SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Baclofen Sintetica 0.5 mg/ml
Baclofen Sintetica 2 mg/ml

2. Qualitative and quantitative composition

Active substance:
baclofen

Baclofen Sintetica 0.5 mg/ml
1 ml of solution for infusion contains 0.5 mg (500 micrograms) baclofen.
20 ml ampoule contains 10 mg (10,000 micrograms) baclofen.
Excipient with known effect
20 ml ampoule contains 69.3 mg sodium.

Baclofen Sintetica 2 mg/ml
1 ml of solution for infusion contains 2.0 mg (2000 micrograms) baclofen, 3.5 mg sodium
1 ampoule contains 10 mg (10,000 micrograms) baclofen, 17.5 mg sodium
20 ml ampouleBaclofen Sintetica ampoules 40 mg/20 ml solution for infusion
1 ml of solution for infusion contains 2.0 mg (2000 micrograms) baclofen, 3.5 mg sodium
1 ampoule contains 40 mg (40,000 micrograms) baclofen 69.3 mg sodium

Excipient with known effect
5 ml ampoule contains 17.5 mg sodium.
20 ml ampoule contains 69.3 mg sodium.

For a full list of excipients see section 6.1.

3. Pharmaceutical form

Solutions for intrathecal infusion.

4. Clinical particulars

4.1 Therapeutic indications

Baclofen Sintetica is indicated in patients with severe chronic spasticity resulting from trauma, multiple sclerosis or other spinal cord disorders, who are unresponsive to oral baclofen or other orally administered antispastic agents and/or those patients who experience unacceptable side effects at effective oral doses.

Baclofen Sintetica is effective in adult patients with severe chronic spasticity of cerebral origin, resulting e.g. from cerebral palsy, brain trauma or cerebrovascular accident; however, clinical experience is limited.

Pediatric population:

Baclofen Sintetica is indicated in patients aged 4 to <18 years with severe chronic spasticity of cerebral origin or of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) who are unresponsive to orally administered antispastics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses.

4.2 Posology and 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 implantation, programming and/or refilling of the implantable pump are given by the pump manufacturers, and must be strictly adhered to.
Baclofen Sintetica 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 Sintetica 10 mg/5 ml and 40 mg/20 ml into the intrathecal space. Establishment of the optimum dose schedule requires that each patient undergoes an initial screening phase with intrathecal bolus, followed by a very careful individual dose titration prior to maintenance therapy.
Respiratory function should be monitored and appropriate resuscitation facilities should be available during the introduction of treatment with Baclofen Sintetica. Only pumps constructed of material known to be compatible with the product and incorporating an in-line bacterial retentive filter should be used.

Adult Screening Phase
Prior to initiation of a chronic infusion, the patient's response to intrathecal bolus doses administered via a catheter or lumbar puncture must be assessed. Low concentration ampoules containing 500 micrograms baclofen in 1 ml are available for the purpose. Patients should be infection-free prior to screening, as the presence of a systemic infection may prevent an accurate assessment of the response.
The usual initial test dose in adults is 25 or 50 micrograms, increasing step-wise by 25 microgram increments at intervals of not less than 24 hours until a response of approximately 4 to 8 hours duration is observed. Each dose should be given **slowly** (over at least one minute). In order to be considered a responder the patient must demonstrate a significant decrease in muscle tone and/or frequency and/or severity of muscle spasms.
The variability in sensitivity to intrathecal baclofen between patients is emphasised. Signs of severe overdose (coma) have been observed in an adult after a single test dose of 25 micrograms. It is recommended that the initial test dose is administered with resuscitative equipment on hand.
Patients who do not respond to a 100 micrograms test dose should not be given further dose increments or considered for continuous intrathecal infusion.
Monitoring of respiratory and cardiac function is essential during this phase, especially in patients with cardiopulmonary disease and respiratory muscle weakness or those being treated with benzodiazepine-type preparations or opiates, who are at higher risk of respiratory depression.

Pediatric population Screening Phase
The initial lumbar puncture test dose for patients 4 to <18 years of age should be 25-50 micrograms/day based upon age and size of the child. Patients who do not experience a response may receive a 25 microgram/day dose escalation every 24 hours. The maximum screening dose should not exceed 100 micrograms/day in pediatric patients.

