VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Not Applicable

VI.2.2 Summary of treatment benefits

No post-authorization efficacy studies are on-going or planned.

VI.2.3 Unknowns relating to treatment benefits

Not Applicable.

No post-authorization efficacy studies are on-going/planned.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Abrupt discontinuation of the treatment (Withdrawal syndrome)	Potentially life-threatening withdrawal syndrome, as a result of sudden interruption of drug delivery, is classified in the SmPC as a rare *'general disorder and administration site condition'*. Abrupt discontinuation of baclofen intrathecal, 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. 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 status hypermetabolicus or extensive rhabdomyolysis. 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	Yes, by avoid rapid interruption of the treatment and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. All patients receiving treatment with intrathecal baclofen are potentially at risk for withdrawal. 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. 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 Intrathecal, or oral, enteral, or intravenous benzodiazepines may prevent potentially fatal sequelae. Oral or enteral Baclofen 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

Risk	What is known	Preventability
	(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. A local infection or catheter misplacement can also cause interruption of drug delivery, which may result in abrupt baclofen intrathecal withdrawal, accompanied by its symptoms. Muirhead et al. in 2010 investigated the clinical features similarity between the life-threatening dystonic episode experienced by a patient, and those reported in intrathecal baclofen withdrawal. The case highlights the possibility that, rather than representing a true physiological withdrawal syndrome, abrupt withdrawal of intrathecal baclofen may simply precipitate an episode of status dystonicus in susceptible individuals. Acute intrathecal baclofen withdrawal is managed by restoring the delivery of intrathecal baclofen, providing supportive care in an intensive care setting and using drugs like low dose propofol or benzodiazepines in selected cases (Watve et al. 2012) Morr et al. presented in 2015 a case of successful treatment of acute severe baclofen withdrawal with the α2-adrenergic agonist	strictly followed. The filling of the reservoir 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 Baclofen Intrathecal withdrawal

Risk	What is known	Preventability
	dexmedetomidine infusion (commonly used for the treatment of ethanol withdrawal). The authors reported a case of safe and efficacious use in a patient with spastic quadriparesis on chronic intrathecal baclofen therapy.	
Epilepsy	Epileptic seizures are classified in the SmPC as common *'nervous system disorders'.* Treatment with intrathecal baclofen is contraindicated in case of patients with epilepsy refractory to therapy. Symptoms of overdose with intrathecal baclofen are represented by excessive muscular hypotonia, drowsiness, light-headedness, dizziness, sedation, epileptic seizures. Certain reports suggest that physostigmine is capable of abolishing the central nervous effects, particularly drowsiness and respiratory depression caused by intrathecal baclofen overdose. However, caution must be exercised when intravenously injecting physostigmine, as it might induce epileptic seizures, bradycardia and cardiac conduction disturbances. Abrupt discontinuation of baclofen intrathecal has given in rare cases progression to epileptic seizures/status epilepticus.	Yes, by monitoring for early symptoms, by avoiding overdose or rapid suspension of the drug and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. Caution in the use of intrathecal baclofen is needed in patients with epilepsy or other convulsive conditions, cortical or subcortical brain damage or significant EEG abnormalities, since the treatment may causes deterioration of seizure control and EEG changes and may precipitate convulsions. In patients with epilepsy and muscle spasticity, baclofen intrathecal can be employed under appropriate supervision; provided adequate anticonvulsive therapy is continued. Lowering of the convulsion threshold may occur and seizures have been reported occasionally after cessation of intrathecal baclofen or with overdosage. 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 Baclofen Intrathecal. For the treatment of the overdose symptoms, intravenously injecting

Risk	What is known	Preventability
	Concomitant use of intrathecal baclofen and general anaesthetics (e.g. fentanyl, propofol) may increase the risk of cardiac disturbances and seizures. Rapid changes in the dose of intrathecal baclofen may carry a higher risk of seizure induction (D'Aleo et al 2011). In children with spasticity of cerebral origin, intrathecal baclofen does not seem to aggravate or induce seizure activity (Buonauguro et al. 2005). A case of prolonged episode of dystonia and dyskinesia resembling status epilepticus following acute intrathecal baclofen withdrawal has been reported in 2011 by Specchio et al. All symptoms are related to overexcitability of the extrapyramidal and autonomic systems.	physostigmine must be administered with caution for the potential induction of epileptic seizures. 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. Particular caution should be exercised when general anaesthetics are administered to patients receiving Baclofen Intrathecal for the potential increased risk of seizures. To avoid abrupt withdrawal of the drug, 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. 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. In maintenance therapy, the lowest dose producing an adequate response should be used. 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. The risk-benefit for an intrathecal approach of the therapy by means of an implanted pump must be strictly evaluated by specialized physicians.

