SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Baclofen 10 mg/5 ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Baclofen 10 mg/5 ml solution for infusion:
1 ml solution for infusion contains 2.0 mg baclofen.

Each 5 ml ampoule contains 10 mg baclofen.
Each 5 ml vial contains 10 mg baclofen.

Each 20 ml vial contains 40 mg baclofen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Baclofen 10 mg/5 ml solution for infusion:

Solution for infusion

Clear, colourless solution for infusion with pH 5.0-7.0 and osmolarity260-320 mOsm/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Baclofen 10 mg/20 ml and Baclofen 10 mg/5 ml solution for infusion:
For the treatment of severe chronic spasticity associated with multiple sclerosis, with injuries to the spinal cord or of cerebral origin that cannot be treated successfully with a standard treatment.

Paediatric population *(*4 to <18 years)
Baclofen 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

Method of administration
The efficacy of Baclofen SUN has been demonstrated in clinical studies using the SyncroMed infusion system. This system is a delivery system with a refillable reservoir that is implanted subcutaneously, usually in the abdominal wall. The instrument is connected to an intrathecal catheter that also runs subcutaneously into the subarachnoid space. There is as yet no confirmed experience with other implantable pump systems.

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.

Dosage
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 intrathecal baclofen into the intrathecal space (EU certified pumps). 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

The testing, implantation and dosage-titration phases of the intrathecal administration must be performed under in-patient conditions in centres with specific experience with close medical supervision by suitably qualified doctors. Intensive medical care should be immediately available owing to possible life-threatening events or serious adverse reactions.

In order to establish the optimal dosage regimen for Baclofen, every patient receives an intrathecal bolus injection of Baclofen 0.05 mg/1 ml during an initial test phase before starting the long-term treatment, either via an intrathecal catheter or by lumbar puncture. This is followed by very careful patient-tailored dosage titration. This procedure is necessary because of the large differences between the therapeutically effective dosages required by different patients. Long-term administration is achieved by means of an implantable pump for continuous delivery of baclofen solution to the cerebrospinal fluid using Baclofen 10mg/20ml or Baclofen 10mg/5ml.

Before Baclofen is administered, the subarachnoid space of patients with post-traumatic spasticity should be investigated by myelography. If radiological signs of arachnoiditis are found, treatment with Baclofen should not be instituted.

Before administration of Baclofen, the solution should be checked for clarity and colourlessness. Only clear solutions practically free from particles should be used. If clouding or discoloration is evident, then the solution should not be used and should be discarded.
The solution it contains is stable, isotonic, pyrogen and antioxidant free and has a pH-value of 5.5–7.0.
Every ampoule is intended for single use only.

Baclofen 10 mg/20 ml solution for infusion:
Baclofen 10 mg/5 ml solution for infusion:

Implantation phase/dosage-titration phase (under inpatient conditions)
After the action of baclofen has been confirmed in the test phase, intrathecal infusion is started using one of the implantable infusion pumps given above. The antispastic action of baclofen sets in 6 to 8hours after the start of continuous infusion and reaches its maximum within 24 to 48hours.

The initial total daily dosage of Baclofen is calculated as follows:
If the duration of action of the test dose is more than 12hours, this is taken as the initial daily dose. If the duration of action of the test dose is shorter than 12hours, then the initial daily dose is double the test dose. The dosage should not be increased within the first 24hours.

After the first day of treatment, the dosage can slowly be titrated from day to day in order to achieve the desired action. The increase in the dosage per day should not exceed 10 to 30% of the previous dose in patients with spinal spasticity and 5 to 15% in patients with cerebral spasticity. When using a programmable pump, it is advisable to adjust the dosage only once in any 24-hour period. With non-programmable pumps with a 76cm catheter length that release 1ml of solution per day, intervals of 48hours are recommended in order to be able to assess the reaction to the dosage. If a considerable rise in the daily dosage does not increase the clinical action, then the function of the pump and the patency of the catheter should be checked.

In general, the dosage is increased to a maintenance dosage of 300 to 800microgram/day in patients with spinal spasticity. Patients with cerebral spasticity usually require lower doses (see below).

Long-term treatment phase
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. The lowest dose with which the spasticity can be well controlled without the appearance of unacceptable adverse reactions 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.

