Applicant	:	Umsebe Healthcare
Proprietary name (dosage form)	:	Bacentra Intrathecal 0,05 mg/ml (solution for injection), Bacentra Intrathecal 0,5 mg/ml (solution for infusion) and Bacentra Intrathecal 2 mg/ml (solution for infusion)
Strength	:	Each ml contains 0,05 mg, 0,5 mg and 2 mg baclofen

PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Bacentra Intrathecal 0,05 mg/ml, solution for injection

Bacentra Intrathecal 0,5 mg/ml, solution for infusion

Bacentra Intrathecal 2 mg/ml, solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bacentra Intrathecal 0,05 mg/ml: 1 ml contains 0,05 mg (50 micrograms) Baclofen as active ingredient.

Bacentra Intrathecal 0,5 mg/ml: 1 ml contains 0,5 mg (500 micrograms) Baclofen as active ingredient.

Bacentra Intrathecal 2 mg/ml: 1 ml of solution contains 2,0 mg (2000 micrograms) of Baclofen as active ingredient.

Bacentra Intrathecal 0,05 mg/ml, Bacentra Intrathecal 0,5 mg/ml and Bacentra Intrathecal 2 mg/ml contain 3,5 mg/ml sodium.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

Bacentra Intrathecal 0,05 mg/ml is a clear and colourless solution filled into 2 ml (filled to 1 ml) clear Type I glass ampoules.

Bacentra Intrathecal 0,5 mg/ml is a clear and colourless solution filled into 20 ml clear Type I glass ampoules.

Bacentra Intrathecal 2 mg/ml is a clear and colourless solution filled into 5 ml and 20 ml clear Type I glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Patients with spasticity due to traumatic brain injury should wait at least 1 year before considering long term intrathecal therapy.

Paediatric population

Bacentra Intrathecal 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

Posology

Switching of a patient from oral to intrathecal therapy or initiation of therapy up to achieving a stable maintenance phase of treatment should be done in hospital care setting with full resuscitation care, ventilation facilities and under supervision of a medical practitioner or physiotherapists.

Baclofen Intrathecal is intended for administration in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, in implantable pumps suitable for continuous administration of Baclofen Intrathecal into the intrathecal space (suitably SAHPRA 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. Intrathecal administration of baclofen through an implanted delivery system should only be undertaken by medical practitioners 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.

Efficacy of baclofen intrathecal has been demonstrated in controlled randomised studies using certified implantable administration infusion pumps. This is an implantable administration system: a refillable reservoir is implanted beneath the skin, mostly into the abdominal wall. This system is connected to an intrathecal catheter that passes subcutaneously into the subarachnoid space.

Test phase

Prior to administering baclofen as a continuous intrathecal infusion, patients must show a positive response to administration of an intrathecal test dose in an initial test phase. 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 dose is generally 25 or 50 micrograms; the dose is generally increased in increments of 25 micrograms at intervals of at least 24 hours, until a response lasting approximately 4 to 8 hours is obtained. The dose must be injected over at least one minute via barbotage. Low-dose ampoules (Bacentra Intrathecal 0,05 mg/ml) are available for this test phase. Resuscitative equipment must be on hand during injection of the first dose. Patients are considered to be positive responders if they show a significant decrease in muscle tone and/or frequency and/or severity of spasms.

There is much variability with regard to sensitivity to intrathecal baclofen. 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-microgram test dose must not be given further doses and are not eligible for continuous intrathecal infusions.

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 depressions.

Paediatric population

Screening phase

The initial lumbar puncture test dose for patients 4 to <18 years of age should be 25 - 50 µg/day based upon age and size of the child. Patients who do not experience a response

may receive a 25 µg/day dose escalation every 24 hours. The maximum screening dose should not exceed 100 µg/day in paediatric patients.

Titration phase

Once the patient's response to Bacentra Intrathecal has been established as positive via test doses, intrathecal infusion with a suitable administration system is introduced. Infection may increase the risk of surgical complications and complicate attempts to adjust the dose.

