# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Baclofen Aguettant 2 mg/ml solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

*Baclofen Aguettant 2 mg/ml solution for infusion*
1ml of solution for infusion contains 2.0 mg (2000 micrograms) baclofen,
5 ml ampoule contains 10 mg (10'000 micrograms) baclofen,
20 ml ampoule contains 40 mg (40'000 micrograms) baclofen,

Excipient(s) with known effect:
Each 5 ml ampoule of Baclofen Aguettant 2 mg/ml contains 17.5 mg of sodium
Each 20 ml ampoule of Baclofen Aguettant contains 2 mg/ml 70 mg of sodium

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for infusion.

Clear and colourless solution in ampoules.

The pH of the solution is comprised between 5.5 and 6.8.

The osmolarity of the solution is comprised between 270 - 300 mOsm/kg.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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

*Paediatric population*

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

## 4.2 Posology and method of administration

Intrathecal Baclofen is intended for administration in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, in implantable pumps suitable for continuous administration of baclofen into the intrathecal space (EU certified pumps). Establishment of the optimum dose schedule requires that each patient undergoes an initial screening phase with an intrathecal bolus, followed by a very careful individual dose titration prior to maintenance therapy. Intrathecal administration of Intrathecal Baclofen through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience. Specific instructions for implantation, programming and/or refilling of the implantable pump are given by the pump manufacturers and must be strictly adhered to.

Efficacy of intrathecal baclofen has been demonstrated in controlled randomised studies with an EU certified pump. 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.

Before administering Baclofen Aguettant, a myelography of the subarachnoid space should be performed in patients with post-traumatic spasticity. In the event of radiological signs of arachnoiditis, treatment with Baclofen Aguettant should not be initiated.

Posology

Due to the highly variable inter-individual sensitivity to baclofen, an optimal dosage should be determined for the treatment of each patient, according to a defined protocol, in three phases:

• Test phase: initial selection using the intrathecal bolus technique (test dose),

• Titration phase: determination of the dose,

• Maintenance phase.

*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. 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 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 (0.05 mg/ml, corresponding to 50 micrograms/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.

*Titration phase*

Once the patient's response to Intrathecal Baclofen 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 l0-30%.

Patients with spasticity of cerebral origin: 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 1,000 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 minimize the frequency and severity of spasms without inducing intolerable side effects. The lowest dose producing an adequate response should be used. Due to a decreasing response to treatment or due to disease progression, patients on chronic treatment gradually require higher doses to maintain an optimal long-term response. In the majority of cases, the dose stabilizes after 1.5 to 2 years of treatment. 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.

*Delivery regimen*

To maintain adequate symptom control the daily dose may be increased gradually by 10-30% adapting the pump flow and / or the concentration of Baclofen Aguettant in the reservoir.

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 is between 10 and 1,200 micrograms/day, with an adequate response being achieved in most patients with 300-800 micrograms/day.

Around 5-10% 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 "drug holiday" consisting of the gradual reduction of intrathecal baclofen 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 intrathecal baclofen 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 intrathecal baclofen to morphine and vice versa (see "Interactions").

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.

*Discontinuation of treatment.*

Except in emergency cases associated with an overdose, treatment should be discontinued gradually with successive dose reductions. Intrathecal Baclofen should not be abruptly discontinued (see "Special warnings and precautions").

*Administration: particular specifications.*

Ampoules of 10mg/5ml, 40mg/20ml and l0mg/20ml Baclofen Aguettant 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 pump manufacturer's manual, which contains all specific recommendations.

*Method of administration.*

In most cases, Intrathecal Baclofen 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.

Each ampoule is exclusively single-use. Do not resterilise.

The medicinal product has to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

Instructions for use/operating instructions.

Baclofen Aguettant is intended for intrathecal injections and continuous infusions and is administered according to the specifications accompanying each infusion system.

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

Special populations

*Paediatric population*

*Test phase*

The initial lumbar puncture test dose for patients 4 to <18 years of age should be 25-50 micrograms/day based upon age and size of the child. Patients who do not experience a response may receive a 25 micrograms/day dose escalation every 24 hours. The maximum screening dose should not exceed 100 micrograms/day in paediatric patients. The safety measures to take are the same in adults and children, please refer to the subsection test phase above.