As over the course of the treatment the therapeutic effect can diminish or the severity of the spasticity can alter, dosage titration under in-patient conditions is usually necessary in the long-term treatment phase. Here also, the daily dosage can be increased by 10 to 30% in patients with spinal spasticity and 5

to 20% (upper limit) in patients with cerebral spasticity by altering the delivery rate of the pump or by changing the concentration of baclofen in the reservoir. Conversely, if adverse reactions occur, the daily dosage can be reduced by 10 to 20%.

If the dosage must suddenly be increased in order to achieve a sufficient effect, the possibility of a pump malfunction or a kink, rupture (tear) or displacement of the catheter must be considered.

The maintenance dosage for the long-term treatment of patients with **spinal spasticity** using continuous intrathecal infusion of Baclofen is normally 300 to 800microgram of baclofen per day. The lowest and highest daily dosages recorded as administered to individual patients during dosage titration are 12microgram and 2003microgram respectively (US studies). Experience with dosages above 1000microgram/day is limited. During the first few months of treatment, the dosage must be checked and adjusted particularly often.

In patients with **cerebral spasticity**, the maintenance dosages reported during long-term therapy with continuous intrathecal infusion of Baclofen range from 22 to 1400microgram of baclofen per day, with mean daily doses of 276microgram after an observation period of 1year and 307microgram after 2years. Children under 12years of age usually require lower dosages (range: 24 to 1199microgram/day; mean: 274microgram/day).

If technically possible for the pump, once a constant daily dosage is reached and the antispastic action is stabilised, it can be attempted to adapt the administration to the daily rhythm of the spasticity. For example, if spasms occur more frequently at night, this may require a 20% increase in the hourly infusion delivery rate. Changes in the infusion rate should be programmed so that they start 2hours before the desired clinical effect.

Throughout the period of treatment, regular checks in the treatment centre for the tolerability of Baclofen and for signs of infection are necessary at least at monthly intervals. The functioning of the infusion system must be checked regularly. A local infection or a malfunction of the catheter can cause interruption of the intrathecal delivery of baclofen with life-threatening consequences (see section 4.4).

The necessary concentration of baclofen when filling the pump depends on the total daily dose and on the rate of delivery of the pump. If baclofen concentrations other than 0.05mg/ml, 0.5mg/ml or 2mg/ml are required, Baclofen must be diluted under aseptic conditions with sterile preservative-free sodium chloride solution for injections. The instructions of the pump manufacturer should be observed here.

About 5% of patients may show a need for an increased dosage due to a loss of efficacy (development of tolerance) during long-term treatment. As described in the literature, a baclofen-free interval of 10 to 14days in which morphine sulphate without preservatives is administered intrathecally will counteract this development of tolerance. After this interval, responsiveness to the treatment with Baclofen may again be possible. Caution should be exercised when switching from baclofen to morphine and vice versa (see section 4.5). The therapy should then be resumed at the initial dosage for the continuous

infusion, and the dosage must be re-titrated in order to avoid adverse events due to overdosing. This should again be performed under inpatient conditions.

Special patient groups
In patients with slowed CSF circulation due, for example, to blockage caused by inflammation or trauma, the delayed migration of Baclofen can reduce the antispastic efficacy and boost the adverse reactions (see section 4.3).

Renal impairment
No studies have been performed in patients with renal impairment with baclofen therapy.
In patients with impaired renal function, the dosage may need to be reduced to take account of the clinical condition or the level of reduced renal clearance.

Hepatic impairment
No studies have been performed in patients with hepatic impairment receiving baclofen 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).

Paediatric population

Maintenance Therapy
The implantation of the pump requires a certain body size.

The experience in children under 6 years of age is limited.
The safety and efficacy of Baclofen 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).

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 ranges from 25 to 200 mcg/day (median dose: 100 mcg/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.

Elderly
As part of clinical studies, some patients over 65years of age have been treated with Baclofen without specific problems being observed. Experience with Baclofen tablets shows, however, that adverse reactions can occur more frequently in this patient group. Elderly patients should therefore be monitored carefully for the development of adverse reactions.