Following implantation, the initial total daily dose should be determined by doubling the dose that gave a positive effect in the test phase and administering it over a 24-hour period, unless the effect of the bolus dose is maintained for more than 12 hours. In this latter case, the initial daily dose should be similar to the dose in the test phase and should be administered over a 24-hour period. 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. To avoid any overdose, increments must not exceed 10 – 30 %. Patients with spasticity of cerebral genesis: After the first 24 hours the dose is adjusted slowly on a daily basis, to obtain the desired effect. To avoid any overdose, increments must not exceed 5 – 15 %.

If a programmable pump is used, dosage should only be increased once every 24 hours. For non-programmable pumps attached to a 76 cm catheter and with a delivery rate of 1 ml/day, it is recommended that the response should only be evaluated at 48-hour intervals. If the daily dosage has been significantly increased without any clinical effect having been observed, pump functioning and catheter permeability should be verified.

Only limited experience is available with doses exceeding 1000 micrograms/day.

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.

Maintenance therapy

The clinical goal is to maintain as normal a muscle tone as possible, and to minimise the frequency and severity of spasms without inducing intolerable side effects. 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 the daily dose may be increased gradually by 10 – 30 % to maintain adequate symptom control. Where the spasticity is of cerebral origin any increase in dose should be limited to 20 % (range: 5 – 20 %).

In both cases the daily dose may also be reduced by 10 – 20 % if patients suffer side effects.

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

For long-term maintenance treatment via continuous infusion, the intrathecal baclofen dosage for patients with spasticity of spinal genesis is between 10 and 1200

micrograms/day, with an adequate response being achieved in most patients with 300 – 800 micrograms/day.

In patients with spasticity of cerebral origin maintenance dosage has been found to range from 22 to 1400 micrograms/day, with a mean daily dosage of 276 micrograms per day at 12 months and 307 micrograms per day at 24 months.

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 hospital by a “medicine holiday” consisting of the gradual reduction of 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.

Caution should be exercised when switching from Baclofen Intrathecal to intrathecal preservative-free morphine sulphate and vice versa (see section 4.5).

Regular clinical monitoring is needed to assess the patient’s dosage requirements, to check that the administration system is working properly and to note any undesirable effects or the presence of infection.

Paediatric population

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 Intrathecal 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 1000 micrograms/day.

The safety and efficacy of Intrathecal Baclofen for the treatment of severe spasticity of cerebral or spinal origin in children younger than 4 years of age have not been established (see section 4.4).

Discontinuation of treatment

Except in emergency cases associated with an overdose, treatment should be discontinued gradually with successive dose reductions. Bacentra Intrathecal should not be abruptly discontinued (see section 4.4).

Administration: particular specifications

Bacentra Intrathecal ampoules containing 0,5 mg/ml (20 ml), 2 mg/ml (5 ml) and 2 mg/ml (20 ml) baclofen have been specially developed for infusion pumps. The exact concentration to be selected depends on the total daily dose needed, as well as the minimum infusion rate of the pump. Please refer to the manufacturer's manual, which contains all specific recommendations.

Method of administration

In most cases, Bacentra Intrathecal is administered as a continuous infusion directly after implantation. Once the patient is stabilised in terms of daily dosage and functional aspects, and provided that the pump allows it, a switch can be made to a more complex method of administration, to allow optimal control over spasticity at different times of the day. For example, patients with increased night-time spasms may require a 20 % increase in the

hourly infusion rate. This altered rate of infusion must be programmed about 2 hours in advance of the expected clinical effect.

Every ampoule is exclusively single-use. Any remaining product must be disposed of. Do not resterilize.

Bacentra Intrathecal must be visually inspected prior to use. Only clear solutions practically free from particles should be used.

For instructions on dilution of the product before administration, see section 6.6.

Special populations

Renal impairment

No studies have been performed in patients with renal impairment receiving Bacentra Intrathecal therapy. Because baclofen is primarily excreted unchanged by the kidneys it should be given with special care and caution in patients with impaired renal function.

