SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gablofen 0.5 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 0.5 mg (500 micrograms) baclofen.

Each 20 ml vial contains 10 mg (10000 micrograms) baclofen.

Excipient with known effect:

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless solution.
pH: 5.5 – 7.5
Osmolality: 255 mOsm/kg -320 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Gablofen 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 medicinal products and/or those patients who experience unacceptable side-effects at effective oral doses. Gablofen is effective in patients with severe chronic spasticity of cerebral origin, resulting e.g. from cerebral palsy, brain trauma or cerebrovascular accident.

Paediatric population

Gablofen is indicated in patients aged 4 to <18 years with severe chronic spasticity of spinal or cerebral 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 undesirable effects at effective oral doses.

4.2 Posology and method of administration

Efficacy of baclofen intrathecal has been demonstrated in clinical studies with an EU certified pump. This is an implantable administration system with a refillable reservoir that is implanted subcutaneously, usually in the abdominal wall. The instrument is connected to an intrathecal catheter that passes subcutaneously into the subarachnoid space.

Intrathecal administration of Gablofen 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.

Posology

Gablofen 50 micrograms/1ml 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 Gablofen 500 micrograms/ml, 1000 micrograms/ml, or 2000 micrograms/ml 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 individualized 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 physicians. Intensive medical care should be immediately available owing to possible life-threatening events or serious adverse reactions.

Only pumps constructed of material known to be compatible with the product and incorporating an in-line bacterial retentive filter should be used.

Before Gablofen is administered, the subarachnoid space of patients with post-traumatic spasticity should be investigated by an appropriate imaging technique (myelography) as clinically indicated. If radiological signs of arachnoiditis are found, treatment with Gablofen should not be instituted.

Before administration of Gablofen, 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 5.5–7.5.
Every pre-filled syringe is intended for single use only.
Every vial is intended for single use only.

Adult screening phase
Prior to pump implantation and initiation of chronic infusion of baclofen, patients must demonstrate a positive response to intrathecal test dose in an initial test phase. Usually, a bolus test dose is administered via lumbar puncture or an intrathecal catheter, in order to provoke a response. Patients should be infection-free prior to screening, as the presence of a systemic infection may prevent an accurate assessment of the response.

The initial test phase must only be performed with low concentration solution containing 50 micrograms baclofen in 1 ml.

The screening procedure is as follows. The usual initial test dose in adults is 25 or 50 micrograms which is administered slowly into the intrathecal space by barbotage (alternating intrathecal baclofen administration and distraction of cerebrospinal fluid to obtain an appropriate mixture) over a period of not less than one minute. A positive response consists of a significant decrease in muscle tone and/or frequency and/or severity of spasms. At intervals of at least 24 hours the dosage can be increased by increments of 25 micrograms to a maximum test dosage of 100 micrograms, if the response is less than desired.

After every bolus injection the patient must be supervised for 4 to 8 hours.
The action of a single intrathecal dose generally sets in ½ to 1 hour after administration. The maximum spasmolytic effect sets in about 4 hours after administration and lasts about 4 to 8 hours. The time to onset of action, the peak action and the duration of action vary from patient to patient and are dependent on the dosage, on the severity of symptoms, and on the mode and speed of administration.

There is much variability with regard to sensitivity to intrathecal baclofen between patients. Signs of severe overdose (coma) have been observed in an adult after a single test dose of 25 micrograms.

Patients who do not respond to a 100 micrograms test dose should not be given further dose increments and treatment should not progress to continuous intrathecal infusion.

Resuscitative equipment and trained staff must be available during screening, dose titration, and refills.
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.

<u>Paediatric population screening phase</u>
The recommended initial lumbar puncture test dose for patients 4 to <18 years of age is 25 - 50 micrograms/day which is administered slowly into the intrathecal space by barbotage over a period of not less than one minute. Patients who do not experience a response may receive a 25 micrograms/day dose escalation every 24 hours. The maximum screening dose should not exceed 100 micrograms/day in paediatric patients.

Dose titration phase

Once the patient's responsiveness to baclofen has been established, an intrathecal infusion may be introduced. Baclofen 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 centres to minimise risks during the perioperative phase.