Discontinuation of treatment
No specific limit to the duration of treatment is foreseen.

Except in emergencies due to overdosing or following development of serious adverse reactions, the treatment should always be discontinued by gradual reduction in the dosage. Baclofen must not be abruptly discontinued. In the event of abrupt discontinuation of intrathecal administration of baclofen, sequelae such as high fever, changes in mental state, increased spasticity as a rebound effect and muscle rigidity may occur regardless of the cause of the discontinuation, and in rare cases these may progress to seizures/status epilepticus, rhabdomyolysis, multiorgan failure and death (see section 4.4).

Abrupt discontinuation of Baclofen, especially at doses above the normal range, can lead to an intolerable increase in spasticity. Abrupt discontinuation of Baclofen tablets has also been followed by confusion, sensory disturbances, disturbed mood states with hallucinations, seizures/status epilepticus, and sometimes increased spasticity, particularly after long-term therapy.

Withdrawal symptoms
In the event of abrupt discontinuation of intrathecal administration of baclofen, sequelae such as high fever, changes in mental state, increased spasticity as a rebound effect and muscle rigidity may occur regardless of the cause of the discontinuation, and in rare cases these may progress to seizures/status epilepticus, rhabdomyolysis, multiorgan failure and death (see section 4.4).

Discontinuation symptoms can possibly be confused with poisoning symptoms. They also require inpatient admission of the patient.

Therapy in the event of occurrence of withdrawal symptoms
A rapid correct diagnosis and treatment in an emergency medical or intensive care unit are important to prevent the possibly life-threatening central nervous and systemic effects of withdrawal of intrathecal baclofen (see section 4.4).

4.3 Contraindications

Baclofen must not be administered in case of:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,)
- therapy-resistant epilepsy.

Baclofen should be administered only into the subarachnoid space. Baclofen must not be administered by the intravenous, intramuscular, subcutaneous or epidural routes.

4.4 Special warnings and precautions for use

Baclofen may be administered only with special caution to patients with:
- ***impaired CSF circulation due to passage constriction,***
- ***epilepsy or other cerebral seizure illnesses,***
- ***bulbar paralytic symptoms or partial paralysis of the respiratory musculature,***
- ***acute or chronic confusional states,***
- ***psychotic states, schizophrenia or Parkinson's disease,***
- ***a history of dysreflexia of the autonomic nervous system,***

- ***cerebrovascular and respiratory failure,***
- ***pre-existing hypertension of the bladder sphincter,***
- ***impaired renal function,***
- ***peptic ulcers,***
- ***severe hepatic dysfunction***

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.

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).

Precautions in paediatric patients
Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Use of baclofen in the paediatric 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 in children under the age of four years.

The testing, implantation and dosage-titration phases of the intrathecal treatment must be performed in hospital under close medical supervision by suitably qualified doctors in centres with specific experience in order to ensure the continuous monitoring of the patients.

Owing to possible life-threatening events or severe adverse reactions, suitable intensive medical care facilities should be immediately available. Suitable precautionary measures must be taken before the start of treatment.

In the event of abrupt discontinuation of intrathecal administration of baclofen, sequelae such as high fever, changes in mental state, increased spasticity as a rebound effect, and muscle rigidity may occur regardless of the cause of the discontinuation, and in rare cases may progress to seizures / status epilepticus, rhabdomyolysis, multiple organ failure and death.

Before the start of treatment with Baclofen, any unsatisfactory treatment with other antispastic medications should be tailed off.

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
The patients should be free from infection prior to the test phase with Baclofen SUN 0.05 mg/1 ml, as systemic infections 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 SUN 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 SUN 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.

Medical environment
Initial intrathecal administration, infusion system implantation, and initial infusion and dose adjustments of baclofen are associated with risks such as CNS attenuation, cardiovascular collapse, and respiratory failure, respectively. Therefore, these steps must be taken under inpatient conditions when intensive care measures are available and dosing instructions are followed. Necessary equipment should be available to perform resuscitation measures immediately in case of life-threatening symptoms of severe overdose. The attending physician must have special experience in handling intrathecal administration and infusion systems.