*Titration phase*

The recommendations are the same in adults and children, please refer to the subsection titration phase above.

*Maintenance therapy*

In children aged 4 to <18 years with spasticity of cerebral and spinal origin, the initial maintenance dosage for long-term continuous infusion of Intrathecal 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.

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 (also see section 4.4).

*Renal impairment*

No studies have been performed in patients with renal impairment receiving Intrathecal Baclofen 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 Intrathecal Baclofen therapy. No dosage adjustment is recommended as the liver does not play any

significant role in the metabolism of baclofen after intrathecal administration of Baclofen. Therefore, hepatic impairment is not expected to impact the drug systemic exposure.

*Elderly population*

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

## 4.3 Contraindications

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

Pharmaco-resistant epilepsy.

The drug should not be administered by any route other than intrathecal.

## 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 directives given in section "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. .

*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 Intrathecal Baclofen, as a systemic infection might falsify the evaluation of the patient's response to the Intrathecal Baclofen injection.

*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 drug delivery, which may result in abrupt Intrathecal Baclofen withdrawal, accompanied by its symptoms (see "Interruption of treatment").

*Filling the reservoir*

This must be performed by trained and fully qualified personnel, 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 Intrathecal Baclofen 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 an overdose threatening the vital prognosis.**

Dose adjustment: additional comments.

Intrathecal Baclofen 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 Intrathecal Baclofen infusion and under close medical surveillance. However, any abrupt reduction or discontinuation of the concomitant antispasmodic medication should be avoided during chronic treatment with Intrathecal Baclofen.

*Precaution for patients driving or using machines*

Patients should be especially vigilant when driving vehicles, handling dangerous machinery and performing activities made dangerous in case of loss of attention.

*Precautions in special populations.*

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

Patients with *psychotic disorders, schizophrenia, confusional states or Parkinson's disease* must be cautiously treated with Intrathecal Baclofen and undergo strict surveillance whenever exacerbation of such conditions has been observed following oral baclofen administration.

Close supervision of patients with additional risk factors for suicide should accompany drug therapy with Baclofen Aguettant. Patients (and caregivers of patients) should be alerted about the need to monitor for clinical worsening, suicidal behaviour or thoughts or unusual changes in behaviour and to seek medical advice immediately if these symptoms present (see section 4.8).

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 Intrathecal Baclofen.

Intrathecal Baclofen must be used with caution in patients with a history of *autonomic dysreflexia*. Nociceptive stimulation or abrupt withdrawal of Intrathecal Baclofen may precipitate such episodes.

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

Intrathecal Baclofen 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.

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, renal impairment.

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).

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

*Precautions in paediatric patients*

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Use of intrathecal Baclofen in the paediatric population should be only prescribed by medical specialists with the necessary knowledge and experience. There is very limited clinical data regarding the safety and efficacy of the use of Intrathecal Baclofen in children under the age of four years.

Transcutaneous catheter insertion during the pump implantation and the presence of a PEG tube increase the incidence of infections in children.

*Women of childbearing age*

In view of the potential risk in the event of exposure during pregnancy, women of childbearing age should use an effective contraception during treatment (see "Fertility, pregnancy and lactation").

*Renal impairment*

Serious adverse neurological effects have been observed following oral administration of baclofen to patients with renal impairment, therefore great caution is advised when administering Baclofen Aguettant to patients with renal impairment. The dosage may need to be reduced to take account of the clinical condition or the level of reduced renal clearance.

*Elderly Patients >65*

Several patients over 65 years of age have been treated with intrathecal baclofen 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 Intrathecal Baclofen. However, as optimal dose finding is individualised, treatment of elderly patients is unlikely to pose any specific problems.

*Interruption of treatment.*

Abrupt discontinuation of intrathecal baclofen, 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, tachycardia, neuroleptic malignant syndrome (NMS) or other conditions associated with status hypermetabolicus 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 (e.g. priapism).

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, end of pump battery life and malfunction of the device. Malfunctions of the device were reported, which resulted in a modified administration of the drug, resulting in withdrawal symptoms, including death.