Hepatic impairment

No studies have been performed in patients with hepatic impairment receiving Bacentra Intrathecal therapy. No dosage adjustment is recommended as the liver does not play any significant role in the metabolism of baclofen after intrathecal administration of Bacentra Intrathecal. Therefore, hepatic impairment is not expected to impact the medicines systemic exposure.

Elderly population

Several patients over the age of 65 years have been treated with intrathecal baclofen during clinical trials, without increased risks compared to younger patients. Problems specific to this age group are not expected as doses are individually titrated.

4.3 Contraindications

Known hypersensitivity to the active substance, baclofen, or to any of the excipients.

Epilepsy refractory to therapy.

Bacentra Intrathecal should not be administered by any route other than intrathecal.

Porphyria.

Infection at the site of catheter insertion.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Medical management

The pump should only be implanted after strict evaluation of the patient's response to intrathecal baclofen bolus injections and/or dose titration. Given the risks associated with initial administration and dose adjustment of intrathecal baclofen (general depression of CNS functions, cardiovascular collapse and/or respiratory depression), these steps must only be performed under medical surveillance at a centre with the required equipment, in compliance with the directions given in "Posology and method of administration". Resuscitative equipment must be on immediate stand-by in the event of overdose symptoms that threaten the vital prognosis. Doctors must be adequately experienced in the chronic treatment with intrathecal infusions.

Patient surveillance

The patient must be closely monitored after surgical implantation of the pump, especially during the initial phase of pump use and each time that its delivery rate and/or the baclofen

concentration in the reservoir are readjusted, until the patient's response to the infusion is acceptable and stabilised within reasonable limits.

It is essential that the risks of such a method of treatment are precisely known by the patient, doctors in charge of him/her and all caregivers. All persons participating in the treatment or care given to the patient must be clearly informed about the symptoms of under- and overdosing, procedures to be implemented in the event of intoxication, as well as the measures to be taken at home with regard to the pump and the insertion site.

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).

Test phase

Close monitoring of respiratory and cardiovascular functions is essential during the initial test phase, particularly in the presence of a cardiopulmonary condition or respiratory muscle weakness, as well as in patients concomitantly receiving benzodiazepine- or opiate-type medications, as the risk of respiratory depression is increased in such cases.

Any infection must be excluded prior to the test phase with Bacentra Intrathecal, as a systemic infection might falsify the evaluation of the patient's response to the Bacentra Intrathecal injection.

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 Bacentra Intrathecal, 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 medicines or admixtures that include opioids. In patients with new neurological signs or symptoms suggestive of an inflammatory mass, consider a neurosurgical consultation since many of the symptoms of inflammatory mass are not unlike the symptoms experienced by patients with severe spasticity from their disease. In some cases, performance of an imaging procedure may be appropriate to confirm or rule-out the diagnosis of an inflammatory mass.

Pump implantation

The patient must be free from infection prior to pump implantation, as the risk of postoperative complications would be increased. Furthermore, a systemic infection could complicate dose adjustment. A local infection or catheter misplacement can also cause interruption of medicine delivery, which may result in abrupt Bacentra Intrathecal withdrawal, accompanied by its symptoms (see “Interruption of treatment”).

Filling the reservoir

This must be performed by trained and fully qualified personnel, in an appropriate facility with necessary resuscitation equipment and in accordance with the manufacturer's instructions. Intervals between each refill should be carefully calculated to avoid depletion of the reservoir, which would lead to severe recurrence of spasticity or potentially life-threatening symptoms of Bacentra Intrathecal withdrawal (see "Interruption of treatment"). Filling should be performed under strictly aseptic conditions, in order to avoid any microbial contamination or any serious CNS infection. There should be an observation period, adapted to the clinical situation, after each refill or handling of the reservoir.

Extreme caution is required when filling an implantable pump fitted with a port with direct access to the intrathecal catheter, as direct injection into the catheter may lead to a potentially life-threatening overdose.

Dose adjustment: additional comments

Bacentra Intrathecal must be used with caution to avoid excessive weakness or a fall when a certain degree of spasticity is needed for standing up and gait balance, or whenever spasticity contributes to functional maintenance. It may be important to retain a certain amount of muscle tone and to tolerate occasional spasms, in order to facilitate circulatory function and prevent possible formation of deep vein thrombosis.