Monitoring the patients

The patient must be monitored closely until his condition is stable. The treating doctor, the patient and the hospital staff as well as other persons involved in the care of the patient must be adequately informed about the risks of this method of treatment. In particular, the symptoms of overdosing or sudden withdrawal, the measures to be taken in these cases, and the care of the pump and of the implantation site must be known.

Test phase
The respiratory and cardiovascular functions should be carefully monitored following administration of the initial test doses. This is especially true for patients with heart or lung diseases and with weakness of the respiratory musculature. Attention should be paid to an

increased risk of respiratory depression in patients who are receiving concurrent benzodiazepines or opiates.

Prior to testing with Baclofen SUN, patients should be free of infection, as systemic infection may increase the risk of surgical complications. Systemic infection can also complicate dosage adjustment. A local infection or an improperly installed catheter may also lead to administration problems that may result in abrupt discontinuation of baclofen SUN and associated symptoms (see section 4.4 - Special precautions for use, "treatment withdrawal" section)

Additional notes on dosage adjustment

Occasionally a certain level of spasticity is necessary to maintain body posture and balance or other functions. In order to avoid excessive weakness and thus to prevent the patient from falling over, Baclofen should be administered with care in these cases. A certain level of muscle tone and occasional spasms may also be necessary to support circulatory function and prevent deep-vein thrombosis.

Treatment withdrawal (including associated with catheter or device malfunction)

Abrupt discontinuation of Baclofen, regardless of cause, manifested by increased spasticity as a rebound effect, pruritis, paraesthesia (tingling or burning) and hypotension has resulted in sequelae including a hyperactive state with rapid and uncontrolled spasms, hyperthermia and symptoms consistent with malignant neuroleptic syndrome, e.g. changes in mental state and muscle rigidity. In rare cases these symptoms have developed further to seizures/ status epilepticus, muscle degradation (rhabdomyolysis), clotting disorders (coagulopathy), multiple organ failure and death. All patients receiving intrathecal baclofen therapy are potentially at risk for abrupt withdrawal. 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. priaprism).

The early symptoms of baclofen withdrawal include recurrence of the spasticity originally present, itching, low blood pressure and paraesthesia. Some clinical signs of advanced withdrawal syndrome resemble those of autonomic dysreflexia, infection or sepsis, malignant hyperthermia, malignant neuroleptic syndrome or other conditions that accompany a hypermetabolic state or extensive rhabdomyolysis.

Other symptoms of abrupt discontinuation can be: hallucinations, psychotic, manic or paranoid states, severe headaches and sleeplessness. An autonomic crisis with heart failure has been observed in one case of a patient with a syndrome resembling stiff-man syndrome.

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.

Therapy of discontinuation symptoms/withdrawal symptoms

Rapid and correct confirmation of the diagnosis and treatment in an emergency medical or intensive care unit are important to prevent the possibly life-threatening CNS and systemic effects of withdrawal of intrathecal baclofen. The recommended treatment is resumption of the intrathecal baclofen administration at the same or approximately the same dosage as before interruption of the intrathecal baclofen delivery. However, if intrathecal baclofen administration can be resumed only after a delay, treatment with GABA-agonists such as oral or enteral baclofen or oral, enteral or intravenous benzodiazepines can prevent the potentially fatal sequelae. However, there is no guarantee that mere administration of oral

or enteral baclofen is sufficient to prevent the progression of the symptoms of withdrawal of intrathecal baclofen.

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. 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 as well as in patients maintained on therapeutic doses.
Intrathecal baclofen should be used with caution in patients with a history of **autonomic dysreflexia.** The presence of nociceptive stimuli or abrupt withdrawal of Baclofen may precipitate an autonomic dysreflexic episode.
Baclofen should be used with caution in patients with **cerebrovascular or respiratory insufficiency.**
An effect of Baclofen on **underlying, non-CNS related diseases** is unlikely because its systemic availability is substantially lower than after oral administration. Observations after oral baclofen therapy suggest that caution should be exercised in patients with a history of peptic ulcers and 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 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.

Elderly patients >65 years
Elderly patients may be more susceptible to the side effects of oral baclofen in the titration stage and this may also apply to baclofen.

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

Sodium content
This medicinal product contains solution for injection contains less than 1 mmol sodium (23 mg) per maximum of 2ml (corresponding to 100 microgram baclofen), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies with other medications have been performed.

