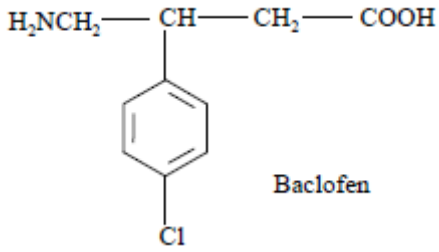
1 PRODUCT NAME

Baclofen Sintetica 0.05 mg/mL, solution for injection
Baclofen Sintetica 0.5 mg/mL, solution for infusion
Baclofen Sintetica, 2 mg/mL, solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is baclofen ((RS)-4-amino-3-(4-chlorophenyl)butanoic acid).
The chemical structure of baclofen (CAS number: 1134-47-0) is:



Baclofen

Baclofen is a chemical analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

Baclofen Sintetica is a solution for intrathecal injection and intrathecal infusion. It contains no preservatives.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ampoules containing 0.05 mg in1 mL are available for administering low-dose bolus injections during the screening phase.

Ampoules containing 10 mg in 5 mL, 10 mg in 20 mL and 40 mg in 20 mL, are available for use with infusion pumps. The concentration chosen for use depends upon the total daily dose required as well as the delivery rate of the pump. Please consult the pump manufacturer's manual for specific recommendations.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intrathecal baclofen is indicated in patients with severe chronic spasticity of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) or of cerebral origin who are unresponsive to orally administered antispastics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses.

4.2 Dose and method of administration

Method of administration

Intrathecal administration of baclofen through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience. Specific instructions for implanting, programming and/or refilling the implantable pump are given by the pump manufacturers, and must be strictly adhered to.

Dosage

Intrathecal baclofen is intended for administration in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, in implantable pumps suitable for continuous administration of baclofen solution into the intrathecal space.

For patients with spasticity due to head injury, it is recommended not to proceed to long-term intrathecal baclofen therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

Establishment of the optimum dose schedule requires that each patient undergoes an initial screening phase with test doses by intrathecal bolus, followed by a very careful individual dose titration prior to maintenance therapy. This is due to the great variability in the effective individual therapeutic dose.

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 available for immediate use in case of life-threatening or intolerable adverse reactions. Implantation of pumps should only be performed by experienced clinicians in properly equipped centres in order to minimise the risks in the perioperative phase (see section 4.4).

Screening phase:

Prior to initiation of chronic infusion of intrathecal baclofen, patients must demonstrate a response to an intrathecal bolus of baclofen in a screening trial. A bolus test dose of baclofen is usually administered via a lumbar puncture or an intrathecal catheter to elicit a response. In adults, the usual initial test dose is 25 micrograms or 50 micrograms and is stepped up by 25 microgram increments at least 24 hours apart, until a response lasting approximately 4 to 8 hours is observed; the dose should be given by barbotage over at least one minute. In children, the recommended initial test dose is 25 micrograms. For the test dose, low concentration ampoules of 0.05 mg/mL are available.

The first dose should be performed with resuscitative equipment on stand-by. Patients should demonstrate a significant decrease in muscle tone and/or frequency and/or severity of spasms in order to be considered responders to treatment.

There is great variability in sensitivity to intrathecal baclofen. Signs of severe overdose (coma), have been observed in an adult patient after a single test dose of 25 micrograms.

Patients who do not respond to a 100 microgram test dose should not be given further increases of dose or be considered for continuous intrathecal infusion.

Dose titration phase:
After confirmation that the patient is responsive to intrathecal baclofen by means of bolus test doses, intrathecal infusion is established using a suitable delivery system.

To determine the initial total daily dose of intrathecal baclofen following implant, the screening dose which 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 12 hours. In this case the starting daily dose should be the screening dose delivered over a 24-hour period. No dose increases should be administered in the first 24 hours.

Patients with spasticity of spinal origin: After the first 24 hours, the dosage should be adjusted slowly on a daily basis to achieve the desired clinical effect, with dosage increments limited to 10 - 30% to avoid possible overdosing.

Patients with spasticity of cerebral origin: After the first 24 hours, the dosage should be adjusted slowly on a daily basis to achieve the desired clinical effect, with dosage increments limited to 5 - 15% to avoid possible overdosing.

With programmable pumps, the dose should be increased only once every 24 hours. For nonprogrammable pumps with a 76 cm catheter delivering 1 mL/day, intervals of 48 hours are suggested for evaluation of response. If the daily dose has been substantially increased and no clinical effect is achieved, check for proper pump function and catheter patency.

There is limited experience with doses greater than 1000 micrograms/day.

Maintenance therapy:
The clinical goal is to maintain as normal a muscle tone as possible and to minimise the frequency and severity of spasms without inducing intolerable side effects, or to titrate the dose to the desired degree of muscle tone for optimal function when patients with cerebral spasticity are treated. The lowest dose producing an adequate response should be used. Most patients require gradual increases in dose over time to maintain optimum response during chronic therapy due to decreased responsiveness to therapy or due to disease progression.