Dose-Titration Phase
Once the patient's responsiveness to Baclofen Sintetica has been established, an intrathecal infusion may be introduced. Baclofen Sintetica is most often administered using an infusion pump which is implanted in the chest wall or abdominal wall tissues. Implantation of pumps should only be performed in experienced centers to minimize risks during the perioperative phase.
Infection may increase the risk of surgical complications and complicate attempts to adjust the dose.
The initial total daily infused dose is determined by doubling the bolus dose which gave a significant response in the initial screening phase and administering it over a 24 hour period.
However, if a prolonged effect (i.e. lasting more than 12 hours) is observed during screening the starting dose should be the unchanged screening dose delivered over 24 hours. No dose increases should be attempted during the first 24 hours.
After the initial 24 hour period dosage should be adjusted slowly to achieve the desired clinical effect. If a programmable pump is used the dose should be increased only once every 24 hours; for non-programmable multi-dose reservoir pumps intervals of 48 hours between dose adjustments are recommended. In either case increments should be limited as follows to avoid possible overdosage:

Patients with spasticity of spinal origin:	10-30% of the previous daily dose

Patients with spasticity of cerebral origin: 5-15% of the previous daily dose.
If the dose has been significantly increased without apparent clinical effect pump function and catheter patency should be investigated.
There is limited clinical experience using doses greater than 1,000 micrograms/day.
It is important that patients are monitored closely in an appropriately equipped and staffed environment during screening and immediately following pump implantation. Resuscitative equipment should be available for immediate use in case of life-threatening adverse reactions.

Adult Maintenance Therapy
The clinical goal is to maintain as normal a muscle tone as possible, and to minimize the frequency and severity of spasms without inducing intolerable side effects. The lowest dose producing an adequate response should be used. 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.
In patients with spasticity of spinal origin maintenance dosing for long-term continuous infusions of intrathecal baclofen has been found to range from 12 to 2,003 micrograms/day, with most patients being adequately maintained on 300 to 800 micrograms/day.
In patients with spasticity of cerebral origin maintenance dosage has been found to range from 22 to 1,400 micrograms/day, with a mean daily dosage of 276 micrograms per day at 12 months and 307 micrograms per day at 24 months.

Pediatric population Maintenance Therapy
In children aged 4 to <18 years with spasticity of cerebral and spinal origin, the initial maintenance dosage for long-term continuous infusion of Baclofen Sintetica ranges from 25 to 200 micrograms/day (median dose: 100 micrograms/day). The total daily dose tends to increase over the first year of therapy, therefore the maintenance dose needs to be adjusted based on individual clinical response. There is limited experience with doses greater than 1,000 micrograms/day.
The safety and efficacy of Baclofen Sintetica for the treatment of severe spasticity of cerebral or spinal origin in children younger than 4 years of age have not been established (also see section 4.4).

Delivery specifications
Baclofen Sintetica ampoules of 20 ml containing 500 micrograms/ml and 5 ml / 20 ml containing 2 mg (2,000 micrograms)/ml are intended for use with infusion pumps. The concentration to be used depends on the dose requirements and size of pump reservoir. Use of the more concentrated solution obviates the need for frequent re-filling in patients with high dosage requirements.

Delivery regimen
Baclofen Sintetica is most often administered in a continuous infusion mode immediately following implant. After the patient has stabilized with regard to daily dose and functional status, and provided the pump allows it, a more complex mode of delivery may be started to optimize control of spasticity at different times of the day. For example, patients who have increased 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 desired onset of clinical effect.
Most patients require gradual dose increases to maintain optimum response during chronic therapy due to decreased responsiveness or disease progression. In patients with spasticity of spinal origin the daily dose may be increased gradually by 10-30% to maintain adequate symptom control. Where the spasticity is of cerebral origin any increase in dose should be limited to 20% (range: 5-20%). In both cases the daily dose may also be reduced by 10-20% if patients suffer side effects.
A sudden requirement for substantial dose escalation is indicative of a catheter complication (i.e. a kink or dislodgement) or pump malfunction.
In order to prevent excessive weakness the dosage of Baclofen Sintetica should be adjusted with caution whenever spasticity is required to maintain function.
During long-term treatment approximately 5% of patients become refractory to increasing doses due to tolerance or drug delivery failure (see Section 4.4 – Special Warnings and Precautions for Use “Treatment Withdrawal” section). This “tolerance” may be treated by gradually reducing Baclofen Sintetica dose over 2 to 4 week period and switching to alternative methods of spasticity management (e.g.