Infection may increase the risk of surgical complications and complicate attempts to adjust the dose.

A very careful patient tailored dosage titration is necessary because of the potential for large response differences with a given dose among patients.
Following implantation, if the duration of action of the test dose is more than 12 hours, this is taken as the initial daily dose. If the duration of action of the test dose is shorter than 12 hours, then the initial daily dose is double the test dose. The dose must not be increased during the first 24 hours. After the first 24 hours the dose is adjusted slowly on a daily basis, to obtain the desired effect.

The antispastic action of baclofen sets in 6 to 8 hours after the start of continuous infusion and reaches its maximum within 24 to 48 hours.

Adult Patients with Spasticity of Spinal Cord Origin: After the first 24 hours, for adult patients, the daily dosage should be increased slowly by 10% to 30% increments and only once every 24 hours, until the desired clinical effect is achieved.

Adult Patients with Spasticity of Cerebral Origin: After the first 24 hours, the daily dose should be increased slowly by 5% to 15% only once every 24 hours, until the desired clinical effect is achieved.

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 76 cm catheter that release 1 ml of solution per day, intervals of 48 hours 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 pump function and the catheter permeability should be verified.

During the test phase, as well as during the titration period following implantation, patients should be closely monitored at an institution with all the necessary equipment and personnel. Resuscitative equipment must be on immediate stand-by in the event of any reaction that threatens the vital prognosis, or onset of very serious undesirable effects. In order to limit risks in the perioperative phase, the pump must only be implanted at centres with experienced personnel.

Adult maintenance therapy

The clinical goal is to maintain muscle tone as close to normal as possible, and to minimise the frequency and severity of spasms without inducing intolerable undesirable 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 is normally 300 to 800 micrograms of baclofen/day. The lowest and highest daily dosages recorded as administered to

individual patients during dosage titration are 12 micrograms and 2003 micrograms respectively (US studies). Experience with dosages above 1000 micrograms/day is limited. During the first few months of treatment, the dosage must be checked and adjusted particularly often.

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

Paediatric population initial maintenance therapy
In children aged 4 to <18 years with spasticity of cerebral and spinal origin, the initial maintenance dose for long-term continuous infusion of baclofen 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.

Method of administration
Baclofen is most often administered in a continuous infusion mode immediately following implant. 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 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 undesirable effects.

If a significant dose increase should suddenly be necessary, this is indicative of a catheter complication (kink, tear or dislodgement) or pump malfunction.

In order to prevent excessive weakness the dosage of baclofen should be adjusted with caution whenever spasticity is required to maintain function.

Around 5% of patients receiving long-term treatment become refractory to dose escalation. This may be due to therapeutic failure. There is insufficient experience available to make any recommendations on dealing with treatment failure. However, this phenomenon has occasionally been treated in hospitals by a “drug holiday” consisting of the gradual reduction off baclofen intrathecal over a period of 2 to 4 weeks and switching to alternative methods of spasticity therapy (e.g. intrathecal preservative -free morphine sulphate). After this period, sensitivity to baclofen intrathecal may be re-established: treatment should be resumed at the initial continuous infusion dose, followed by a titration phase to avoid overdose. This should again be performed under inpatient conditions.
Caution should be exercised when switching from baclofen to morphine and vice versa (see section 4.5).

Through the treatment period, regular checks for therapeutic and adverse effects of Gablofen are appropriate. These checks may occur more frequently during the titration phase of therapy than during the chronic maintenance phase. 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).

Discontinuation of treatment
Except in overdose related emergencies, the treatment with baclofen should always be gradually discontinued with successive dose reductions. Baclofen must not be abruptly discontinued (see section 4.4 “Special warnings and precautions”).

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 is important to prevent the possibly life-threatening central nervous and systemic effects of withdrawal of intrathecal baclofen (see section 4.4).

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 4.4).

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 systemic exposure of baclofen (see section 5.2).

Renal impairment
No studies have been performed in patients with renal impairment receiving baclofen therapy. In patients with impaired renal function, the dosage may need to be reduced to take account the clinical condition and the level of reduced renal function (see section 5.2).