The retention of some spasticity is desirable to avoid a sensation of “paralysis” on the part of the patient. In addition, a degree of muscle tone and occasional spasms may help support circulatory function and possibly prevent the formation of deep vein thrombosis.

Patients with spasticity of spinal origin: The daily dose may be gradually increased in steps of 10 - 30% to maintain adequate symptom control by adjusting the dosing rate of the pump and/or the concentration of baclofen in the reservoir. The daily dose may also be reduced by 10 - 20% if patients experience side effects.

Patients with spasticity of cerebral origin: The daily dose may be gradually increased by 5 - 20%, but no more than 20%, to maintain adequate symptom control by adjusting the dosing rate of the pump and/or the concentration of baclofen in the reservoir. The daily dose may also be reduced by 10 - 20% if patients experience side effects.

A sudden requirement for substantial dose escalation suggests a catheter complication (i.e., catheter

kink or dislodgement) or pump malfunction.

Maintenance dosage for long-term continuous infusion of intrathecal baclofen in patients with spasticity of spinal origin ranges from 10 micrograms /day to 1200 micrograms /day, most patients being adequately maintained on 300 - 800 micrograms/day.

In patients with spasticity of cerebral origin, the maintenance dosage for long-term continuous infusion of intrathecal baclofen ranges from 22 micrograms/day to 1400 micrograms/day, with a mean daily dose of 276 micrograms/day at 12 months and 307 micrograms/day at 24 months. Paediatric patients under twelve years of age generally require lower dosages than do older patients; the dose ranges from 24 - 1199 micrograms/day, with a mean daily dose of 274 micrograms/day.

Regular clinical review remains necessary throughout, to assess dosage requirements, functioning of the delivery system, and to watch for possible adverse drug reactions or evidence of infection.

Delivery regimen:
Intrathecal baclofen is most often administered in a continuous infusion mode immediately after pump implantation. However, after the patient has stabilised with regard to daily dose and functional status, and provided the pump allows it, a more complex mode of delivery may be started to optimise control of spasticity at different times of the day. For example, patients who have greater spasm 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.

Development of tolerance:
During long-term treatment approximately 5% of patients become refractory to increasing doses. After a few days cessation of baclofen, the sensitivity to baclofen may be restored and treatment should be resumed at the initial continuous infusion dose. This must be performed in a hospital unit. (also see section 4.4 “Withdrawal effects (including associated with catheter or device malfunction)”). Caution should be exercised when switching from intrathecal baclofen to morphine and vice versa (see Interactions in section 4.5).

Special populations

Renal impairment:
No studies have been performed in patients with renal impairment with intrathecal baclofen therapy. Because baclofen is primarily excreted unchanged by the kidneys (see section 5 “Pharmacology”) it should be given with special care and caution in patients with impaired renal function (see section 4.4).

Hepatic impairment:
No studies have been performed in patients with hepatic impairment receiving intrathecal baclofen therapy. No dosage adjustment is recommended as the liver does not play any significant role in the metabolism of baclofen after intrathecal administration. Therefore, hepatic impairment is not expected to impact the medicine systemic exposure (see section 5 “Pharmacology”).

Geriatrics:
Several patients over the age of 65 years have been treated with intrathecal baclofen during the clinical trials without increased risks compared to younger patients. Problems specific to this age group are not expected as doses are individually titrated (see section 4.4 “Precautions” and section 5 “Pharmacology”).

4.3 Contraindications

- Known hypersensitivity to baclofen or to any of the excipients.
- The medicine should not be administered by the intravenous, intramuscular, epidural or subcutaneous routes.
- Epilepsy refractory to therapy.

4.4 Special warnings and precautions for use

Withdrawal effects (including associated with catheter or device malfunction)
Except in overdose-related emergencies, treatment with baclofen should always be gradually discontinued by successively reducing the dosage. Baclofen should not be discontinued suddenly.

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 seizures/status epilepticus, coagulopathy, rhabdomyolysis, multiple organsystem 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.

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 paraesthesias. 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 medicines 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 baclofen as well as in patients maintained on therapeutic doses of baclofen.

Common reasons for abrupt interruption of intrathecal baclofen therapy included malfunction of the catheter (especially disconnection), low volume in the pump reservoir, end of pump battery life and

device malfunction. Device malfunction resulting in altered medicine delivery leading to withdrawal symptoms including death has been reported.

Human error may have played a causal or contributing role in some cases. Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to proper programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of baclofen withdrawal (e.g. priapism). 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. 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 medicines 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.

Safety considerations during use:
It is mandatory that the patient, the physicians responsible for the patient, and all those involved in the care of the patient receive adequate information about the risks of this mode of treatment. Physicians must be adequately trained in chronic intrathecal infusion therapy. Everyone concerned with the treatment and care of the patient should be instructed on the signs and symptoms of overdose, procedures to be followed in the event of overdose, and proper home care of the pump and insertion site.