The co-administration of other intrathecal agents with Baclofen is not recommended. However, abrupt reduction or discontinuation during chronic intrathecal baclofen therapy should be avoided.
There is little experience with the use of 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).

Experience with oral baclofen would suggest that:

Alcohol and other compounds affecting the CNS
Baclofen should not be used concomitantly with other antispasticity medications to avoid possible adverse reactions.
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.
In particular, the concomitant intake of alcohol should be avoided as the interactions with alcohol are unpredictable.

Tricyclic Antidepressants
When taken concomitantly with baclofen tablets, some specific medications for the treatment of depression (tricyclic antidepressants) can potentiate the effect, and as a result considerable muscle relaxation may occur. For this reason, such an interaction during concomitant administration of Baclofen and tricyclic antidepressants cannot be excluded.

Antihypertensives
The combination of baclofen tablets and antihypertensive medication can result in an enhanced reduction in blood pressure. For this reason, blood pressure should be checked regularly in the event of concomitant administration of Baclofen and medications for lowering blood pressure. If applicable, the dosage of the antihypertensive medication must be reduced.

Morphine
When Baclofen is combined with morphine, a drop in blood pressure has occurred in one case. It cannot be excluded that in such cases respiratory disturbances or CNS disturbances may also occur. For this reason, an increased risk of these disturbances should be borne in mind during concomitant administration of opiates or benzodiazepines.

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

Levodopa/DDC inhibitor
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.

There is hitherto no information on the concomitant administration of Baclofen with other intrathecally administered medications.

4.6 Fertility, pregnancy and lactation

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

After intrathecal administration of baclofen small amounts of baclofen can be detected in maternal plasma (see section 5.2). Baclofen crosses the placenta and has shown reproductive toxicity (see section 5.3). In contrast to oral administration, intrathecally infused baclofen was not teratogenic in mice, rats and rabbits (see section 5.3).
Baclofen should not be used during pregnancy unless the expected benefit for the mother outweighs the possible risks for the child.

Breastfeeding
Baclofen is excreted in breast milk. No statement concerning breast milk concentration can be made as there is insufficient data available. Baclofen should not be used during lactation, unless the expected benefit for the mother outweighs the possible risks for the child.

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

The ability to drive or operate machinery may be considerably impaired during treatment with Baclofen. Alcohol consumption increases this impairment still further.

Central nervous system (CNS) depressant effects such as somnolence and sedation have been reported in some patients on baclofen. Other listed events include ataxia, hallucination, diplopia, vision blurred and withdrawal symptoms. Operating equipment or machinery may be hazardous.

In patients treated with inthrathecal baclofen, the ability to continue driving or operating complex machinery should be routinely evaluated by the treating physician.

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 2) 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: 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), not known (cannot be estimated from the available data).

Table 2

Metabolism and nutrition disorders	
Uncommon:	Dehydration.
Psychiatric disorders	

Common:	Depression, Agitation, Anxiety.
Uncommon:	Suicidal ideation, Suicide attempt (see section 4.4 – Precautions in special patient populations), Paranoia, Hallucinations, Euphoric mood, Dysphoria.
Nervous system disorders	
Very common:	Somnolence.
Common:	Convulsion, Confusional State, Disorientation, Lethargy, Dysarthria, Headache, Paraesthesia, Insomnia, Sedation, Dizziness.
Uncommon:	Ataxia, Memory impairment, Nystagmus, Hypothermia.
Convulsion and headache occur more frequently in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.	
Eye disorders	
Common:	Accommodation disorders, vision blurred, diplopia.
Cardiac disorders	
Uncommon:	Bradycardia.
Vascular disorders	
Common:	Orthostatic hypotension
Uncommon:	Deep vein thrombosis, Hypertension, Flushing, Pallor.
Respiratory, thoracic and mediastinal disorders	
Common:	Respiratory depression, Aspiration Pneumonia, Dyspnoea, Bradypnoea.
Gastrointestinal disorders	
Common:	Vomiting, Constipation, Diarrhoea, Nausea, Dry mouth, Decreased appetite, Increased salivation
Uncommon:	Ileus, Dysphagia, Hypogeusia.
Nausea and vomiting occur more frequently in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin	
Skin and subcutaneous tissue disorders	
Common:	Urticaria, Pruritus, Oedema peripheral and/or Face oedema.
Uncommon:	Alopecia, Hyperhidrosis.
Musculoskeletal and connective tissue disorders	
Very common:	Hypotonia.
Common:	Increased muscle tension
Not known:	Scoliosis
Renal and urinary disorders	
Common:	Urinary retention, Urinary incontinence.
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 (Baclofen may compromise erection and ejaculation. This effect is usually reversible on withdrawal of Baclofen).
Not known:	Erectile dysfunction
General disorders and administration site conditions	
Common:	Asthenia, Pain, Pyrexia, Chills.
Rare:	Life-threatening withdrawal symptoms due to drug delivery failure (see section 4.4).