Risk	What is known	Preventability
Mental illness (Psychiatric disorders - suicidal ideation, suicidal attempt and depression)	The causality of psychiatric disorders with intrathecal baclofen therapy was frequently assessed as possible. These identified risks are defined as common (depression, anxiety, agitation), uncommon (suicidal ideation, suicidal attempt, hallucinations, paranoia, euphoric mood) and not known (dysphoria), as reported in the SmPC. Baclofen may precipitate or exacerbate psychotic symptoms, both during therapy and following abrupt withdrawal of the drug. Confusion, disorientation, hallucinations and impaired memory were already reported in the SmPC as common *'nervous system disorders'*. Anxiety, agitation, depression, suicidal ideation and attempt, euphoria, dysphoria, hallucinations and paranoia have been included at a later stage in the SmPC as '*psychiatric disorders'*. Suicidal ideation, suicidal attempt and depression have been classified as important identified risks. Baclofen intrathecal is frequently used for the treatment of substance abuse and alcohol dependency (Dore 2011, Shoptaw et al. 2003, Imbert 2014). To note, the role of intrathecal baclofen in the amelioration of psychological distress symptoms	Yes, by monitoring for early symptoms, by avoiding rapid suspension of the drug and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. These adverse reactions are most likely possible in patient with preexisting psychiatric and/or nervous system disorders. Therapy with intrathecal baclofen should be administered cautiously in critical subjects (patients with a history of nervous system /psychiatric disorders, patients with co-existing nervous system /psychiatric disorders , patients with spasticity of cerebral origin, elderly patients). 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. In maintenance therapy, the lowest dose producing an adequate response should be used. To avoid abrupt withdrawal of the drug, 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. 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.

Risk	What is known	Preventability
	has been investigated in 2014 by Margetis et al. An interesting trend was noted in the subscales of general severity index, depression, and obsession-compulsion. Intrathecal baclofen might be also associated with a significant improvement in the disorder of consciousness (Margetis et al. 2014).	The risk-benefit for an intrathecal approach of the therapy by means of an implanted pump must be strictly evaluated by specialized physicians.
Reaction of the involuntary nervous system to overstimulation (Autonomic Dysreflexia)	The causality of autonomic dysreflexia with intrathecal baclofen therapy was frequently assessed as possible. Abrupt withdrawal of intrathecal baclofen may trigger an episode of autonomic dysreflexia. Some clinical characteristics associated with intrathecal baclofen withdrawal can resemble autonomic dysreflexia. The presence of nociceptive stimuli may also generate an episode of autonomic dysreflexia. This identified potential risk occurs more often in people who have spinal cord injuries at the level of T6 and above (upper back). It is also more common in people with recent spinal cord injuries. Autonomic dysreflexia is a reaction of the autonomic (involuntary) nervous system to overstimulation. It is characterized by paroxysmal hypertension (the sudden onset of severe high blood pressure) associated with throbbing	Yes, by monitoring for early symptoms, by avoiding rapid suspension of the drug and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. Therapy with intrathecal baclofen should be administered cautiously in patients with a history of autonomic dysreflexia. Immediate steps to reduce high blood pressure due to autonomic dysreflexia include: - Relieving pain stimulus below spinal cord injury level - Sitting patient in an upright position to use gravity to reduce intra cranial blood pressure In severe cases of autonomic dysreflexia a blood pressure lowering drug should be administered such as: - Phentolamine 5-10mg intravenously - Gylceryl trinitrate 300 micrograms sublingually or - Nifedipine 5-10mg sublingually. Patients with spinal cord injury should be educated to recognize the early symptoms of autonomic dysreflexia and understand the common causes and management.