Paediatric population
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.
The implantation of the pump requires a certain body size.
Use of intrathecal baclofen in the paediatric population should only be prescribed by medical specialists with the necessary knowledge and experience.
The experience in children under 4 years of age is limited.

Elderly patients

As part of clinical studies, some patients over 65 years 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. Older patients should therefore be monitored carefully for the development of adverse reactions.

Administration: particular specifications
Gablofen 500 micrograms/ml, 1000 micrograms/ml, and 2000 micrograms/ml are intended for use with infusion pumps. The concentration to be used depends on the dose requirements and size of pump reservoir.
Please refer to the manufacturer`s manual, which contains all specific recommendations.

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 50 micrograms/ml, 500 micrograms/ml, 1000 micrograms/ml or 2000 micrograms/ml are required, Gablofen in vials may be diluted to a lower concentration; dilution must be performed under aseptic conditions with sterile preservative-free sodium chloride solution for injections. The instructions of the pump manufacturer should be observed here. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Therapy-resistant epilepsy.

The medicinal product should not be administered by any route other than intrathecal. Gablofen 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.

Patients with additional suicidal risk factors must be closely monitored while undergoing drug treatment with Gablofen Intrathecal. Patients (as well as their carers) must be made aware of the need for monitoring of worsening clinical symptoms, suicidal behavior or ideation, or unusual behavioral changes, and instructed to seek medical assistance immediately if these symptoms appear.

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

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.

After refilling the pump, the patient must be supervised for 24 hours. A doctor must be rapidly accessible during this period.

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.

In order to prevent abrupt discontinuation of intrathecal administration of baclofen, special attention should be paid to the correct programming and monitoring of the infusion system, to the time schedules and procedures for refilling the pump and to the alarm signals of the pump. The patients and their caregivers must be instructed about the need to observe the set appointments for refilling and about the early symptoms of baclofen withdrawal (e.g. priapism). Particular attention must be paid to patients with an evident risk (e.g., patients with spinal cord injuries in the region of the sixth thoracic vertebra or higher, patients who have difficulty making themselves understood, or patients who already have a history of exhibiting withdrawal symptoms after discontinuing oral or intrathecal baclofen).

The manufacturers of infusion systems give specific instructions for the programming and refilling of the pumps, and these must be followed exactly. Experience with continuous intrathecal baclofen infusion is available only for the use of one particular pump model. Confirmed experience with other implantable pump systems is not available.

Preconditions for treatment with intrathecal baclofen include the ability to tolerate and respond to the single intrathecal injection of a dose of up to 100 micrograms of baclofen as a bolus injection in the form of intrathecal solution containing 50 micrograms baclofen in 1 ml.

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

Medical Support

The infusion system should not be implanted before the reaction of the patient to the single intrathecal injections of baclofen 50 micrograms/1 ml is sufficiently established. The first intrathecal administration, the implantation of the infusion system, and the first infusion and dosage-titration of baclofen are associated with risks such as CNS suppression, cardiovascular collapse and respiratory failure. These steps must therefore be performed under in-patient conditions with the availability of intensive medical care, and the instructions on dosage must be observed. The necessary facilities and support for immediate resuscitation in cases of life-threatening symptoms should be available. The treating physician must have specific experience in dealing with intrathecal administration and related infusion systems.

Monitoring the patients

After surgical implantation of the pump and particularly during the initial phase of pump activity and on changing the baclofen concentration or the infusion rate, the patient must be monitored closely until his/her 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.

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. However, a causal relationship with intrathecal baclofen could not be established. 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 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.

Implantation of the pump

Prior to implantation of the pump, patients should be free from infection, since an infection increases the risks of surgical complications. Moreover, a systemic infection may complicate attempts to adjust the dose.

Refilling the pump reservoir

The pump reservoir is to be re-filled by specially trained doctors according to the instructions given by the pump manufacturer. Re-fill intervals should be carefully calculated to prevent depletion of the reservoir, as this would result in recurrence of severe spasticity (see Discontinuation phenomena section).