In approximately 5% of female patients with multiple sclerosis treated with baclofen tablets for more than one year, ovarian cysts were detected by palpation. In most cases, these cysts disappeared spontaneously, although therapy was continued. Ovarian cysts are known to form spontaneously in a proportion of the healthy female population.

A definite causal relationship between the observed side effects and the administration of baclofen is not always possible, since part of the observed side effects may also be symptoms of the underlying disease being treated. In particular, frequently occurring side effects such as dizziness, drowsiness, somnolence, headache, nausea, drop in blood pressure and muscle weakness are mostly caused by the drug.

Adverse events associated with the delivery system
These can include inflammatory mass at the tip of the catheter, dislocation/kinking/rupture (tearing) of the catheter with possible complications, infection of the implantation site, meningitis, septicaemia, pump-pocket seroma and haematoma with a possible risk of inflammation, failure of the pump function and CSF leakage, as well as skin perforation after a long time, and overdosing or underdosing due to incorrect handling, whereby in some cases a causal relationship with baclofen cannot be excluded (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

At the first signs of overdosing with Baclofen, the patient should be admitted to inpatient care if being treated as an outpatient.

Attention should be paid to symptoms of overdosing throughout the period of treatment, but especially during the test phase and the dosage adjustment phase and on restarting Baclofen after a pause in treatment. For example, an overdose may be the result of accidental delivery of the catheter contents during a patency check or catheter position check. Other possible causes include programming errors, extremely rapid dose increases, concurrent oral administration of baclofen, or pump malfunction.

In one case, an adult patient showed signs of severe overdosing (coma) after injection of a single dose of 25 microgram of baclofen (Baclofen). Conversely, daily dosages of 4000 microgram have been required and tolerated in isolated cases (German studies). The lowest lethal dose reported in German studies is 4000 microgram, and the highest recorded dose survived without sequelae is 20000 microgram of baclofen (Baclofen).

Symptoms of poisoning
Increasing muscle hypotension, dizziness, sedation, convulsion, loss of consciousness, hypothermia, salivary hypersecretion, nausea and vomiting.

Respiratory depression, apnoea and coma may result from serious overdosing. 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.

Therapy in overdosing
There is no known specific antidote for the treatment of overdosing with Baclofen. In general the following measures should be performed:

- Removal as rapidly as possible of the remaining baclofen solution from the pump.
- Patients with respiratory depression should be intubated until baclofen has been eliminated.
- Support of the cardiovascular function. If spasms occur, diazepam intravenous should be administered carefully.
- Blood pressure, pulse, body temperature, cardiac rhythm and respiratory rate should be monitored.

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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: muscle-relaxants, other centrally acting agents, ATC code: M03BX01

Baclofen is a p-chlorophenyl derivative of gamma-aminobutyric acid (GABA), which is ubiquitous in the central nervous system and is the most important inhibitory transmitter in the CNS.
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.
Baclofen can cause general attenuation of the central nervous system in both humans and animals, resulting in sedation, somnolence, and respiratory and cardiovascular depression. In addition, it has been shown to have a dose-dependent inhibitory effect on erectile function in males by stimulating the $GABA_B$ receptor.

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

The systemic availability of baclofen after intrathecal administration (Baclofen) is considerable less than after oral administration (Baclofen tablets).