Intrathecal preservative-free morphine sulphate). Baclofen Sintetica should be resumed at the initial continuous infusion dose. Caution should be exercised when switching from Baclofen Sintetica to morphine and vice versa (see section 4.5).

Discontinuation
Except in overdose-related emergencies, the treatment with Baclofen Sintetica should always be gradually discontinued by successively reducing the dosage. Baclofen Sintetica should not be discontinued suddenly (see section 4.4).

Special populations
Renal impairment
No studies have been performed in patients with renal impairment receiving Baclofen Sintetica therapy. Because baclofen is primarily excreted unchanged by the kidneys (see section 5.2) 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 Baclofen Sintetica therapy. No dosage adjustment is recommended as the liver does not play any significant role in the metabolism of baclofen after intrathecal administration of baclofen. Therefore, hepatic impairment is not expected to impact the drug systemic exposure (see section 5.2).

Elderly population
Several patients over the age of 65 years have been treated with Baclofen Sintetica 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.

4.3 Contraindications
Known hypersensitivity to baclofen or any of its excipients (see section 6.1).
The drug should not be administered by any route other than intrathecal.

4.4 Special warnings and precautions for use
Intrathecal baclofen therapy is valuable but hazardous. Careful pre-operative assessment is mandatory. The patient must be given adequate information regarding the risks of this mode of treatment, and be physically and psychologically able to cope with the pump. It is essential that the responsible physicians and all those involved in the care of the patient receive adequate instruction on the signs and symptoms of overdose, procedures to be followed in the event of an overdose and the proper home care of the pump and insertion site.

***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, including paralysis, have been reported. Although they have been reported with baclofen, they have not been confirmed by contrast MRI or histopathology. 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. Clinicians should use their medical judgement regarding the most appropriate monitoring specific to their 'patients' medical needs to identify prodromal signs and symptoms for inflammatory mass especially if using pharmacy compounded drugs 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.

Pump Implantation

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 drug delivery failure, which may result in sudden Baclofen Sintetica withdrawal and its related symptoms (see Section 4.4 – Special Precautions for Use “Treatment Withdrawal” section).

Reservoir refilling
Reservoir refilling must be performed by trained and qualified personnel in accordance with the instructions provided by the pump manufacturer. Refills should be timed to avoid excessive depletion of the reservoir, as this would result in the return of spasticity or potentially life-threatening symptoms of Baclofen Sintetica withdrawal (see Section 4.4 – Special Precautions for Use “Treatment Withdrawal” section).
When refilling the pump care should be taken to avoid discharging the contents of the catheter into the intrathecal space.
Strict asepsis is required to avoid microbial contamination and infection.
Extreme caution must be taken when filling a pump equipped with an injection port that allows direct access to the intrathecal catheter as a direct injection into the catheter through the access port could cause a life-threatening overdose.

Precautions in pediatric patients
For patients with spasticity due to head injury, it is recommended not to proceed to long-term Baclofen Sintetica 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 Baclofen Sintetica in the pediatric population should be only prescribed by medical specialists with the necessary knowledge and experience. There is very limited clinical data regarding the safety and efficacy of the use of Baclofen Sintetica in children under the age of four years.

Precautions in special patient populations
In patients with **abnormal CSF flow** the circulation of drug and hence antispastic activity may be inadequate.

Psychotic disorders, schizophrenia, confusional states or Parkinson's disease may be exacerbated by treatment with oral baclofen. Patients suffering from these conditions should therefore be treated cautiously and kept under close surveillance.
Close supervision of patients with additional risk factors for suicide should accompany therapy with Baclofen Sintetica. Patients (and caregivers of patients) should be alerted about the need to monitor for clinical worsening, suicidal behaviour or thoughts or unusual changes in behaviour and to seek medical advice immediately if these symptoms present (see section 4.8 – Psychiatric disorders).
Special attention should be given to patients known to suffer from **epilepsy** as seizures have occasionally been reported during overdose with, and withdrawal from, Baclofen Sintetica as well as in patients maintained on therapeutic doses.
Baclofen Sintetica should be used with caution in patients with a history of **autonomic dysreflexia.** The presence of nociceptive stimuli or abrupt withdrawal of Baclofen Sintetica may precipitate an autonomic dysreflexic episode.
Baclofen should be used with caution in patients with **cerebrovascular or respiratory insufficiency.**
An effect of Baclofen Sintetica on **underlying, non-CNS related diseases** is unlikely because its systemic availability is substantially lower than after oral administration. Caution should be exercised in patients with a history of peptic ulcers and based on observations after oral baclofen therapy, in those with 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 Baclofen Sintetica in patients with renal impairment.