Risk	What is known	Preventability
	headaches, profuse sweating, nasal stuffiness, slow heart rate, anxiety, and sometimes by cognitive impairment. The sympathetic discharge that occurs is usually in association with spinal cord injury or disease (e.g. multiple sclerosis). Autonomic dysreflexia is believed to be triggered by afferent stimuli that trigger and maintain an increase in blood pressure via a sympathetically mediated vasoconstriction in muscle. Autonomic dysreflexia is usually caused when a painful stimulus occurs below the level of spinal cord injury. The autonomic nervous system is responsible for the signs and symptoms of autonomic dysreflexia. In some patients with a high-level spinal cord injury, intact lower motor neurons sense the painful stimuli below the level of injury and transmit the message up the spinal cord. At the level of the spinal cord injury, the pain signal is interrupted and prevented from being transmitted to the cerebral cortex. The site of the spinal cord injury also interrupts the two branches of the autonomic nervous system and disconnects the feedback loop, causing the two branches to function independently. The ascending information reaches the major splanchnic sympathetic outflow (T5-T6) and stimulates a sympathetic response. The sympathetic response causes vasoconstriction, resulting in hypertension, pounding headache, visual	Those with recurrent symptoms should be educated on home blood pressure monitoring. 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. In maintenance therapy, the lowest dose producing an adequate response should be used. To avoid abrupt withdrawal of the drug, 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. 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. The risk-benefit for an intrathecal approach of the therapy by means of an implanted pump must be strictly evaluated by specialized physicians.

Risk	What is known	Preventability
	changes, anxiety, pallor, and goose bumps below the level of injury. To note, intrathecal baclofen administration may help in some cases to stabilize autonomic dysreflexia and orthostatic hypotension in patients with spinal cord lesions (Kofler et al. 2009).	
Illness pertaining to the kidneys (Impaired renal function)	Baclofen is primarily eliminated by the kidney. No pharmacokinetic data is available in patients with renal impairment after administration of Baclofen Intrathecal. Since baclofen is majorly eliminated unchanged through the kidneys, accumulation of unchanged drug in patients with renal impairment cannot be excluded. Patients with severely impaired renal function generally develop baclofen intoxication soon after the initiation of low-dose therapy. Thus, the administration of baclofen, regardless of the dosage, in these patients is not appropriate. Abdominal pain, in addition to altered consciousness, is a common presenting feature in patients with renal failure who have baclofen intoxication. Dose adjustment recommendations of baclofen in patients with chronic kidney disease have been detailed by Vlavonou et al. 2014.	Yes, by monitoring for early symptoms, by avoiding overdose and rapid suspension of the drug and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. Therapy with intrathecal baclofen should be administered cautiously in patients with impaired renal function. Patients with impaired renal function may be at greater risk for adverse effects from baclofen due to decreased drug clearance. 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. A dosage reduction is advised to avoid drug accumulation. Baclofen should be used with caution in critical patients (patients with renal insufficiency, patients with a history of renal impairment, elderly patients) and should only be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk.

Risk	What is known	Preventability
	Besides discontinuing treatment, unscheduled haemodialysis might be considered as a treatment alternative in patients with severe baclofen toxicity. Haemodialysis effectively removes baclofen from the body, alleviates clinical symptoms of overdose and shortens the recovery time in these patients.	Particular caution is required when combining baclofen to drugs or medicinal products that can significantly impact renal function. Renal function shall be closely monitored and baclofen daily dosage adjusted accordingly to prevent baclofen toxicity. 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. In maintenance therapy, the lowest dose producing an adequate response should be used. 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. The risk-benefit for an intrathecal approach of the therapy by means of an implanted pump must be strictly evaluated by specialized physicians.
Illness pertaining to heart and blood flow (Cardiovascular disorders)	Cardiovascular disorders are classified in the SmPC as uncommon (bradycardia hypertension, deep vein thrombosis, flushing, pallor) and common (hypotension). Baclofen depresses the CNS in general, causing sedation, somnolence, as well as respiratory and cardiovascular depression. Rifici et al. in 2011 suggested that intrathecal baclofen may herald cardiovascular dysfunction in predisposed patients.	Yes, by monitoring for early symptoms, by avoiding overdose and rapid suspension of the drug and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. Monitoring of respiratory and cardiac function is essential during test 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 is increased in such cases.