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

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

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. The most frequent symptoms associated with inflammatory mass are: 1) decreased therapeutic response (worsening spasticity, return of spasticity when previously well controlled, withdrawal symptoms, poor response to escalating doses, or frequent or large dosage increases), 2) pain, 3) neurological deficit/dysfunction. Clinicians should monitor patients on intraspinal therapy carefully for any new neurological signs or symptoms. Clinicians should use their medical judgement regarding the most appropriate monitoring specific to their patients' medical needs to identify prodromal signs and symptoms for inflammatory mass especially if using pharmacy compounded drugs or admixtures that include opioids. In patients with new neurological signs or symptoms suggestive of an inflammatory mass, consider a neurosurgical consultation since many of the symptoms of inflammatory mass are not unlike the symptoms experienced by patients with severe spasticity from their disease. In some cases, performance of an imaging procedure may be appropriate to confirm or rule-out the diagnosis of an inflammatory mass.

**Scoliosis**

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

Important information on excipients

Baclofen Aguettant 10mg/5ml

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially ‘sodium-free’.

Baclofen Aguettant 40mg/20ml

This medicinal product contains 70 mg sodium per ampoule, equivalent to 3.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

Suspected interactions due to which concurrent use is not recommended.

*Levodopa/DOPA-decarboxylase inhibitors*

Concomitant use of *oral* baclofen and a levodopa / DOPA-decarboxylase inhibitor resulted in an increased risk of side effects such as visual hallucinations, confusion, headache and nausea. Worsening of Parkinsonism symptoms have also been reported. Thus, caution should be exercised when administering Baclofen Aguettant to patients under levodopa / DOPA-decarboxylase inhibitor therapy

Interactions noted and to be taken into consideration

*Anesthetics*

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

Interactions foreseen and to be taken into consideration

*Spasmolytics*

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

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

*Morphine*

A combination of morphine and intrathecal baclofen has caused hypotension in one patient. The potential for dyspnoea or other central nervous symptoms cannot be excluded 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.

*Alcohol and other CNS depressant*

The CNS-depressant effect of alcohol and other compounds acting at this level may be additive to those of Intrathecal Baclofen.Impaired alertness can make driving vehicles and using machines dangerous. Avoid taking alcoholic beverages and medicines containing alcohol.

*Tricyclic antidepressants*

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

*Antihypertensive*

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.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing age

Women of childbearing age should use effective contraception during treatment.

Pregnancy

There are no or limited amount of data from the use of baclofen in pregnant women.Cases of malformations have been reported in children exposed in utero to baclofen, with types of malformations consistent with those observed in animals (central nervous system, skeletal anomalies and omphalocele) (See section 5.3). In the case of oral baclofen use until delivery, cases of withdrawal syndrome (including convulsions postnatal) have been reported in neonates (see “Special warnings and precautions for use”). This syndrome may be delayed for several days after the birth.

In the event of exposure during pregnancy, specialized prenatal monitoring, focused on the malformations described previously must be put in place. In the event of exposure at the end of pregnancy, monitoring and appropriate management of the newborn will have to be implemented. Following intrathecal administration of Baclofen Aguettant, small amounts of baclofen were detected in the mother's plasma.

Baclofen crosses the placental barrier. Intathecal Baclofen must not be used during pregnancy, unless the potential benefits outweigh the possible risks to the foetus.

Studies in animals have shown a reproductive toxicity of baclofen by oral administration.

Breast-feeding

It is not known whether measurable levels of the product can be detected in the maternal milk of lactating mothers treated with Intrathecal Baclofen. At oral therapeutic doses, the active substance passes into breast milk, but in amounts so small that the infant will probably not experience any undesirable effects.

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

## 4.7 Effects on ability to drive and use machines

Baclofen Aguettant has major influence on the ability to drive and use machines. 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. Patients with these side effects should be advised not to drive or use machines.

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

## 4.8 Undesirable effects

The most common reactions observed during baclofen Aguettant administration are: somnolence, hypotonia, depression, convulsions, hypotension and diarrhoea.