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

Precautions in special populations

Precautions in paediatric patients

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. The use of Bacentra Intrathecal in the paediatric population should only be 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 Intrathecal in children under the age of four years.**

Transcutaneous catheter insertion during the pump implantation and the presence of a percutaneous endoscopic gastrostomy (PEG) tube increase the incidence of infections in children.

Special patient groups

In patients with slowed CSF circulation due, for example, to blockage caused by inflammation or trauma, the delayed migration of Bacentra Intrathecal can reduce the antispastic efficacy and boost the adverse reactions.

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.

Patients with psychotic disorders, schizophrenia, confusional states or Parkinson’s disease must be cautiously treated with Bacentra Intrathecal and undergo strict surveillance whenever exacerbation of such conditions has been observed following oral baclofen administration. Patients with epilepsy must be particularly monitored, as seizures may occasionally occur in the event of an overdose or withdrawal of the medication and even during maintenance treatment at therapeutic doses of Bacentra Intrathecal.

Bacentra Intrathecal must be used with caution in patients with a history of autonomic dysreflexia. Nociceptive stimulation or abrupt withdrawal of Bacentra Intrathecal may precipitate such episodes (see “Interruption of treatment”).

The same caution is required in the presence of cerebrovascular or respiratory insufficiency, as baclofen can aggravate such states.

Bacentra Intrathecal is unlikely to have any effect on underlying, non-CNS related diseases, as systemic bioavailability of the product following intrathecal administration is considerably lower than with the oral route.

Renal impairment

Based on observations made during baclofen treatment via the oral route, caution is recommended in the following cases: history of gastro duodenal ulcers, pre-existing sphincter hypertonia and renal impairment.

With oral baclofen, rare cases of elevated SGOT (AST), alkaline phosphatase and blood glucose levels have been recorded.

Elderly Patients

Several patients over 65 years of age have been treated with baclofen intrathecal during clinical studies without any specific problems. Elderly patients are more likely to experience undesirable effects with oral baclofen in the titration phase and this may also apply to Bacentra Intrathecal. However, as optimal dose finding is individualised, treatment of elderly patients is unlikely to pose any specific problems. This medicinal product contains less than 1 mmol sodium (23 mg) per maximum daily dose, i.e. essentially “sodium free”.

Interruption of treatment

Abrupt discontinuation of baclofen intrathecal, for whatever reason, manifested by increased spasticity, pruritus, paraesthesia and hypotension, has given rise to sequelae including a hyperactive state with rapid uncontrolled spasms, hyperthermia and symptoms consistent with neuroleptic malignant syndrome (NMS), e.g. confused mental state and muscle rigidity. In rare cases, this has progressed to epileptic seizures/status epilepticus, rhabdomyolysis, coagulopathy, multiple organ failure and death. All patients receiving treatment with intrathecal baclofen are potentially at risk for withdrawal. Some clinical characteristics associated with intrathecal baclofen withdrawal can resemble autonomic dysreflexia, infection (sepsis), malignant hyperthermia, neuroleptic malignant syndrome (NMS) or other conditions associated with hypermetabolic state or extensive rhabdomyolysis.

Patients and their caregivers must be advised of the importance of keeping a timetable for refill visits and must be alerted to the signs and symptoms of baclofen withdrawal, particularly those that appear early on during the withdrawal syndrome.

In most cases, withdrawal symptoms appeared within a few hours after discontinuation of intrathecal baclofen treatment. Common reasons for abrupt withdrawal of intrathecal baclofen treatment included catheter malfunctioning (especially disconnection), excessively low volume in the pump reservoir and end of pump battery life; in some cases, human error may have been to blame or played a contributing role. Prevention of abrupt withdrawal of intrathecal baclofen requires careful attention to programming and surveillance of the infusion system, refill scheduling/procedures and pump alarms.