In rare instances elevated SGOT, alkaline phosphatase and glucose levels in the serum have been recorded when using oral baclofen.

Treatment withdrawal *(including associated with catheter or device malfunction)*

Abrupt discontinuation of Baclofen Sintetica, regardless of cause, manifested by increased spasticity, pruritus, paraesthesia and hypotension, has resulted in sequelae including a hyperactive state with rapid uncontrolled spasms, hyperthermia, tachycardia and symptoms consistent with neuroleptic malignant syndrome, e.g. altered mental status and muscle rigidity. In rare cases this has advanced to seizures/status epilepticus, rhabdomyolysis, coagulopathy, multiple organ failure and death. All patients receiving intrathecal baclofen therapy are potentially at risk for withdrawal.
Some clinical characteristics associated with intrathecal baclofen withdrawal may resemble autonomic dysreflexia, infection (sepsis), malignant hyperthermia, neuroleptic-malignant syndrome, or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis.
Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the signs and symptoms of baclofen withdrawal particularly those seen early in the withdrawal syndrome (e.g. priapism).
In most cases, symptoms of withdrawal appeared within hours to a few days following interruption of baclofen therapy. Common reasons for abrupt interruption of intrathecal baclofen therapy included malfunction of the catheter (especially disconnection), low volume in the pump reservoir, end of pump battery life and device malfunction. Device malfunction resulting in altered drug delivery leading to withdrawal symptoms including death has been reported.

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. The suggested treatment for intrathecal baclofen withdrawal is the restoration of intrathecal baclofen at or near the same dosage as before therapy was interrupted. However, if restoration of intrathecal delivery is delayed, treatment with GABA-ergic agonist drugs such as oral or enteral baclofen, or oral, enteral, or intravenous benzodiazepines may prevent potentially fatal sequelae. Oral or enteral baclofen alone should not be relied upon to halt the progression of intrathecal baclofen withdrawal.

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

Excipients:

Baclofen Sintetica 0.5 mg/ml and Baclofen Sintetica 2 mg/ml 20 ml ampoules contain 69.3 mg sodium per dose, equivalent to 3.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Baclofen Sintetica 2 mg/ml 5 ml ampoule contains 17.5 mg sodium per dose, that is to say essentially 'sodium-free'

This medicinal product may be diluted with sodium-containing solutions (see section 6.2); this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction
The co-administration of other intrathecal agents with Baclofen Sintetica is not recommended.
An attempt should be made to reduce or discontinue concomitant oral antispastic medications, preferably before initiating baclofen infusion. However, abrupt reduction or discontinuation during chronic intrathecal baclofen therapy should be avoided.

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

• **Alcohol and other compounds affecting the CNS:** There may be increased sedation where baclofen is taken concomitantly with other drugs acting on the CNS (e.g. analgesics, neuroleptics, barbiturates, benzodiazepines, anxiolytics) or with alcohol.

• **Tricyclic antidepressants:** During concurrent treatment with tricyclic antidepressants, the effect of baclofen may be potentiated, resulting in muscular hypotonia.

• **Antihypertensives and other drugs known to lower blood pressure:** Since concomitant treatment with drugs that lower blood pressure is likely to increase the fall in blood pressure, dosage of concomitant medications should be adjusted accordingly.

• **Levodopa:** Concomitant use of **oral** baclofen and levodopa/dopa-decarboxylase (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.

Morphine

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

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.

4.6 Fertility, pregnancy and lactation

Women of child bearing potential

Preconceptual counselling before programmable baclofen pump placement and in women with intrathecal baclofen pumps already implanted is recommended to ensure proper preparation and management throughout pregnancy and the peripartum period.

Pregnancy

There are limited data on the use of Baclofen Sintetica in pregnant women.

Reproductive toxicity has been observed at high oral doses of baclofen (see section 5.3). After intrathecal administration of Baclofen Sintetica small amounts of baclofen can be detected in maternal plasma (see section 5.2). Animal data show that baclofen can cross the placental barrier. Therefore, Baclofen Sintetica should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus.

Breast-feeding

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 of Baclofen Sintetica small amounts of baclofen can be detected in maternal plasma (see section 5.2). Therefore, no baclofen is expected to be found in the milk of the mother receiving Baclofen Sintetica therapy and no special recommendations are given.