This re-filling should be performed under strictly aseptic conditions in order to prevent contamination by microorganisms and infections. Every re-filling and every manipulation of the pump reservoir should be followed by an observation phase

appropriate for the clinical situation. Extreme caution is indicated when filling an implanted pump that possesses an access port with direct access to the intrathecal catheter. Injection via the access port directly into the catheter can cause life-threatening overdosing.

Potential for Contamination due to non-sterile external surface of prefilled syringe
The solution and the pathway of the prefilled syringes are sterile, while the external surface of the prefilled syringes is not sterile. Contamination of aseptic settings when filling or refilling sterile intrathecal pumps with prefilled syringes should be avoided.

Additional notes on dose 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.

Discontinuation phenomena
Abrupt discontinuation of baclofen, regardless of cause, may manifest itself in increased spasticity as a rebound effect, pruritis, paraesthesia (tingling or burning) and hypotension. This can lead to sequelae such as a hyperactive state with rapid and uncontrolled spasms, to elevated body temperature, and to symptoms similar to those of a malignant neuroleptic syndrome such as 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. For this reason, the patients and their caregivers must be informed about the need to observe the set appointments for re-filling the pump and be instructed about the signs and symptoms of baclofen withdrawal, especially those that occur in an early phase (e.g. priapism).

The early symptoms of baclofen withdrawal include recurrence of the spasticity originally present, itching, low blood pressure and paraesthesia and priapism. 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 the withdrawal symptoms set in within hours or a few days after interruption of the intrathecal administration. Common reasons for the abrupt interruption of intrathecal administration are malfunctions of the catheter (especially problems with the connection), low volume in the pump reservoir, or a discharged battery in the pump. In order to prevent abrupt interruption of intrathecal administration of baclofen, particular care should be paid to the programming and the monitoring of the infusion system, the time schedule and procedure for re-filling the pump and the alarm signals of the pump.

Therapy of discontinuation/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 baclofen. The recommended treatment is resumption of the baclofen administration at the same or approximately the same dosage as before interruption of the baclofen delivery. However, if 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 baclofen.

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.

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

Scoliosis
The development of scoliosis or exacerbation of existing scoliosis cannot be excluded in a limited number of patients treated with Gablofen. Signs of scoliosis should be monitored during treatment with Gablofen.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.
However, if Gablofen is diluted in sodium chloride solution, the sodium content will be higher.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies have been performed.

There is little experience with the use of intrathecal baclofen in combination with systemic medicinal products 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).

Whenever possible, all concomitant oral antispastic medications should be discontinued, to prevent a possible overdose or undesirable interactions; preferably prior to initiating the baclofen infusion and under close medical surveillance. However, any abrupt reduction or discontinuation of the concomitant antispastic medication should be avoided during chronic treatment with baclofen.

Alcohol and other compounds affecting the CNS

The concomitant administration of baclofen and other medicinal products that have a suppressing effect on functions of the central nervous system (e.g. analgesics,

neuroleptics, barbiturates, benzodiazepines, anxiolytics) can enhance the action of baclofen. 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 medicinal products 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

As concomitant use of oral baclofen and antihypertensive medicinal products may increase any fall in blood pressure, it may prove necessary to monitor blood pressure. If applicable, the dosage of the antihypertensive medication must be reduced.

Levodopa/Dopa decarboxylase inhibitor

Concomitant use of oral baclofen and levodopa/Dopa decarboxylase 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/Dopa decarboxylase inhibitor therapy.

Morphine

The combined use of morphine and intrathecal baclofen has been responsible for hypotension in one patient.

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.

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.

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 intrathecal baclofen in pregnant women. After intrathecal administration, small amounts of baclofen can be detected in maternal plasma (see section 5.2). Baclofen crosses the placenta and has shown reproduction toxicity (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, however clinically relevant levels are not expected due to the low plasma concentration of baclofen in mothers treated with intrathecal baclofen. Gablofen can be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

The ability to drive or use machines may be considerably impaired during treatment with intrathecal 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 intrathecal baclofen. Other listed events include ataxia, hallucinations, diplopia and withdrawal symptoms.