The suggested treatment for intrathecal Bacentra Intrathecal withdrawal is the restoration of intrathecal Bacentra Intrathecal at or near the same dosage as before therapy was interrupted. However, if restoration of intrathecal delivery is delayed, treatment with GABA-

ergic agonist medicines such as oral or enteral Bacentra Intrathecal, or oral, enteral, or intravenous benzodiazepines may prevent potentially fatal sequelae. Oral or enteral Bacentra Intrathecal alone should not be relied upon to halt the progression of intrathecal baclofen withdrawal.

It is extremely important that the manufacturer's instructions for implantation, pump programming and/or refilling of the reservoir should be strictly followed.

4.5 Interaction with other medicines and other forms of interaction

Available experience is not systematic enough to predict what would be the specific interactions of Bacentra Intrathecal with other medications.

Whenever possible, all concomitant oral antispasmodic medications should be discontinued, to prevent a possible overdose or undesirable interactions; preferably prior to initiating the Bacentra Intrathecal infusion and under close medical surveillance.

However, any abrupt reduction or discontinuation of the concomitant antispasmodic medication should be avoided during chronic treatment with Bacentra Intrathecal.

A combination of parenteral morphine and baclofen intrathecal has caused hypotension. The potential for dyspnoea or other central nervous symptoms cannot be excluded with a combination of baclofen intrathecal and parenteral or intrathecal preservative-free morphine sulphate during concomitant medication.

Co-administration with other agents via the intrathecal route has been tested to a limited extent and little is known about the safety of such combinations.

The CNS-depressant effect of alcohol and other compounds acting at this level may be additive to those of Bacentra Intrathecal.

Concomitant treatment with oral baclofen and tricyclic antidepressants may enhance the effect of baclofen and induce marked muscle hypotonia. Caution is advised when using Bacentra Intrathecal in this type of combination.

As concomitant use of oral baclofen and antihypertensive agents may increase any fall in blood pressure, it may prove necessary to monitor blood pressure and readjust the antihypertensive dosage.

During concomitant administration with levodopa, there is a risk of increasing the undesirable effects associated with the latter (mental confusion, hallucinations, headaches, nausea, agitation).

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 Bacentra Intrathecal.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see section 4.3). Baclofen crosses the human placental barrier. Studies in animals have shown that baclofen is embryotoxic in rats, following oral administration (see section 5.3). The clinical relevance of these findings in humans is not known.

Lactation

Safety during lactation has not been established (see section 4.3). It is not known whether measurable levels of the product can be detected in the maternal milk of lactating mothers treated with Bacentra Intrathecal. At oral therapeutic doses, the active substance passes into breast milk. Mothers who are receiving Bacentra Intrathecal are advised not to breastfeed their infants.

Fertility

Ovarian cysts have been found by palpation in about 4 % of the multiple sclerosis patients who were treated with oral baclofen for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the medicine.

4.7 Effects on ability to drive and use machines

Onset of drowsiness has been reported in patients on baclofen intrathecal treatment. Patients must be urged to exercise caution when driving their car, using hazardous machinery or performing any potentially hazardous activity in case of reduced alertness.

4.8 Undesirable effects

In many cases, a causal link between the effects observed and baclofen administration cannot be established, as most of the undesirable effects reported may also be associated with the underlying disease. Nevertheless, some commonly reported reactions (somnolence, dizziness, sedation, difficulty in seizure control, constipation, headache, nausea, hypotension, hypotonia) are medicine-related.

Adverse medicine reactions are listed according to system organ classes in MedDRA. Undesirable effects are ranked according to system class and frequency.