Fertility

Animal studies have shown that intrathecal baclofen is unlikely to have an adverse effect on fertility under clinically-relevant conditions (see section 5.3).

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, and patients should be advised to exercise due caution. Other listed events include ataxia, hallucinations, vision blurred, diplopia and withdrawal symptoms. Operating equipment or machinery may be hazardous.

4.8 Undesirable effects
Some of the adverse reactions listed below have been reported in patients with spasticity of spinal origin but could also occur in patients with spasticity of cerebral origin. Adverse reactions that are more frequent in either population are indicated below.
Adverse drug reactions (Table 1) 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 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to<1/1,000); very rare (<1/10,000), and Not known (cannot be estimated from available data).
Table 1 Adverse drug reactions

Metabolism and nutritional disorders	
Uncommon:	Dehydration
Psychiatric disorders	
Common:	Depression, anxiety, agitation.
Uncommon:	Suicidal ideation (see section 4.4 – Precautions in special patient populations), suicide attempt, hallucinations, paranoia, euphoric mood.
Not known:	Dysphoria
Nervous system disorders	
Very common:	Somnolence
Common:	Convulsion, confusional state, sedation, dizziness, headache, paraethesia, 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.
Cardiovascular disorders	
Uncommon:	Bradycardia,
Vascular disorders	
Common:	Hypotension
Uncommon:	Hypertension, deep vein thrombosis, flushing, pallor.
Respiratory, thoracic and mediastinal disorders	
Common:	Respiratory depression, pneumonia, dyspnoea .
Not known:	Bradypnoea
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.
Musculoskeletal and connective tissue disorders	
Very common:	Hypotonia
Common:	Hypertonia
Not known:	Scoliosis (see section 4.4)
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).	
Reproductive system and breast disorders	
Common:	Sexual dysfunction (Intrathecal baclofen may compromise erection and ejaculation. This effect is usually reversible on withdrawal of Baclofen Sintetica).
Not known:	Erectile dysfunction
General disorders and administration site conditions	
Common:	Asthenia, pyrexia, pain, chills.
Uncommon:	Hypothermia.
Rare:	Life threatening withdrawal symptoms due to drug delivery failure (see section 4.4 – Special warnings and precautions for use “Treatment Withdrawal”).
Immune system disorders	
Not known:	Hypersensitivity

Adverse events associated with the delivery system
Adverse events associated with the delivery system (inflammatory mass at the tip of the catheter, catheter dislocation with possible complications, pocket infection, meningitis, overdose due to wrong manipulation of the device) have been reported.
Device malfunction resulting in altered drug delivery leading to withdrawal symptoms including death has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose
Special attention should be given to recognising the signs and symptoms of overdosage at all times, but especially during the initial "screening" and "dose-titration" phases and also during reintroduction of Baclofen Sintetica after an interruption of therapy.

Signs of overdose may appear suddenly or (more usually) insidiously.

Symptoms of overdose: excessive muscular hypotonia, drowsiness, light-headedness, dizziness, somnolence, seizures, loss of consciousness, hypothermia, excessive salivation, nausea, vomiting, tachycardia and tinnitus.

Respiratory depression, apnoea, and coma result from serious overdosage. Seizures may occur with increasing dosage or, more commonly, during recovery from an overdose. Serious overdose may occur through the inadvertent delivery of the catheter contents, errors in pump programming, excessively rapid dose increases or concomitant treatment with oral baclofen. Possible pump malfunction should also be investigated.

Treatment
There is no specific antidote for treating overdoses of intrathecal baclofen. Any instructions provided by the pump manufacturer should be followed, and the following steps should generally be undertaken:
• Where a programmable continuous infusion pump is used further delivery of baclofen should be halted immediately by removal of residual drug solution from the reservoir.
• If it is possible to do so without surgical intervention the intrathecal catheter should be disconnected from the pump as soon as possible, and infusion fluid allowed to drain back together with some CSF (up to 30-40 ml is suggested).
• Patients with respiratory depression should be intubated if necessary and ventilated artificially if required. Cardiovascular functions should be supported and in the event of convulsions, iv diazepam cautiously administered.
• Blood pressure, pulse, body temperature, cardiac rhythm and respiratory rate should be monitored.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Antispastic with a spinal site of attack: (ATC Code: M03B X01).
Baclofen depresses both monosynaptic and polysynaptic reflex transmission in the spinal cord by stimulating the $GABA_B$ receptors. Baclofen is a chemical analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).
Neuromuscular transmission is not affected by baclofen. Baclofen exerts an antinociceptive effect. In neurological diseases associated with spasm of the skeletal muscles, the clinical effects of baclofen take the form of a beneficial action on reflex muscle contractions and of marked relief from painful spasm, automatism, and clonus. Baclofen improves the patient's mobility, makes it easier for him/her to manage without aid, and facilitates physiotherapy.
Consequent important gains include 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 catheterization 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. Baclofen when introduced directly into the intrathecal space, permits effective treatment of spasticity with doses at least 100 times smaller than those for oral administration.