For patients with spasticity due to head injury, it is recommended not to proceed to long-term baclofen therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

Screening phase:
The pump system should not be implanted until the patient's response to bolus intrathecal baclofen injection and/or dose titration is adequately evaluated and found to be clinically safe and effective. Because of the risks associated with the initial administration and titration of intrathecal baclofen (CNS depression, cardiovascular collapse and/or respiratory failure), these steps must be conducted in a medically supervised and adequately equipped environment, following the instructions outlined in the Dosage and Administration section 4.2. The preliminary screening phase should be performed in a hospital and implantation of the pump system should be undertaken only in specialist units. Resuscitative equipment should be available for immediate use in case of life-threatening symptoms of severe overdose.

Careful monitoring of respiratory and cardiovascular functions is essential during administration of the initial test doses (screening phase), especially in patients with cardiopulmonary disease and respiratory muscle weakness as well as those being treated concomitantly with benzodiazepine-type preparations or opiates, who are at higher risk of respiratory depression.

Patients should be infection-free prior to the screening trial with baclofen because the presence of a systemic infection may interfere with an assessment of the patient's response to bolus intrathecal baclofen.

Before use of the medicine, myelography of the subarachnoid space should be performed in patients with postraumatic spasticity. If signs of arachnoiditis are detected, treatment should not be given.

Pump implantation and use:
Intrathecal administration of baclofen through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience in properly equipped centres in order to minimise the risks in the perioperative period. Specific instructions for implanting, programming and/or refilling the implantable pump are given by the pump manufacturers, and must be strictly adhered to.

Patients should be infection-free prior to pump implantation because the presence of infection may increase the risk of surgical complications. Moreover, a systemic infection may complicate attempts to adjust the dose. A local infection or catheter malplacement can also lead to medicine delivery failure, which may result in sudden baclofen withdrawal and its related symptoms (see section 4.4 “Withdrawal effects (including associated with catheter or device malfunction)”).

Reservoir refilling:
Reservoir refilling must be performed by qualified and fully trained personnel following the directions provided by the pump manufacturer. Strictly aseptic filling is required to avoid microbial contamination and serious infection.

Refill intervals should be carefully calculated to prevent depletion of the reservoir, as this would result in the return of severe spasticity or potentially life-threatening symptoms of withdrawal (see section 4.4 “Withdrawal effects (including associated with catheter or device malfunction)”).

Extreme caution must be used when filling an implantable pump equipped with an injection port that allows direct access to the intrathecal catheter. Direct injection into the catheter through the access port may cause a life-threatening overdose.

Patient monitoring after pump implantation:
Following surgical implantation of the pump, particularly during the initial phases of use, and on each occasion that the dosing rate of the pump and/or the concentration of baclofen in the reservoir is adjusted, the patient should be monitored closely until it is certain that the patient's response to the infusion is acceptable and reasonably stable. A period of observation appropriate to the clinical situation should follow each refill or manipulation of the medicine reservoir.

Inflammatory mass at the tip of the implanted catheter:
Cases of inflammatory mass at the tip of the implanted catheter that can result in serious neurological impairment, have been reported. Preclinical studies in animal models have demonstrated that the formation of inflammatory mass is directly related to high dose and/or high concentration of intrathecal opioids and no inflammatory mass is formed with intrathecal baclofen as a sole agent. The most frequent symptoms associated with inflammatory 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, especially if using pharmacy compounded medicines or admixtures that include opioids. In patients with new neurological signs or symptoms

suggestive of an inflammatory 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 inflammatory mass.

Repeated dose toxicity
Repeated intrathecal administration of baclofen was not associated with the development of inflammatory masses in studies in rats and dogs. No changes to the spinal cord and adjacent tissue and no signs of irritation or inflammation of the spinal cord and surrounding tissues were noted in either species.

Scoliosis
The onset of scoliosis or worsening of a pre-existing scoliosis has been reported in patient treated with baclofen. Signs of scoliosis should be monitored during treatment with baclofen.

Additional considerations pertaining to dosage adjustment:
In order to prevent excessive weakness and falling, intrathecal baclofen should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion or whenever spasticity is used to obtain optimal function and care. It may be important to maintain some degree of muscle tone and allow occasional spasms to help support circulatory function and possibly prevent the formation of deep vein thrombosis.

Withdrawal of oral antispastic medication:
An attempt should be made to discontinue concomitant oral antispastic medication to avoid possible overdose or adverse drug interactions. This should preferably be done before initiating baclofen infusion and requires careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispastics during chronic intrathecal therapy with baclofen should be avoided.

Precautions in special patient populations:
In patients with **abnormal CSF flow** the distribution of baclofen and its antispastic activity may be inadequate.

Patients suffering from **psychotic disorders, schizophrenia, confusional states or Parkinson's disease** should be treated cautiously with intrathecal baclofen and kept under careful surveillance because exacerbations of these conditions have been observed with oral baclofen administration.