Adverse drug reactions are listed according to MedDRA system organ classes in. Table 1.
Undesirable effects are ranked according to system class and frequency, within each frequency grouping, undesirable effects are presented in order of decreasing seriousness, according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

*Table 1*

| | |
|---|---|
| *Immune System Disorders* | |
| *Not known* | Hypersensitivity |
| *Metabolism and nutritional disorders* | |
| *Uncommon* | Dehydration |
| *Psychiatric disorders* | |
| *Common* | Depression, anxiety, agitation, insomnia |
| *Uncommon* | Suicide attempt, suicidal ideation (see section 4.4 special warning and precautions for use), hallucinations, paranoia, euphoric mood |
| *Not known* | Dysphoria |
| *Nervous system disorders* | |
| Very common | Somnolence (especially during the test phase) |
| Common | Convulsion, headache, dysarthria, dizziness/ light-headedness, sedation, epileptic seizures (especially upon abrupt discontinuation of treatment), lethargy, paraesthesia, confusion/ disorientation. |
| Uncommon | Ataxia, impaired memory nystagmus |
| Convulsion and headache occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin | |
| *Eye disorders* | |
| Common | Diplopia, vision blurred accommodation disorders, |
| *Cardiac disorders* | |
| Uncommon | Bradycardia |
| *Vascular disorders* | |
| Common | Hypotension. |
| Uncommon | Hypertension, deep vein thrombosis, flushing, pallor. |
| *Respiratory, thoracic and mediastinal disorders* | |
| Common | Respiratory depression, pneumonia, dyspnoea |
| Not known | Bradypnoea |
| *Gastrointestinal disorders* | |
| Common | Diarrhoea, vomiting, nausea, constipation, decreased appetite, dry mouth, increased salivation. |
| Uncommon | Ileus, dysphagia, hypogeusia. |
| Nausea and vomiting occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin | |
| *Skin and subcutaneous tissue disorders* | |
| Common | Urticaria, pruritus, facial or peripheral oedema. |
| Uncommon | Hyperhidrosis, alopecia. |
| *Musculoskeletal and connective tissue disorders* | |
| Very common | Muscular hypotonia (especially during the test phase – transient effects). |

| | |
|---|---|
| Common | Muscular hypertonia. |
| Not known | Scoliosis (see section 4.4 special warning and precautions for use) |
| *Renal and urinary disorders* | |
| Common | Urinary retention, urinary incontinence |
| Urinary retention occurs more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin | |
| *Reproductive system and breast disorders* | |
| Common | Sexual dysfunction (Intrathecal Baclofen may compromise erection and ejaculation. This effect is usually reversible on withdrawal of Baclofen Aguettant) |
| Not known | Erectile dysfunction |
| *General disorders and administration site conditions* | |
| Common | Pyrexia, asthenia, pain, chills |
| Uncommon | Hypothermia |
| Rare | Potentially life-threatening withdrawal symptoms, as a result of sudden interruption of drug delivery (see "Interruption of treatment") |

Undesirable effects due to the administration system (e.g. inflammatory mass at the tip of the implanted catheter, catheter dislodgement with possible complications, local infection, meningitis, overdose due to incorrect manipulation of the system) have been mentioned and in some of these cases a causal link with baclofen cannot be excluded. Device malfunctions have been reported, resulting in altered drug delivery, leading to withdrawal symptoms, including death (see section 4.4 special warnings and precautions for use).

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 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 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

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 Intrathecal Baclofen is resumed after brief suspension.

Signs of overdose may appear suddenly or insidiously.

*Symptoms of overdose:* excessive muscular hypotonia, drowsiness, light-headedness, dizziness, sedation, seizures, loss of consciousness, ptyalism, nausea, vomiting, tachycardia and tinnitus.

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 represent other possible causes of overdose. Pump malfunction should also be investigated.

*Treatment*

There is no specific antidote for the treatment of overdose with Intrathecal Baclofen. 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 drug 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. A test can be performed with 1-2 mg physostigmine IV over a period of 5 to 10 minutes. During this time, patients should be subject to strict surveillance. 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.

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

Provided that lumbar puncture is not contraindicated, evacuation of 30-40 ml CSF can be considered at an early stage of intoxication, in order to reduce the baclofen concentration within the CSF.

Maintenance of cardiovascular function. During seizures: cautious IV injection of diazepam.

Physostigmine is only recommended for severe toxicity not responsive to supportive measures.

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 l0 minute intervals until a therapeutic effect is obtained or a total dose of 2 mg has been administered.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Muscle Relaxants, Other Centrally Acting Agents

ATC code: M03B X01

*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 has also been shown to have a dose-dependent effect on erectile dysfunction in men via $GABA_B$ receptor stimulation (see section 4.8).

