intravascular infusion of floxuridine (FUDR) or methotrexate for the treatment of primary or metastatic cancer. **Outside of US:** Chronic infusion of drugs or fluids tested as compatible and listed in the product labeling.

Contraindications:

When infection is present; when the pump cannot be implanted 2.5 cm or less from the surface of the skin; when body size is not sufficient to accept pump bulk and weight; when contraindications exist relating to the drug. Do not use the Personal Therapy Manager accessory to administer opioid to opioid-naïve patients or to administer ziconotide.

Warnings:

Comply with all product instructions for initial preparation and filling, implantation, programming, refilling, and injecting into the catheter access port (CAP) of the pump. Failure to comply with all instructions can lead to technical errors or improper use of implanted infusion pumps and result in additional surgical procedures, a return of underlying symptoms, or a clinically significant or fatal drug under- or overdose. Refer to the appropriate drug labeling for specific under- or overdose symptoms and methods of management. Avoid using short wave (RF) diathermy within 30 cm of the pump or catheter. Diathermy may produce significant temperature rises in the area of the pump and continue to heat the tissue in a localized area. If overheated, the pump may over infuse the drug, potentially causing a drug overdose. Effects of other types of diathermy (microwave, ultrasonic, etc.) on the pump are unknown. An inflammatory mass that can result in serious neurological impairment, including paralysis, may occur at the tip of the implanted catheter. Clinicians should monitor patients on intraspinal opioid therapy carefully for any new neurological signs or symptoms. For intraspinal therapy, use only preservative-free sterile solution indicated for intraspinal use. Use only Medtronic components indicated for use with this system. Failure to firmly secure connections can allow drug or cerebrospinal fluid (CSF) leakage into tissue and result in tissue damage or inadequate therapy. A postoperative priming bolus should not be programmed if the pump is a replacement and the catheter has not been aspirated.

Refer to appropriate drug labeling for indications, contraindications, warnings, precautions, dosage and administration information, and screening procedures. Physicians must be familiar with the drug stability information in the technical manual and must understand the dose relationship to drug concentration and pump flow rate before prescribing pump infusion. Implantation and ongoing system management must be performed by individuals trained in the operation and handling of the infusion system.

Inform patients of the signs and symptoms of drug under- or overdose, appropriate drug warnings and precautions regarding drug interactions, potential side effects, and signs and symptoms that require medical attention. Instruct patients to notify their clinician of travel plans, to return for refills at prescribed times, avoid activities such as strenuous exercise or contact sports that jar, impact, twist, or stretch the body, to always carry their Medtronic device identification card, to avoid manipulating the pump through the skin, and to notify healthcare professionals of the implanted pump before medical tests/procedures. Patients must consult their physician before engaging in activities involving pressure or temperature changes (e.g., scuba diving, saunas, hot tubs, hyperbaric chambers, flights, skydiving, etc.) Inform patients that pump has an Elective Replacement Indicator (ERI) that sounds when the pump is nearing its end of service. When the alarm sounds, patients must contact their doctor to schedule pump replacement.

Precautions:

The pump is ethylene oxide sterilized. Do not use if the product or package is damaged, the sterile seal is broken, or the "Use By" date has expired. Do not reuse or resterilize the pump; it is intended for "single use only." Do not expose the pump to temperatures above 43°C or below 5°C. Consider use of peri- and post-operative antibiotics for pump implantation, for any subsequent surgical procedure, or if infection is present. For patients prone to CSF leaks, clinicians should consider special procedures, such as a blood patch. Follow instructions for emptying and filling the pump during a replacement or revisions that require removal of the pump from the pocket. Explant the pump postmortem if incineration is planned (to avoid explosion), or if local environmental regulations mandate removal. Return explanted devices to Medtronic for analysis and safe disposal. Do not implant a pump dropped onto a hard surface or showing signs of damage. Implant the pump less than 2.5 cm from the surface of the skin. Ensure pump ports will be easy to access after implant, that the catheter is not kinked and secured well away from pump ports before suturing. Keep the implant site clean, dry, and protected from pressure or irritation. If therapy is discontinued for an extended period of time, fill the reservoir with preservative-free saline in intraspinal applications or appropriate heparinized solution (if not contraindicated) in vascular applications.

The magnetic field or telemetry signals produced by the programmer may cause sensing problems and inappropriate device responses with an implantable pacemaker and/or defibrillator. Electromagnetic interference (EMI) is an energy field generated by equipment found in the home, work, medical, or public environments. Most EMI normally encountered will not affect the operation of the pump. Exceptions include: injury resulting from heating of the pump which can damage surrounding tissue (diathermy, MRI), system damage which can require surgical replacement or result in loss/change in symptom control (defibrillation, electrocautery, high-output ultrasonics, radiation therapy), and operational changes to the pump causing the motor to stop, loss of therapy, return of underlying symptoms, and require confirmation of pump function (diathermy, high magnetic field devices, hyperbaric/hypobaric conditions,

magnetic resonance imaging (MRI)). MRI will temporarily stop the pump motor's rotor due to the magnetic field of the MRI scanner and suspend drug infusion during MRI exposure which will cause the pump alarm to sound. The pump should resume normal operation upon termination of MRI exposure. Prior to MRI, the physician should determine if the patient can safely be deprived of drug delivery. If not, alternative delivery methods for the drug can be utilized during the MRI scan. Prior to scheduling an MRI scan and upon its completion, pump status should be confirmed.

Adverse Events:

Include, but are not limited to, cessation of therapy due to end of device service life or component failure, change in flow performance due to component failure, inability to program the device due to programmer failure, CAP component failure; inaccessible refill port due to inverted pump, pocket seroma, hematoma, erosion, infection, post-lumbar puncture (spinal headache), CSF leak, radiculitis, arachnoiditis, bleeding, spinal cord damage, meningitis (intrathecal applications), anesthesia complications, damage to the pump, catheter and catheter access system due to improper handling and filling before, during, or after implantation; change in catheter performance due to catheter kinking, disconnection, leakage, breakage, occlusion, dislodgement, migration, or catheter fibrosis; body rejection phenomena, surgical replacement of pump or catheter due to complications; local and systemic drug toxicity and related side effects, complications due to use of unapproved drugs and/or not using drugs in accordance with drug labeling, or inflammatory mass at the tip of the catheter in patients receiving intraspinal morphine or other opioid drugs. **USA Rx Only.**

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