Special attention should be given to patients known to suffer from **epilepsy** or with a history of seizures, since seizures have been reported occasionally during overdose with, or withdrawal from, intrathecal baclofen, as well as in patients maintained on therapeutic doses of intrathecal baclofen.

Intrathecal baclofen should be used with caution in patients with a history of **autonomic dysreflexia**. The presence of nociceptive stimuli on abrupt withdrawal of baclofen may cause an autonomic dysreflexic episode (see section 4.4 “Abrupt effects (including associated with catheter or device malfunction)”).

Intrathecal baclofen should be used with caution in patients with **cerebrovascular or respiratory insufficiency** as these conditions may be exacerbated by baclofen.

An effect of intrathecal baclofen on **underlying, non-CNS related diseases** is unlikely because the systemic availability of the medicine after intrathecal administration is substantially lower than after oral administration. Nevertheless, observations after oral baclofen therapy suggest that caution should be exercised in the following situations: history of peptic ulcers, pre-existing sphincter hypertonia.

Renal impairment:
After **oral** baclofen dosing severe neurological outcomes have been reported in patients with renal impairment. Thus, caution should be exercised while administering intrathecal baclofen in patients with renal impairment.

Use in children:
For patients with spasticity due to head injury, it is recommended not to proceed to long-term intrathecal baclofen therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Use of intrathecal baclofen in the paediatric population should be only prescribed by medical specialists with the necessary knowledge and experience. There are very limited clinical data on the use of intrathecal baclofen in children under age six. The safe use of intrathecal baclofen in children under the age of four has not yet been established.

Use in the elderly:
Elderly patients may be more susceptible to the side effects of oral baclofen in the titration stage and this may also apply to intrathecal baclofen.

4.5 Interaction with other medicines and other forms of interaction

There is little experience with the use of intrathecal baclofen in combination with systemic medications to predict specific drug-drug interactions, although it is suggested that the low baclofen systemic exposure observed after intrathecal administration could reduce the potential for pharmacokinetic interactions (see section 5.2).

Anticipated interactions resulting in concomitant use not being recommended

Levodopa/DDC inhibitor:
Concomitant use of **oral** baclofen and levodopa/DDC inhibitor resulted in increased risk of adverse events like visual hallucinations, confusional state, headache and nausea. Worsening of the symptoms of Parkinsonism has also been reported. Thus, caution should be exercised when intrathecal baclofen is administered to patients receiving levodopa/DDC inhibitor therapy.

Observed interactions to be considered
Anaesthetics:
Concomitant use of intrathecal baclofen and general anaesthetics (e.g. fentanyl, propofol) may increase the risk of cardiac disturbances and seizures. Thus, caution should be exercised when anaesthetics are administered to patients receiving intrathecal baclofen.

Anticipated interactions to be considered

Morphine:

The combined use of intramuscular morphine and intrathecal baclofen was responsible for hypotension in one patient. The potential for this combination to cause dyspnoea or other CNS symptoms cannot be excluded.

The co-administration of other intrathecal agents with intrathecal baclofen has not been tested and its safety is unknown.

Alcohol and other compounds affecting the CNS

The central nervous system depressant effects of alcohol and other compounds affecting the CNS (e.g. analgesics, neuroleptics, barbiturates, benzodiazepines, anxiolytics) may be additive to the effects of baclofen.

Tricyclic antidepressants

When using **oral** baclofen, concurrent treatment with tricyclic antidepressants may potentiate the effect of baclofen, resulting in pronounced muscular hypotonia. Caution is advised when using intrathecal baclofen in this combination.

Antihypertensives

Since concomitant treatment with **oral** baclofen and antihypertensives is likely to further increase a possible fall in blood pressure, it may be necessary to monitor blood pressure and adjust the dosage of the antihypertensive medication accordingly.

4.6 Fertility, pregnancy and lactation

Fertility

Animal studies have shown that intrathecal baclofen is unlikely to have an adverse effect on fertility under clinically-relevant conditions.

Women of Child-bearing Potential

There are no special recommendations for women of child-bearing potential.

Use in Pregnancy (Category B3)

There is limited data on the use of intrathecal baclofen in pregnant women.

After intrathecal administration, small amounts of baclofen can be detected in maternal plasma (see section 5 “Pharmacology”). Animal data showed that baclofen can cross the placental barrier. Therefore, intrathecal baclofen should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus.

Bacofen is not teratogenic in mice, rats and rabbits at doses at least 125-times the maximum intrathecal mg/kg dose. Baclofen given **orally** has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 500-times the maximum intrathecal dose expressed as a mg/kg dose. This abnormality was not seen in mice or rabbits. Baclofen dosed **orally** has been shown to cause delayed fetal growth (ossification of bones) at doses that also caused maternal toxicity in rats and rabbits. Baclofen caused widening of the vertebral arch in rat fetuses at a high intraperitoneal dose.

Use in Lactation
After oral administration of baclofen at therapeutic doses, baclofen passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected.