Intrathecal bolus:
The onset of action is generally half an hour to one hour after administration of a single intrathecal dose. 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 dose and severity of symptoms and the method and speed of drug administration.

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

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.

Distribution
After single intrathecal bolus injection/short-term infusion the volume of distribution, calculated from CSF levels, ranges from 22 to 157 ml.
With continuous intrathecal infusion daily doses of 50 to 1200 micrograms result in lumbar CSF concentrations of baclofen as high as 130 to 1240 ng/ml at steady state. According to the half-life measured in the CSF, CSF steady-state concentrations will be reached within 1-2 days.
During intrathecal infusion the plasma concentrations do not exceed 5 ng/ml, confirming that baclofen passes only slowly across the blood-brain barrier.

Elimination
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. Elimination half-life of baclofen after having reached steady-state in the CSF has not been determined.
After both single bolus injection and chronic lumbar subarachnoid infusion using an implantable pump system, the mean CSF clearance was about 30 ml/h.
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 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 due to effects on the brain centers.

Special populations
Elderly Patients
No pharmacokinetic data is available in elderly patients after administration of Baclofen Sintetica. 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.

Pediatrics
In pediatric 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 Baclofen Sintetica. 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 patients with hepatic impairment.

Renal impairment
No pharmacokinetic data is available in patients with renal impairment after administration of Baclofen Sintetica. Since baclofen is majorly eliminated unchanged through the kidneys, accumulation of unchanged drug 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. 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.

Mutagenicity and carcinogenicity

Baclofen was negative for mutagenic and genotoxic potential in tests in bacteria, mammalian cells, yeast, and Chinese hamsters. There was no evidence of a mutagenic potential of baclofen.

A 2-year rat study (oral administration) showed that baclofen is not carcinogenic. In the same study a dose-related increase in incidence of ovarian cysts and a less marked increase in enlarged and/or haemorrhagic adrenal glands was observed.

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.

Reproduction toxicity

Intrathecal baclofen is unlikely to have adverse effects on fertility or on prenatal or postnatal development based on **oral** studies in rats and rabbits. Baclofen 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.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride; water for injections

6.2 Incompatibilities

If alternative baclofen concentrations are required Baclofen Sintetica may be diluted under aseptic conditions with sterile preservative-free sodium chloride for injections. The ampoules should not be mixed with other solutions for injection or infusion (dextrose has proved to be incompatible due to a chemical reaction with baclofen).

The compatibility of Baclofen Sintetica with the components of the infusion pump (including the chemical stability of baclofen in the reservoir) and the presence of an in-line bacterial retentive filter should be confirmed with the pump manufacturer prior to use.

6.3 Shelf life

The expiry date of the product is printed on the package materials.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.

Store in the original package in order to protect from light.

After opening the product must be used immediately. Any remaining product not administered to the pump must be disposed of.

Medicines should be kept out of the reach and sight of children.

6.5 Nature and contents of container

Baclofen Sintetica 0.5 mg/5 ml

Type I clear colourless glass 20 ml ampoules.

Boxes of 1 ampoule or 5 ampoules containing 20 ml of solution.

Baclofen Sintetica 2 mg/ml

Type I clear colourless glass 5 ml ampoules

Box of 10 ampoules containing 5 ml of solution.

Type I clear colourless glass 20 ml ampoules
Box of 1 ampoule containing 20 ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Each ampoule is intended for single use only, and any unused solution not administered to the pump should be discarded. Ampoules should not be autoclaved.

7. Manufacturer

Sintetica SA, Via Penate 5, CH-6850 Mendrisio, Switzerland.

8. License holder

CTS Ltd., 4 Haharash St., Hod-Hasharon, 4524075.

9. Marketing authorization number

Baclofen Sintetica 0.5 mg/ml: 170-36-37175-99

Baclofen Sintetica 2 mg/ml: 156-85-34288-00

Revised in 08/2024 according to MOH guidelines.