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
Metabolism and nutritional disorders	Dehydration	Less frequent
Psychiatric disorders	Depression, anxiety, agitation	Frequent
	Suicidal ideation, suicide attempt, hallucinations, paranoia, euphoric mood	Less frequent
	Dysphoria	Frequency not known
Nervous system disorders	Somnolence (especially during the test phase), convulsion*, sedation, dizziness/ light-headedness, epileptic seizures (especially upon abrupt discontinuation of treatment), headache*, paraesthesia, dysarthria, lethargy, insomnia, confusion/ disorientation, difficulty concentrating	Frequent
	Ataxia, impaired memory, nystagmus	Less frequent
Eye disorders	Accommodation disorders, vision blurred, diplopia	Frequent
Cardiovascular disorders	Bradycardia	Less frequent
Vascular disorders	Hypotension	Frequent
	Hypertension, deep vein thrombosis, flushing, pallor, cerebrovascular disorder	Less frequent
Respiratory , thoracic and	Respiratory depression, pneumonia,	Frequent

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
mediastinal disorders	dyspnoea, bradypnoea, feeling of pressure in the chest (chest tightness)	
Gastrointestinal disorders	Nausea/vomiting[$], constipation, dry mouth, diarrhoea, decreased appetite, increased salivation	Frequent
	Ileus, dysphagia, hypoageusia	Less frequent
Skin and subcutaneous tissue disorders	Urticaria, pruritus, facial or peripheral oedema	Frequent
	Alopecia, hyperhydrosis	Less frequent
Musculoskeletal and connective tissue disorders	Muscular hypotonia (especially during the test phase – transient effects), muscular hypertonia, disturbances of gait and balance	Frequent
	Scoliosis	Frequency not known
Renal and urinary disorders	Urinary incontinence, urinary retention[#]	Frequent
Reproductive system and breast disorders	Sexual dysfunction (Intrathecal Bacentra Intrathecal may compromise erection and ejaculation. This effect is usually reversible on withdrawal of Bacentra Intrathecal)	Frequent
	Erectile dysfunction	Frequency not known
General disorders and administration site conditions	Asthenia, pyrexia, pain, chills	Frequent
	Hypothermia, septicaemia, subdural	Less frequent

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
	haemorrhage, accidental injury, weight loss, potentially life-threatening withdrawal symptoms, as a result of sudden interruption of medicine delivery (see “Interruption of treatment”)	

* Convulsion and headache occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.

$ Nausea and vomiting occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.

Urinary retention occurs more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.

Undesirable effects due to the administration system (e.g. inflammatory mass at the tip of the implanted catheter, catheter dislodgement / kink / rupture, local infection, meningitis (aseptic, chemical, bacterial and fungal), septicaemia, pump-pocket seroma and haematoma (potential risk of inflammation), pump malfunction and CSF leakages and skin ulcers after quite some time, and overdosage or underdosage due to incorrect manipulation of the system) may also occur.

In a screening trial the presence of a PEG tube increased the incidence of deep infections in children.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Deaths due to overdose of intrathecal baclofen have been reported. 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 when administration of Bacentra Intrathecal is resumed after brief suspension. Signs of overdose may appear suddenly or insidiously.

Symptoms of overdose

Excessive muscular hypotonia, myoclonia, hyporeflexia or areflexia, weakness, drowsiness, light-headedness, dizziness, sedation, somnolence, epileptic seizures, loss of consciousness, confusion, hallucinations, agitation, accommodation disorders, absent pupillary reflex, peripheral vasodilation, hypotension or hypertension, bradycardia or tachycardia, hypothermia, elevated lactic acid dehydrogenase (LDH), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) values, diarrhoea, ptyalism, nausea and vomiting. Respiratory depression, apnoea and coma occur in the event of a major overdose.

Serious overdose may occur, for example, if the catheter contents inadvertently pass into the intrathecal space during verification of catheter permeability/positioning. Programming errors, excessively rapid dose increases and concomitant treatment with oral baclofen or other medicines that act on the CNS, represent other possible causes of overdose. Pump malfunction should also be investigated.

Treatment

There is no specific antidote for the treatment of overdose with Bacentra Intrathecal. The following measures are usually taken:

1) Drain any remaining baclofen from the pump as quickly as possible.
2) If necessary, intubate patients with respiratory depression, until the medicine is eliminated.

Certain reports suggest that physostigmine is capable of abolishing the central nervous effects, particularly drowsiness and respiratory depression. However, caution must be exercised when intravenously injecting physostigmine, as it might induce epileptic seizures, bradycardia and cardiac conduction disturbances.