After intrathecal administration, small amounts of baclofen can be detected in maternal plasma (see section 5 "Pharmacology'). Therefore, no baclofen is expected to be found in the milk of the mother receiving intrathecal baclofen therapy and no special recommendations are given.

4.7 Effects on ability to drive and use machines

Central nervous system (CNS) depressant effects such as somnolence and sedation have been reported in some patients receiving intrathecal baclofen. Other listed events include ataxia, hallucinations, diplopia and withdrawal symptoms. Patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness.

4.8 Undesirable effects

Clinical trials in patients with spasticity of spinal origin:
Adverse experiences reported during US studies (both controlled and uncontrolled) are shown in the following table. None of these adverse experiences led to discontinuation of treatment.

INCIDENCE OF MOST FREQUENT ADVERSE EVENTS IN PATIENTS WITH SPASTICITY OF SPINAL ORIGIN IN PROSPECTIVELY MONITORED CLINICAL TRIALS CONDUCTED IN THE US

Adverse Event	Number of Patients Reporting Events		
	N = 244 Screening[a]	N = 214 Titration[b]	N = 214 Maintenance[c]
Drowsiness	13	11	18
Weakness, Lower Extremities	1	11	15
Dizziness/Light-headedness	6	5	12
Seizures	1	4	11
Headache	0	3	9
Nausea/Vomiting	3	5	3
Numbness/Itching/Tingling	2	1	8
Hypotension	3	0	5
Blurred Vision	0	2	5
Constipation	0	2	5
Hypotonia	2	3	2
Speech Slurred	0	1	6
Coma (Overdose)	0	4	3
Lethargy	1	0	4
Weakness, Upper Extremities	1	0	4
Hypertension	1	2	2
Dyspnoea	1	2	1

[a] *Following administration of test bolus*
b Two month period following implant
[c] *Beyond two months following implant*
(N = total number of patients entering each period)

Clinical trials in patients with spasticity of cerebral origin:
Adverse experiences reported during US studies (both controlled and uncontrolled) are shown in the following table. Nine patients discontinued long-term treatment due to adverse events.

INCIDENCE OF MOST FREQUENT (≥ 1%) ADVERSE EVENTS IN PATIENTS WITH SPASTICITY OF CEREBRAL ORIGIN IN PROSPECTIVELY MONITORED CLINICAL TRIALS CONDUCTED IN THE US

Adverse Event	Number and Percent (%) of Patients Reporting Events		
	N = 211 Screening[a]	N = 153 Titration[b]	N = 150 Maintenance[c]
Hypotonia	5 (2.4)	22 (14.4)	52 (34.7)
Somnolence	16 (7.6)	16 (10.5)	28 (18.7)
Headache	14 (6.6)	12 (7.8)	16 (10.7)
Nausea and vomiting	14 (6.6)	16 (10.5)	6 (4.0)
Vomiting	13 (6.2)	13 (8.5)	6 (4.0)
Urinary retention	2 (0.9)	10 (6.5)	12 (8.0)
Seizures	2 (0.9)	5 (3.3)	15 (10.0)
Dizziness	5 (2.4)	4 (2.6)	12 (8.0)
Nausea	3 (1.4)	5 (3.3)	11 (7.3)
Hypoventilation	3 (1.4)	2 (1.3)	6 (4.0)
Hypertonia	0 (0.0)	1 (0.7)	9 (6.0)
Paraesthesia	4 (1.9)	1 (0.7)	5 (3.3)
Hypotension	4 (1.9)	1 (0.7)	3 (2.0)
Increased salivation	0 (0.0)	4 (2.6)	4 (2.7)
Back pain	2 (0.9)	1 (0.7)	3 (2.0)
Constipation	1 (0.5)	2 (1.3)	3 (2.0)
Pain	0 (0.0)	0 (0.0)	6 (4.0)
Pruritus	0 (0.0)	0 (0.0)	6 (4.0)
Diarrhoea	1 (0.5)	1 (0.7)	3 (2.0)
Peripheral oedema	0 (0.0)	0 (0.0)	5 (3.3)
Thinking abnormal	1 (0.5)	2 (1.3)	1 (0.7)
Agitation	1 (0.5)	0 (0.0)	2 (1.3)
Asthenia	0 (0.0)	0 (0.0)	3 (2.0)
Chills	1 (0.5)	0 (0.0)	2 (1.3)
Coma	1 (0.5)	0 (0.0)	2 (1.3)
Dry mouth	1 (0.5)	0 (0.0)	2 (1.3)
Pneumonia	0 (0.0)	0 (0.0)	3 (2.0)
Tremor	1 (0.5)	0 (0.0)	2 (1.3)
Urinary incontinence	0 (0.0)	0 (0.0)	3 (2.0)
Urination impaired	0 (0.0)	0 (0.0)	3 (2.0)

[a] *Following administration of test bolus*
[b] *Two month period following implant*
[c] *Beyond two months following implant*
(N = total number of patients entering each period. 211 patients received drug. 1 of 212 received placebo only)