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

4.8 Undesirable effects

Adverse reactions are ranked under headings of frequency, the most frequent first, 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 (frequency cannot be estimated from the available data).

Metabolism and nutrition disorders	
Common:	Decreased appetite.
Uncommon:	Dehydration.
Psychiatric disorders	
Common:	Depression, Confusional state, Disorientation, Agitation, Anxiety.
Uncommon:	Suicidal ideation, Suicide attempt, Paranoia, Hallucinations, Dysphoria, Euphoric mood.

Nervous system disorders	
Very common:	Somnolence.
Common:	Convulsion, Lethargy, Dysarthria, Headache, Paraesthesia, Insomnia, Sedation, Dizziness. Convulsion and headache occur more frequently in patients with cerebral spasticity.
Uncommon:	Ataxia, Hypothermia, Memory impairment, Nystagmus.
Eye disorders	
Common:	Accommodation disorders with vision blurred or 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, Salivary hypersecretion. Nausea and vomiting occur more frequently in patients with cerebral spasticity
Uncommon:	Ileus, Hypogeusia, Dysphagia.
Skin and subcutaneous tissue disorders	
Common:	Urticaria, Pruritus.
Uncommon:	Alopecia, Hyperhidrosis.
Musculoskeletal and connective tissue disorders	
Very common:	Hypotonia.
Common:	Hypertonia
Not known:	Scoliosis
Renal and urinary disorders	
Common:	Urinary retention, Urinary incontinence. Urinary retention occurs more frequently in patients with cerebral spasticity.
Reproductive system and breast disorders	
Common:	Sexual dysfunction.
Not known:	Erectile dysfunction
General disorders and administration site conditions	
Common:	Oedema peripheral, Face oedema, Pain, Pyrexia, Chills, Asthenia
Rare:	Life-threatening withdrawal symptoms due to drug delivery failure

A reliable causal connection between the observed adverse events and the administration of intrathecal baclofen is not always possible as some of the observed adverse events could also be symptoms of the underlying illness being treated. Particularly frequently occurring adverse events such as dizziness, light-headedness, somnolence, headache, nausea, drop in blood pressure, and muscle weakness are usually due to the medication.

Seizures, headache, nausea, vomiting and urinary retention occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin).

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 medicinal product. Ovarian cysts are known to occur spontaneously in a proportion of the normal female population.

Adverse events due to the infusion 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, Website: 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 intrathecal baclofen, the patient should be admitted to inpatient care if being treated as an outpatient.
The patient must be closely monitored for any signs and symptoms of overdose throughout the entire treatment, particularly during the initial test phase and titration phase, but also during reintroduction of baclofen after an interruption of therapy.

Signs of overdose may appear suddenly or insidiously.

Overdosing can occur, for example, as a result of accidental delivery of the contents of the catheter during checking of the patency or position of the catheter. Other possible causes are errors in the programming, extremely rapid dosage increment, concurrent oral administration of baclofen or malfunction of the pump.
In one case, an adult patient showed signs of severe overdosing (coma) after injection of a single dose of 25 micrograms of intrathecal baclofen.

Symptoms of overdose: excessive muscular hypotonia, light-headedness, dizziness, somnolence, sedation, convulsions, loss of consciousness, hypothermia, excessive salivation, nausea and vomiting.

Respiratory depression, apnoea and coma occur in the event of a major overdose. Seizures may occur with increasing dosage or, more commonly, during recovery from an overdose.

Treatment
There is no specific antidote for the treatment of overdosing with baclofen. In general, the following steps should be undertaken:

- Residual intrathecal baclofen solution should be removed from the pump as soon as possible.
- Patients with respiratory depression should be intubated if necessary until baclofen is eliminated.
- If lumbar puncture is not contraindicated, 30 to 40 ml of CSF may be drawn off in the early stage of intoxication in order to reduce the concentration of baclofen in the CSF.
- Maintenance of cardiovascular function.
- If spasms occur, diazepam intravenous should be administered carefully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Musculo-skeletal system; Muscle-relaxants, centrally acting agents; other centrally acting agents
ATC code: M03BX01

Mechanism of action
The precise mechanism of action of baclofen as a muscle relaxant and antispasticity medicinal product is not fully understood. Baclofen inhibits 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 patient mobility, providing them with greater autonomy, and facilitates physiotherapy. In humans, as well as in animals, baclofen has been shown to have general depressant properties on the central nervous system, causing sedation, somnolence, and respiratory and cardiovascular depression In addition, a dose-dependent inhibitory effect on male erectile function due to stimulation of the $GABA_B$ receptor has been demonstrated..