Risk	What is known	Preventability
	Certain reports suggest that physostigmine is capable of abolishing the central nervous effects, particularly drowsiness and respiratory depression caused by intrathecal baclofen overdose. However, caution must be exercised when intravenously injecting physostigmine, as it might induce epileptic seizures, bradycardia and cardiac conduction disturbances. Concomitant use of intrathecal baclofen and general anaesthetics (e.g. fentanyl, propofol) may increase the risk of cardiac disturbances and seizures.	The intrathecal pump should only be implanted after strict evaluation of the patient's response to baclofen intrathecal bolus injections and/or dose titration. Given the risks associated with initial administration and dose adjustment of baclofen intrathecal (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" of the SmPC. In maintenance therapy, the lowest dose producing an adequate response should be used. For the treatment of the overdose symptoms, intravenously injecting physostigmine must be administered with caution for the potential induction of epileptic seizures. 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. Particular caution should be exercised when general anaesthetics are administered to patients receiving Baclofen Intrathecal for the potential increased risk of cardiac disturbances. Intrathecal baclofen must be administered with caution in critical patient (patients with a history of cardiovascular disorders). During the test phase, as well as during

Risk	What is known	Preventability
		the titration period following implantation, patients should be closely monitored at an institution with all the necessary equipment and personnel. In maintenance therapy, the lowest dose producing an adequate response should be used. 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. The risk-benefit for an intrathecal approach of the therapy by means of an implanted pump must be strictly evaluated by specialized physicians.
Illness pertaining to stomach and intestine (Gastrointestinal disorders)	Gastrointestinal disorders are classified in the SmPC as common (nausea/vomiting, constipation, dry mouth, diarrhoea, decreased appetite, increased salivation). Gastrointestinal disorders raised especially with oral baclofen treatment (van Rijn et al 2009) and in literature are frequently defined unrelated to baclofen intrathecal therapy. To note, baclofen is commonly used for the treatment of gastrointestinal disorders such as gastroesophageal reflux disease (GERD), transient lower esophageal sphincter relaxation, dyspepsia, ruminant syndrome, hiccups (Koek et al. 2003, Omari et al. 2006, Kofler et al. 2002, Blondeau et al. 2012, Cossentino et al. 2012, Abbasinazari et al. 2014, Auteri et al. 2015, Sharma et al. 2015).	Yes, by monitoring for early symptoms. and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. Intrathecal baclofen must be administrated with caution in critical patient (patients with a history of gastrointestinal disorders). 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. In maintenance therapy, the lowest dose producing an adequate response should be used. 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. The risk-benefit for an intrathecal

Risk	What is known	Preventability
	Baclofen has been shown to be effective in the treatment of the above mentioned gastrointestinal disorders by either a central action in the medulla or an effect on gastric afferents. The diversity of gastrointestinal functions regulated by GABAB receptors make baclofen a potentially useful target in the treatment of several gastrointestinal disorders, but may also limit its therapeutic application due to off target side effects, both in the gastrointestinal tract and centrally. For example GERD patients and healthy volunteers treated with baclofen reported adverse effects of a neurological nature that included drowsiness and dizziness (Hyland et al. 2010).	approach of the therapy by means of an implanted pump must be strictly evaluated by specialized physicians.
Psychotic disorders, schizophrenia, confusional states or Parkinson's disease	Patients with psychotic disorders, schizophrenia, confusional states or Parkinson's disease must be cautiously treated with Baclofen Intrathecal and undergo strict surveillance whenever exacerbation of such conditions has been observed following oral baclofen administration. Investigation of the oral baclofen therapy efficacy on schizophrenia has been performed starting from the 70ies. To note, Baclofen therapy may have positive effects on some kind of schizophrenia while worsening other situations (Lund et al. 1976, Schopf and Hucker	Yes, by monitoring for early symptoms. and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. Intrathecal baclofen must be administrated with caution in critical patient (patients with a history of schizophrenia, confusional states or Parkinson's disease). 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. In maintenance therapy, the lowest dose producing an adequate response should

Risk	What is known	Preventability
	1977, Kuhn 1976, Llewellin et al. 1977, Frederiksen 1978, Gulmann et al. 2007).	be used. 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. The risk-benefit for an intrathecal approach of the therapy by means of an implanted pump must be strictly evaluated by specialized physicians.
Cerebrovascular or respiratory insufficiency	In patients with slowed CSF circulation due, for example, to blockage caused by inflammation or trauma, the delayed migration of Baclofen Intrathecal can reduce the antispastic efficacy and boost the adverse reactions. The same caution is required in the presence of cerebrovascular or respiratory insufficiency, as baclofen can aggravate such states. Intrathecal baclofen overdose can cause respiratory depression. In a study conducted in 2006 by Bensamil et al., intrathecal baclofen infusion seemed to not affect respiratory function in comparison with oral baclofen.	Yes, by monitoring for early symptoms. and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. Intrathecal baclofen must be administrated with caution in critical patient (patients with a history of cerebrovascular or respiratory insufficiency). Monitoring of respiratory and cardiac function is essential during test 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 is increased in such cases. 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. In maintenance therapy, the lowest dose producing an adequate response should be used. It is essential that the risks of such a