Maintenance of cardiovascular function. During seizures: cautious IV injection of diazepam. Blood pressure, pulse, body temperature, cardiac rhythm and respiratory rate should be monitored.

For severe toxicity not responsive to supportive measures, intravenous physostigmine may be administered. Physostigmine is only recommended under these circumstances.

In adults, a test can be performed with 1 – 2 mg physostigmine IV over a period of 5 to 10 minutes. Repeated doses of 1 mg can be given at 30 to 60-minute intervals, in order to maintain adequate ventilation and vigilance if the patient responds favourably. In children a dose of 0,02 mg/kg physostigmine may be administered IV at a rate not exceeding 0,5 mg per minute. This dose may be repeated at 5 to 10 minute intervals until a therapeutic effect is obtained or a total dose of 2 mg has been administered. Physostigmine is a short acting agent of 30 to 60 minutes or less.

During physostigmine administration, patients should be subject to strict surveillance.

Physostigmine may be ineffective in cases of massive overdose and the patient may have to be placed under artificial ventilation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A.2.10 Centrally acting muscle relaxants

Mechanism of action

Baclofen slows down mono- and polysynaptic reflex transmission in the spinal cord, by stimulating $GABA_B$ receptors.

Pharmacodynamics effects

The chemical structure of baclofen is analogous to that of gamma-aminobutyric acid (GABA), which is a neurotransmitter inhibitor.

Neuromuscular transmission is not altered by baclofen. Baclofen has an antinociceptive action. In neurological diseases accompanied by musculoskeletal spasms, the properties of baclofen manifest not only in the form of an effect on reflex muscle contractions, but also as a marked reduction in the intensity of painful spasms and clonus.

Clinical efficacy and safety

Baclofen improves patient mobility, providing them with greater autonomy, and facilitates physiotherapy.

Baclofen depresses the CNS in general, causing sedation, somnolence, as well as respiratory and cardiovascular depression.

Baclofen, introduced directly into the intrathecal space, allows treatment of spasticity at doses at least 400 to 1000 times lower than they would be via the oral route.

Intrathecal bolus

Bacentra Intrathecal usually starts to act half an hour to one hour after administration of a single intrathecal dose. The peak spasmolytic effect manifests around 4 hours post-dose and its action lasts for 4 to 8 hours. Onset of action, peak response and duration of effect can vary between individual patients, depending on the dose, severity of symptoms and the method and rate of administration.

Continuous infusion

The antispasmodic effect of baclofen starts 6 to 8 hours following initiation of the continuous infusion and reaches its peak within 24 to 48 hours.

5.2 Pharmacokinetic properties

The intrathecal nature of administration and decelerated circulation of cerebrospinal fluid (CSF) must be taken into account when interpreting the following kinetic parameters.

Absorption

Direct infusion into the cerebrospinal fluid allows absorption processes to be avoided and allows the substance to come into contact, via adsorption, with receptor sites in the dorsal horn of the spinal cord.

Distribution

Following a single intrathecal bolus injection/short-term infusion, the volume of distribution is between 22 and 157 ml, calculated from levels present in the CSF. When given as continuous intrathecal infusions, daily doses of 50 to 1200 micrograms produce baclofen steady-state concentrations of 130 – 1240 ng/ml in lumbar CSF. According to the half-life measured in the CSF, steady-state CSF concentrations are reached within 1 to 2 days. During intrathecal infusion, plasma concentrations do not exceed 5 ng/ml, which confirms that the passage of baclofen through the blood-brain barrier is slow.

Elimination

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

Mean CSF clearance is approximately 30 ml/h after both a single bolus injection and continuous infusion in the lumbar subarachnoid space using an implantable pump.

During continuous intrathecal infusion, 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 medicine’s action on the brain centres.

Special populations

Elderly Patients

No pharmacokinetic data is available in elderly patients after administration of Bacentra Intrathecal. When a single dose of the oral formulation is administered, data suggest that

elderly patients have a slower elimination, but a similar systemic exposure to baclofen compared to young adults. However, the extrapolation of these results to multi-dose treatment suggests no significant pharmacokinetics difference between young adults and elderly patients.