Some of the adverse events listed below have been reported in patients with spasticity of spinal origin but could also occur in patients with spasticity of cerebral origin. Adverse events that are more frequent in either population are indicated below.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked under headings of frequency, the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Metabolism and nutrition disorders	
Uncommon	Dehydration
Psychiatric disorders	
Common	Depression, anxiety, agitation.
Uncommon	Suicidal ideation, suicide attempt, hallucinations, paranoia, euphoric mood.
Nervous system disorders	
Very common	Somnolence
Common	Convulsions, confusional state, sedation, dizziness, headache, paraesthesiae, dysarthria, lethargy, , insomnia, disorientation,
Uncommon	Ataxia, memory impairment, nystagmus Convulsion and headache occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.
Eye disorders	
Common	Accommodation disorder, vision blurred, diplopia.
Cardiac disorders	
Uncommon	Bradycardia.
Vascular disorders	
Common	Hypotension
Uncommon	Hypertension, deep vein thrombosis, flushing, pallor.
Respiratory, thoracic and mediastinal disorders	
Common	Respiratory depression, pneumonia, dyspnoea,
Gastrointestinal disorders	
Common	Nausea, vomiting, constipation, dry mouth, diarrhoea, decreased appetite, increased salivation
Uncommon	Ileus, dysphagia, hypogeusia. Nausea and vomiting occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.
Skin and subcutaneous tissue disorders	
Common	Urticaria, pruritus, facial and/or peripheral oedema.
Uncommon	Alopecia, hyperhydrosis.
Renal and urinary disorders	
Common	Urinary incontinence, urinary retention. Urinary retention occurs more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.
Musculoskeletal and connective tissue disorders	
Very common	Hypotonia
Common	Hypotonia
Reproduction system and breast disorders	
Common	Sexual dysfunction

General disorders and administration side conditions	
Common	Asthenia, pyrexia, pain, chills.
Uncommon	Hypothermia
Rare	Life-threatening withdrawal symptoms due to medicine delivery failure (see section 4.4)

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)
The following adverse drug reactions have been derived from post-marketing experience with intrathecal baclofen via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Nervous system disorders: dysphoria

Respiratory, thoracic and mediastinal disorders: bradypnoea

Musculoskeletal and connective tissue disorders: scoliosis (see section 4.4)

Reproductive system breast disorders: erectile dysfunction

Adverse events associated with the delivery system:
Inflammatory mass at the tip of the catheter, dislodgement/kink/rupture of the catheter with possible complications, infection of place of implantation, meningitis, septicemia, pump-pocket seroma and haematoma (potential risk of inflammation), pump malfunction and CSF leakages and skin ulcers after quite some time, and overdosage or underdosage due to wrong manipulation of the device have been reported, whereby in some cases a causal relationship with baclofen cannot be excluded. Device malfunction resulting in altered medicine delivery leading to withdrawal symptoms including death has been reported (see section 4.4).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Deaths due to overdose of intrathecal baclofen have been reported. Special attention must be given to recognising the signs and symptoms of overdosage at all times, especially during the initial "screening" and "dose-titration" phase of treatment but also during reintroduction of intrathecal baclofen after a period of interruption of therapy. Signs of overdose may appear suddenly or insidiously.

Serious overdose may occur for example by inadvertent delivery of catheter contents during catheter patency/position analysis. Errors in programming, excessively rapid dose increases and concomitant treatment with oral baclofen are other possible causes of overdosage. Possible pump malfunction should also be investigated. Symptoms of severe intrathecal baclofen overdose (coma) were reported in a sensitive adult patient after receiving a 25 microgram intrathecal bolus dose.

Symptoms:
Excessive muscular hypotonia, drowsiness, light-headedness, dizziness, somnolence, seizures, loss of consciousness, hypothermia, excessive salivation, nausea and vomiting. Respiratory depression,

bradycardia, apnoea and coma result from serious overdosage.

Treatment:
There is no specific antidote for treating overdoses of intrathecal baclofen, but the following steps should generally be undertaken:

1. Residual baclofen solution should be removed from the pump as soon as possible.
2. Patients with respiratory depression should be intubated and ventilated, if necessary, until the medicine is eliminated.
3. If lumbar puncture is not contraindicated, consideration should be given, in the early stage of the intoxication, to withdrawing 30 - 40 mL of CSF to reduce CSF baclofen concentration.
4. Cardiovascular function should be supported.
5. In the event of convulsions, diazepam may be administered cautiously i.v.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antispastic with a spinal site of attack: (ATC Code: M03B X01).

Baclofen is an antispastic agent with a spinal site of action. Baclofen also has central sites of action given the adverse event profile. Baclofen is a racemic mixture of the R, (-) and S, (+) isomers. Experimental data indicate that the pharmacological action resides in the R, (-) isomer.