Risk	What is known	Preventability
		method of treatment are precisely known by the patient, doctors in charge of him/her and all caregivers. The risk-benefit for an intrathecal approach of the therapy by means of an implanted pump must be strictly evaluated by specialized physicians.
Infections related to pump implantation	Infections related to pump implantation are classified as undesirable effects due to the administration system such as inflammatory mass at the tip of the implanted catheter, catheter dislodgement, local infection, meningitis, overdose due to incorrect manipulation of the system. Any infection must be excluded prior to the test phase with Baclofen Intrathecal, as a systemic infection might falsify the evaluation of the patient's response to the Baclofen Intrathecal injection. 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 Baclofen Intrathecal withdrawal, accompanied by its symptoms (see "Interruption of treatment" in the SmPC). Once the patient's response to Baclofen Intrathecal has been	Yes, by monitoring for early symptoms. and by supply the SmPC to all clinicians/personnel involved in the pump implantation, pump programming and/or refilling of the reservoir in order to increase the attention on this topic. Baclofen Intrathecal is a sterile solution in sealed glass ampoules; no risks for potential transmission of microorganisms are related to the medicinal product. The main source of infection is related to the pump refill. Therefore, the filling of the reservoir 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. The pump implantation must be performed by trained and fully qualified personnel, in accordance with the manufacturer's instructions. Specific instructions for implantation are given by the pump manufacturers, and must be strictly adhered to. 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.

Risk	What is known	Preventability
	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. 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 status hypermetabolicus or extensive rhabdomyolysis. Transcutaneous catheter insertion during the pump implantation and the presence of a PEG tube increase the incidence of infections in children.	In the 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. 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.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Hiatal hernia	Hiatal hernia has been classified as a potential safety signal for baclofen intrathecal and has to be carefully monitored in the frame of regular signal detection activities. Weber reported in 2013 about a boy with asphyxia-induced severe bilateral cerebral palsy, who suffered from gastroesophageal reflux disease. After open semifundoplication and PEG tube placement, he showed a stabile course of these gastrointestinal symptoms. However, some years later, after implantation of an intrathecal baclofen pump and starting intrathecal baclofen treatment, he developed severe episodes with symptoms of gastroesophageal reflux. A diagnostic work up disclosed a relapse of the hiatus hernia, which was strongly and repeatedly associated with the dose of intrathecal baclofen. Considering the plausible temporality, the recurrence of the events when

Risk	What is known (Including reason why it is considered a potential risk)
	increasing the dose, the role for baclofen in the onset of symptoms of gastroesophageal reflux induced by relapse of the hiatus hernia appears probable. Beaumont and Boeckxstaens studied in 2009 the possible interaction between the presence of a hiatal hernia and the efficacy of baclofen as reflux inhibitor during add-on therapy.
Subdural hematoma	As requested in the last PSUR, the subdural hematoma has been classified as a potential safety signal for baclofen intrathecal and has to be carefully monitored in the frame of regular signal detection activities. This adverse event is not reported in the SmPC. Complications of the subdural hematoma could be raised intracranial pressure, cerebral oedema, recurrent haematoma formation during recovery, seizures, subdural empyema, meningitis, permanent neurological or cognitive deficit due to pressure effects on the brain, coma/persistent vegetative state, death due to cerebellar herniation. Magro et al. in 2011 reported the case of a 41-year-old woman who developed a bilateral subacute subdural hematoma after the placement of an intrathecal catheter connected to a programmable pump for baclofen infusion. Ng et al. in 2014 presented a case report of severe persistent CSF leak after intrathecal pump revision that resulted in a subdural hematoma and postdural puncture headache. In this case, an epidural blood patch was performed using epidural catheter under fluoroscopic guidance to target the site of CSF leak and to avoid damaging the intrathecal catheter. The patient's headache was resolved and intrathecal catheter remained intact after the blood patch. Other reports were retrieved from Eudravigilance, describing cases of subdural hematoma potentially associated with baclofen intrathecal administration. However some of these reports were confounded by co-medication or comorbidities that may also have triggered/ favoured the onset of subdural hematoma.
Accidental overdose	Accidental overdose has been classified as a potential safety signal for baclofen intrathecal and has to be carefully monitored in the frame of regular signal detection activities.