Paediatrics

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

Hepatic impairment

No pharmacokinetic data is available in patients with hepatic impairment after administration of Bacentra Intrathecal. 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 Bacentra Intrathecal. Since baclofen is primarily eliminated unchanged through the kidneys, accumulation of unchanged medicine in patients with renal impairment cannot be excluded.

5.3 Preclinical safety data

A 2-year study with 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. *In vivo* and *in vitro* mutagenesis tests have shown no mutagenic effect.

Oral baclofen increases the incidence of omphaloceles (ventral hernias) in the foetuses of rats at high doses.

No teratogenic effects have been noted in mice.

An increased incidence of incomplete sternebral ossification in foetuses of rats given high doses oral baclofen was observed. High doses oral baclofen also increased the incidence of unossified phalangeal nuclei of forelimbs and hindlimbs in rabbit foetuses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Bacentra Intrathecal 0,05 mg/ml, Bacentra Intrathecal 0,5 mg/ml and Bacentra Intrathecal 2 mg/ml contain sodium chloride and water for injection as inactive ingredients.

6.2 Incompatibilities

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

Bacentra Intrathecal must not be mixed with any other medicinal products or solutions, with the exception of sterile and preservative-free sodium chloride solution for injections, if required.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 30 °C.

Do not refrigerate or freeze.

Store in the original package to protect from light.

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

Bacentra Intrathecal 0,05 mg/ml is presented in a 2 ml (filled to 1 ml) Type I clear, colourless glass ampoule with a score-break and blue coloured ring marker. The ampoules are packed into cardboard boxes in quantities of 5 or 10 ampoules per box. Not all pack sizes may be marketed.

Bacentra Intrathecal 0,5 mg/ml is presented in a 20 ml Type I clear, colourless glass ampoule with a score-break and red coloured ring marker. Each ampoule is packed into a single cardboard box.

Bacentra Intrathecal 2 mg/ml is presented in 5 ml and 20 ml Type I clear, colourless glass ampoules with a score-break and violet (5 ml ampoule) or green (20 ml ampoule) coloured ring marker. The 5 ml ampoules are packed into cardboard boxes in quantities of 5 or 10 ampoules per box. Not all pack sizes may be marketed. The 20 ml ampoules are packed into single cardboard boxes.

6.6 Special precautions for disposal and other handling

Any remaining product must be disposed of.

Instructions for use/operating instructions

Bacentra Intrathecal is designed for intrathecal injections and continuous infusions and is administered according to the specifications accompanying each infusion system.

Stability

Bacentra Intrathecal has been shown to be stable for 180 days in implantable certified pumps. Wherever possible prior to administering them, medicinal products for parenteral use should be checked for the presence of particulate matter and any changes in colour.

Specific instructions for administration

The exact concentration to be selected depends on the total daily dose needed, as well as the minimum infusion rate of the pump. Please refer to the manufacturer's user manual for all specific recommendations.

Dilution

If users wish to obtain concentrations other than 0,05, 0,5 or 2 mg/ml of baclofen, Bacentra Intrathecal must be diluted under aseptic conditions with sterile and preservative-free sodium chloride solution for injections.

Administration systems

Several systems have been used for long-term administration of baclofen intrathecal. Among these, certified pumps can be mentioned, which are implantable systems equipped with refillable reservoirs, and which are implanted – under local or general anaesthetic – under the skin or into a pocket mostly in the abdominal wall. These systems are connected to an intrathecal catheter that passes subcutaneously into the subarachnoid space.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Umsebe Healthcare

506 Sunclare Building

21 Dreyer Street, Claremont

Cape Town, 7708

South Africa

Name of Manufacturer: Sintetica SA

8. REGISTRATION NUMBER(S)

Bacentra Intrathecal 0,05 mg/ml: 54/2.10/0366

Bacentra Intrathecal 0,5 mg/ml: 54/2.10/0367

Bacentra Intrathecal 2 mg/ml: 54/2.10/0368

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 August 2020

10. DATE OF REVISION OF THE TEXT

19 March 2024