The precise mechanisms of action of baclofen as a muscle relaxant and antispastic agent are not fully understood. Baclofen depresses both monosynaptic and polysynaptic reflex transmission in the spinal cord, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals. Actions at supraspinal sites may also contribute to its clinical effect. Baclofen is an analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and may exert its effects by stimulating $GABA_\beta$ receptors. Neuromuscular transmission is not affected. Baclofen exerts an antinociceptive effect. In neurological diseases associated with spasm of the skeletal muscles (for e.g. tetanus), the clinical effects of baclofen take the form of a beneficial action on reflex muscle contractions and of marked relief from painful spasm, automatism, hyperreflexia, trismus and clonus.

Baclofen improves patient mobility and facilitates physiotherapy. The above effects result in improved ambulation, prevention and healing of decubitus ulcers and better sleep patterns due to elimination of painful muscle spasms. In addition, patients experience improvement in bladder and sphincter function and catheterisation is made easier, all representing significant improvements in the patient's quality of life.

Baclofen has been shown to have general CNS depressant properties, causing sedation, somnolence, and respiratory and cardiovascular depression. It has also been shown to have a dose-dependent inhibitory effect on erectile function in men through $GABA_\beta$ receptor stimulation.

Baclofen introduced directly into the intrathecal space permits effective treatment of spasticity with doses at least 100 times smaller than those for oral administration.

Intrathecal baclofen may be considered an alternative to destructive neurosurgical procedures.

There is also some limited evidence of efficacy in reducing spasms in patients with tetanus.

Clinical trials

Spasticity of spinal origin:
Evidence supporting the efficacy of intrathecal baclofen was obtained in randomised, controlled investigations that compared the effects of either a single intrathecal dose or a three day intrathecal infusion of 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 randomised controlled crossover trial of 51 patients with cerebral palsy, provided strong, statistically significant results and was considered to be the pivotal study. intrathecal baclofen was superior to placebo in reducing spasticity as measured by the Ashworth scale. A second crossover 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 favourable results. The last study did not provide data that could be reliably analysed. However, data on the effects of a 50 microgram dose of intrathecal baclofen in both the second and third studies were consistent with the results of the pivotal study.

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

5.2 Pharmacokinetic properties

Because of the slow CSF circulation and the baclofen concentration gradient from the lumbar to the cisternal CSF the pharmacokinetic parameters observed in this fluid and as described below should be interpreted considering a high inter- and intra-patients variability.

Absorption:
Direct infusion into the spinal subarachnoid space by-passes absorption processes and allows exposure to the receptor sites in the dorsal horn of the spinal cord.

Onset of Action:
Intrathecal bolus: The onset of action is generally half an hour to one hour after administration of a single intrathecal dose of baclofen. Peak spasmolytic effect is seen at approximately 4 hours after dosing, the effect lasting 4 to 8 hours. Onset, peak response and duration of action may vary with individual patients depending on the severity of symptoms and the dose, method and speed of medicine administration.

Continuous infusion: Baclofen's antispasmodic action is first seen 6 to 8 hours after initiation of continuous infusion. Maximum efficacy is observed within 24 to 48 hours.

Distribution:
After single intrathecal bolus injection/short-term infusion of baclofen, the volume of distribution, calculated from CSF concentrations, ranges from 22 to 157 mL. The concentrations of baclofen in plasma and the CSF after intrathecal bolus injection and intrathecal infusion have been investigated in three separate studies and the results are depicted in the table below.

Mode of Administration	**Dose**	**Patient No**	**V_d (L)**	**Plasma (ng/mL)**	**CSF (ng/mL)**
Bolus Infusion	100-600 µg 50-1200 µg/24h	14 14	- -	5-20 0-5	- 130-950
Bolus Infusion	75-137 µg 83-210 µg /24h	4 4	0.05-0.16 -	- -	- 132-1240
Bolus Infusion	50-100 µg 96-600 µg /24h	7 10	0.02-0.15 -	- -	- 76-1240

According to the half-life measured in the CSF, steady-state CSF concentrations will be reached within 1-2 days. No data are available for paediatric patients.

At steady-state conditions during continuous intrathecal infusion, a baclofen concentration gradient is built up in the range between 1.8 : 1 and 8.7 : 1 (mean: 4 : 1) from lumbar to cisternal CSF. This is based upon simultaneous CSF sampling via cisternal and lumbar tap during continuous baclofen infusion at the lumbar level in doses associated with therapeutic efficacy; the interpatient variability was great. This is of clinical importance insofar as spasticity in the lower extremities can be effectively treated with little effect on the upper limbs and with fewer CNS adverse reactions resulting from effects on the brain centres.

During intrathecal infusion plasma concentrations do not exceed 5 ng/mL.

There is inadequate information available on the distribution of the two enantiomers.

Elimination:
The pharmacokinetics of Cerebrospinal Fluid (CSF) clearance of baclofen, calculated from intrathecal bolus or continuous infusion studies, approximate CSF turnover, suggesting elimination is by bulk-flow removal of CSF. After both single bolus injection and chronic lumbar subarachnoid infusion using an implantable pump system, the mean CSF clearance is about 30 mL/h.