Risk	What is known (Including reason why it is considered a potential risk)
	Signs of overdose, overdose management and potentially life-threatening overdose symptoms are well documented in different sections of the SmPC (4.2, 4.4 and 4.9). Symptoms of overdose such as loss of consciousness, bradycardia, respiratory insufficiency/arrest, seizure, dizziness, coma and hypotonia are also listed in the SmPC (section 4.9). Incorrect drug delivery (in the side-port of the pump instead of the reservoir port) appears to be the more frequent cause for overdose. During the test phase 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. Except in emergency cases associated with an overdose, treatment should be discontinued gradually with successive dose reductions. Symptoms of overdose with intrathecal baclofen are represented by excessive muscular hypotonia, drowsiness, light-headedness, dizziness, sedation, epileptic seizures. Certain reports suggest that physostigmine is capable of abolishing the central nervous effects, particularly drowsiness and respiratory depression caused by intrathecal baclofen overdose. However, caution must be exercised when intravenously injecting physostigmine, as it might induce epileptic seizures, bradycardia and cardiac conduction disturbances. 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 Baclofen Intrathecal. Clinical and EEG features of acute intrathecal baclofen overdose have been investigated by Sauneuf et al. 2012. Haemodialysis is considered an appropriate treatment of baclofen overdose intoxication (Dias et al. 2011, Hsieh et al. 2012). Continuous venovenous hemofiltration can be used as an alternative to haemodialysis in patients with overdose

Risk	What is known (Including reason why it is considered a potential risk)
	of baclofen (Meulendijks et al. in 2015).

Missing information

Risk	What is known
Safety in pregnant and lactating women	There are no adequate and sufficiently controlled studies in pregnant women. Baclofen crosses the placental barrier. Baclofen Intrathecal must not be used during pregnancy, unless the potential benefits outweigh the possible risks to the foetus. Studies in animals have shown a teratogenic effect of baclofen by oral administration (See section 5.3 of the SmPC). It is not known whether measurable levels of the product can be detected in the maternal milk of lactating mothers treated with Baclofen Intrathecal. 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. In the frame of regular signal detection activities, the Applicant will carefully monitor data regarding the safety and efficacy of the use of Baclofen Intrathecal in pregnant and lactating women. Munoz et al. in 2000 described a case of pregnancy outcome in a woman exposed to continuous intrathecal baclofen infusion. Specific aspects of intrathecal baclofen for severe tetanus in a pregnant woman have been detailed by Engrand et al. in 2001. Roberts et al. in 2003 reported a case of intrathecal baclofen pump implantation during pregnancy.

	The safety of intrathecal baclofen in pregnancy has been also investigated by Dalton et al. in 2008. The authors stated that intrathecal baclofen is safe in pregnancy and may in fact be safer for the infant than oral baclofen. A case of intrathecal baclofen therapy in pregnancy has been described by DeVries-Rizzo et al. in 2009. A literature review is also presented. A case of epidural analgesia in labor for a woman with an intrathecal baclofen pump has been described in 2009 by Ali Sakr Esa et al. No maternal or postnatal complications have been reordered. Méndez-Lucena et al. in 2014 reported a case of intrathecal baclofen for dystonia treatment during pregnancy.
Risk	**What is known**
Safety in paediatric patients < 4 years	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. In the frame of regular signal detection activities, the Applicant will carefully monitor data regarding the safety and efficacy of the use of Baclofen Intrathecal in children under the age of four years. Moran et al. in 2004 investigated a multidisciplinary approach for intrauterine baclofen exposure.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is

provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

Furthermore the medicinal product is subject to medical prescription.

VI.2.6 Planned post authorisation development plan

Not Applicable.

No post-authorization development plan are scheduled.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
01	20 March 2009 (BE/H/0152/001-003/DC, approved on 25 June 2010)	No important identified or potential risks were classified	Version 01 was in previous EU format
02	25 March 2015 (BE/H/0152/001-003/R/001, approved on 19 June 2015)	Classification of identified and potential risks according to the renewal procedure assessment	Version 02 was updated according to the GVP Module V.