Intrathecal bolus
The onset of action is generally one-half hour to one hour after an intrathecal bolus. Peak spasmolytic effect is seen at approximately 4 hours after dosing and effects may last 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
Intrathecal baclofen's antispastic action is first seen at 6 to 8 hours after initiation of continuous infusion. Maximum activity is observed in 24 to 48 hours.

5.2 Pharmacokinetic properties

When considering the pharmacokinetic data on baclofen intrathecal, the effects of the slow CSF circulation should be taken into account.

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.

Baclofen when introduced directly into the intrathecal space permits effective CNS concentrations to be achieved with resultant plasma concentrations at least 100 times lower than those occurring with oral administration.

Distribution
After a single intrathecal bolus injection/rapid infusion, the distribution volume calculated from the concentration in the CSF ranges from 22 to 157 ml. The mean of about 75 ml 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 micrograms, steady-state concentrations of baclofen in the CSF of the lumbar region of 130 to 1240 nanograms/ml are reached within 1 to 2 days.

During continuous intrathecal infusion of daily doses between 95 to 190 micrograms, once steady state has been reached, a baclofen concentration gradient is built up in the range between 1.8: 1 and 8.7: 1 (mean = 4: 1) between lumbar CSF and subarachnoid cisternal CSF. This is of clinical importance, as spasticity of the lower extremities can be effectively treated without greatly influencing the upper limbs, with fewer adverse central nervous effects due to the medicinal product's action on the brain centres.

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. 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 from the CSF after administration of a single intrathecal bolus injection/ rapid infusion of 50 to 135 micrograms of baclofen ranges from 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.

<u>Elderly Patients</u>
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.

<u>Paediatric population</u>
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 patients 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 active substance 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.

Following 3 months intrathecal infusion in sheep, a mild inflammatory mass was observed during histopathological examination without resulting in any clinical observations.

Genotoxicity and carcinogenicity

In vivo and *in vitro* genotoxicity tests have shown no mutagenic effect.

A 2-year study in rats (oral route) has shown that baclofen is not carcinogenic. This study showed a dose-dependent increase in the incidence of ovarian cysts and a less marked increase in the incidence of hypertrophic and/or haemorrhagic adrenal glands. The clinical relevance of these findings is not known.

Reproduction toxicity

Baclofen had no effect on the fertility of female rats. Possible effects on male fertility have not been investigated. Baclofen is not teratogenic in mice, rats, and rabbits at doses at least 125-times the maximum intrathecal mg/kg dose. Orally administered baclofen 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 observed in mice or rabbits.

Oral baclofen has been shown to delay foetal 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.

Intrathecal baclofen is unlikely to have adverse effects on prenatal or postnatal development based on oral studies in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections

6.2 Incompatibilities

Glucose has been shown to be incompatible with baclofen, as a chemical reaction occurs between the two substances.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

After first opening: the product should be used immediately.

6.4 Special precautions for storage

Do not store above 30°C.

Do not freeze.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear, colourless vials of glass type I (Ph. Eur.). Stoppers are made from halobutyl rubber.

Pack size

1 vial of 20 ml.

6.6 Special precautions for disposal

Each vial is intended for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Dilution of Gablofen in vials
If users wish to obtain concentrations other than 500, 1000 or 2000 micrograms/ml, Gablofen must be diluted under aseptic conditions in a sterile and preservative-free sodium chloride 9 mg/ml solution for injections.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 37071/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/10/2019

10 DATE OF REVISION OF THE TEXT

25/03/2022