Intrathecal Baclofen can be regarded as an alternative to destructive neurosurgical procedures.

Baclofen, introduced directly into the intrathecal space, allows treatment of spasticity at doses at least 400 to 1,000 times lower than they would be via the oral route.

*Intrathecal bolus*

The medicinal product 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 nanograms /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 nanograms /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 of 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 drug's action on the brain centres.

Special populations

*Elderly Patients*

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

*Paediatrics*

Paediatric patients, (8-18 years of age) who were infused chronically with intrathecal baclofen at a dose of 77-400 micrograms / day had plasma concentrations at or below 10 nanograms/mL.

*Hepatic impairment*

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

*Renal impairment*
No pharmacokinetic data is available in patients with renal impairment after administration of Intrathecal Baclofen. Since baclofen is majorly eliminated unchanged through the kidneys, accumulation of unchanged drug in patients with renal impairment can not be excluded.

### 5.3 Preclinical safety data

Non-clinical data show no particular risk to humans. These data come from conventional studies conducted in the field of repeated dose toxicity and genotoxicity.

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.

Based on the results of oral studies in rats, intrathecal administration of baclofen is unlikely to influence fertility or pre and post-natal development. Baclofen is not teratogenic in mice, rats or rabbits for doses administered at least 34 times higher than the maximum doses administered intrathecally in mg/kg.

Orally administered baclofen increases the incidence of omphalocele (ventral hernias) in fetuses of rats to whom was administered a dose approximately 135 times higher of the maximum mg/kg human dose administered intrathecally. This abnormality was not observed in mice or rabbits.

Oral administration of baclofen slows fetal growth (ossification of bones) in dosages which also resulted in maternal toxicity in rats and rabbits. After intraperitoneal administration of a high dose, baclofen caused vertebral arch widening in fetus rats.

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

Sodium Chloride

Water for injection

### 6.2 Incompatibilities

Dextrose 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 medicinaI products except those mentioned in section 6.6.**

## 6.3 Shelf life

5 years

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

## 6.4 Special precautions for storage

Do not refrigerate or freeze.

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

## 6.5 Nature and contents of container

*Baclofen Aguettant 2 mg/ml*

Type I clear colourless glass 5 ml ampoules with score-break and violet coloured ring marker.

Box of 1, 5 and 10 ampoules containing 5 ml of solution.

*Baclofen Aguettant 2 mg/ml*

Type I clear colourless glass 20 ml ampoules with score-break and green coloured ring marker.

Box of 1 ampoule containing 20 ml of solution.

*Baclofen Aguettant 2 mg/ml*

Type I clear colorless glass 5 mL ampoules with score-break and violet colored ring marker, packaged in sterile plastic blister.
Box of 5 and 10 ampoules containing 5 ml of solution.
*Baclofen Aguettant 2 mg/ml*

Type I clear colorless glass 20 mL ampoules with score-break and green colored ring marker, packaged in sterile plastic blister.
Box of 1 ampoule containing 20 ml of solution.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

*Instructions for use/operating instructions.*

Baclofen Aguettant is intended for intrathecal injections and continuous infusions and is administered according to the specifications accompanying each infusion system.

Baclofen Aguettant 10mg/5ml:

To open the package of Baclofen Aguettant, please hold the package with the two hands and turn the edges in opposite way until the opening (applicable only for not blistered ampoules packaging).

*Stability.*

Intrathecal baclofen has been shown to be stable for 180 days in implantable EU certified pumps.

Wherever possible prior to administering them, medicinal products for parenteral use should be checked for the presence of particulate matter and any changes in colour.

*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 50, 500 or 2,000 micrograms/ml, Baclofen Aguettant must be diluted under aseptic conditions in a sterile and preservative-free sodium chloride solution for injections.

*Administration systems.*

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

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

## 7 MARKETING AUTHORISATION HOLDER

Laboratoire Aguettant
1, rue Alexander Fleming
69007 Lyon
France

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 14434/0026

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20/08/2010

Date of latest renewal: 25/06/2015

## 10 DATE OF REVISION OF THE TEXT

22/05/2025