The elimination half-life in the CSF after single intrathecal bolus injection/short-term infusion of 50 to 136 micrograms baclofen ranges from 1 to 5 hours. The elimination half-life of baclofen in the CSF at steady-state has not been determined.

Special populations

Elderly Patients
No pharmacokinetic data is available in elderly patients after administration of intrathecal baclofen.

When a single dose of the oral formulation is administered, data suggest that elderly patients have a slower elimination but a similar systemic exposure to baclofen compared to young adults. However, the extrapolation of these results to multi-dose treatment suggests no significant pharmacokinetics difference between young adults and elderly patients.

Paediatrics
In paediatric patients, respective plasma concentrations are at or below 10 ng/mL.

Hepatic impairment
No pharmacokinetic data is available in patients with hepatic impairment after administration of intrathecal baclofen. However, as liver does not play a significant role in the disposition of baclofen it is unlikely that its pharmacokinetics would be altered to a clinically significant level in patient with hepatic impairment.

Renal impairment
No pharmacokinetic data is available in patients with renal impairment after administration of intrathecal baclofen. Since baclofen is majorly eliminated unchanged through the kidneys, accumulation of unchanged medicine in patients with renal impairment cannot be excluded.

5.3 Preclinical safety data

Local tolerance
Subacute and subchronic studies with continuous intrathecal baclofen infusion in two species (rat, dog) revealed no signs of local irritation or inflammation on histological examination.

Carcinogenicity and mutagenicity:
Baclofen was negative for mutagenic and genotoxic potential in tests in bacteria, mammalian cells, yeast, and Chinese hamsters. The evidence suggests that baclofen is unlikely to have mutagenic potential.

A two year carcinogenicity study in rats (oral administration) found no evidence that baclofen had carcinogenicity potential at oral doses up to 100 mg/kg/day. An apparently dose-related increase in the incidence of ovarian cysts and of enlarged and/or haemorrhagic adrenals at the highest two doses (50 and 100 mg/kg/day) was observed in female rats. The clinical relevance of these findings is not known.

Ovarian cysts have been found by palpation in about 5% 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 medicine. Ovarian cysts are known to occur spontaneously in a proportion of the normal female population.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities

Baclofen ampoules for intrathecal administration should not be mixed with other infusion or injection solutions. Glucose solutions are incompatible due to a chemical reaction with baclofen.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25°C, protect from light. Do not refrigerate. Do not freeze.

6.5 Nature and contents of container

Baclofen Sintetica 0.05 mg/ml (0.05mg in 1ml)
Type I clear colourless glass ampoules with score break and blue coloured ring marker.
Box of 10 ampoules.

Baclofen Sintetica 0.5 mg/mL (10mg in 20ml)
Type I clear colourless glass ampoules with score break and red coloured ring marker.
Box of 1 ampoule.

Baclofen Sintetica 2 mg/ml (10mg in 5ml)
Type I clear colourless glass ampoules with score break and violet coloured ring marker.
Box of 10 ampoules.

Baclofen Sintetica 2 mg/ml (40mg in 20ml)
Type I clear colourless glass ampoules with score break and green coloured ring marker.
Box of 1 ampoule.

Not all pack sizes may be available.

6.6 Special precautions for disposal and other handling

Baclofen Sintetica is intended for intrathecal injection and continuous intrathecal infusion. Each ampoule is intended for single use only. Discard any unused portion. Do not freeze. Do not heat-sterilise.

Dilution instructions:
For patients who require concentrations other than 0.05 mg/mL, 0.5 mg/ml or 2 mg/mL, intrathecal baclofen must be diluted, under aseptic conditions, with sterile **preservative-free sodium chloride for injection**.

Pump specifications:

Several systems have been used for long-term administration of baclofen intrathecal. Among these, implantable EU-certified pumps can be mentioned, which are implantable systems equipped with

refillable reservoir, and which are implanted – under local or general anaesthetic – under the skin or into a pocket mostly in the abdominal wall. These systems are connected to an intrathecal catheter that passes subcutaneously into the subarachnoid space.

Before using these systems, users should ensure that the technical specifications, as well as chemical stability of baclofen in the reservoir, fulfil the conditions required for intrathecal administration of baclofen intrathecal.

Stability of intrathecal baclofen in the infusion pump:
Baclofen intrathecal has been shown to be stable for 180 days in implantable EU certified pumps. Wherever possible prior to administering them, medicinal products for parenteral use should be checked for the presence of particulate matter and any changes in colour.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Max Health Ltd
PO Box 65 231
Mairangi Bay
Auckland 0754

Telephone: (09) 815 2664.

9 DATE OF FIRST APPROVAL

21 April 2016

10 DATE OF REVISION OF THE TEXT

04 March 2018

SUMMARY TABLE OF CHANGES

Date of Revision	Section Changed	Summary of new information
04 March 2018	All	• Data sheet updated to new SPC format