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

Infusion directly into the spinal subarachnoid space circumvents absorption processes and allows access to the receptor sites in the posterior horn of the spinal cord.

The direct delivery of baclofen to the cerebrospinal space allows effective treatment of the spasticity with doses that are at least 100 times lower than those of oral therapy (Baclofen tablets).

Distribution

After a single intrathecal bolus injection/rapid infusion, the distribution volume calculated from the concentration in the CSF ranges from 22 to 157ml. The mean of about 75ml corresponds approximately to the human CSF volume, and indicates that it is this in which the baclofen is mainly distributed. With continuous intrathecal infusion of daily doses of between 50 to 1200 microgram, steady-state concentrations of baclofen in the CSF of the lumbar region of 130 to 1240 nanogram/ml are reached within 1 to 2 days. In the steady state with continuous intrathecal infusion of daily doses between 95 to 190 microgram, a mean baclofen concentration gradient from lumbar to cisternal of 4:1 (range 8.7:1-1.8:1) is found. This is independent of the body position of the patient. All three strengths of baclofen solution (density: 1.003 ± 0.001 g/cm^3 at 23°C) are practically isobaric to human CSF (density: 1.006-1.008 g/cm^3). The baclofen plasma concentrations under intrathecal infusion of clinically used doses of baclofen are below 5 nanogram/ml (≤ 10 nanogram/ml in children) and are thus below the analytical quantitation limits.

Elimination

The elimination half-life from the CSF after administration of a single intrathecal bolus injection/ rapid infusion of 50 to 135 microgram of baclofen is 1 to 5 hours. Both after a single bolus injection and after continuous infusion into the spinal subarachnoid space using an implanted pump, the mean clearance from the CSF is about 30 ml/hour (corresponding to the physiological turnover rate of the CSF). Thus the amount of baclofen infused over 24 hours is eliminated almost completely with the CSF over the same period of time. Systemic baclofen is eliminated almost completely renally in the unaltered form. A metabolite (beta-(p-chlorophenyl)-gamma-hydroxybutyric acid) formed in small amounts in the liver by oxidative desamination is inactive. Investigations suggest baclofen is not metabolised in

the CSF. Other routes of elimination are not considered significant according to the information currently available.

From animal experiments it is evident that the active substance cumulates in the CSF after administration of high doses. It has not been investigated to what extent this finding is relevant for humans and what consequences should be expected.

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

Paediatric population
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 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 baclofen. 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
Histological investigations in studies with continuous intrathecal infusion of baclofen to rats (2-4 weeks) and dogs (2-4 months) have revealed no signs of a local reaction or inflammation due to baclofen. Reactions are ascribed to the irritation due to the infusion catheter.

Mutagenicity and Carcinogenicity
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 2-year 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 were observed in female rats.

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

foetuses 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 foetuses at a high intraperitoneal dose.

Baclofen had no effect on the fertility of female rats. Possible effects on male fertility have not been investigated.

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other infusion or injection solutions.

6.3 Shelf life

Shelf life in unopened containers:
Baclofen 10 mg/5 ml solution for infusion: 2 years

The product should be used immediately after opening.

Shelf life after dilution:
Chemical and physical in-use stability has been demonstrated for 6 months at 37°C.

6.4 Special precautions for storage

This product does not require any special storage conditions.

6.5 Nature and contents of container

Baclofen 10 mg/5 ml solution for infusion:
Clear, colourless ampoules of glass type I (Ph.Eur.) containing 5 ml of solution for infusion.
Clear, colourless vials of glass type I (Ph. Eur.) containing 5 ml or 20 ml of solution for infusion.
The 5 ml vials are sealed with grey rubber stoppers (bromobutyl) and royal blue flip-off aluminium caps.
The 20 ml vials are sealed with grey rubber stoppers (bromobutyl) and pink flip-off aluminium caps.

Packs with 1 or 5 ampoules.

Packs with 1 or 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unrequired fraction must be destroyed.

If required, Baclofen 10mg/20ml and 10mg/5ml solution for infusion may be diluted under aseptic conditions with sterile, preservative-free sodium chloride solution for injection.

7 MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe B.V.

Polarisavenue 87

2132 JH Hoofddorp

The Netherlands

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