VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Spasticity of spinal origin may be related to spinal cord injury or multiple sclerosis, and spasticity of cerebral origin may be associated with traumatic brain injury, cerebral palsy, multiple sclerosis, anoxic brain damage, certain metabolic disorders, tumours or stroke.

Spasticity varies from being a clinical sign with no functional impact to being a gross increase in tone, with uncontrollable painful spasms, interfering with mobility/personal care.

It is estimated that spasticity affects more than 12 million people worldwide. Cerebral palsy is reported to occur in 2 per 1000 live-births of which a majority has a spastic syndrome. In multiple sclerosis, about 34% of the patients suffer from moderate to severe, disabling spasticity. The proportion of patients with spasticity is 38% and 60% in post-stroke and post-traumatic spinal cord injury, respectively. Amyotrophic lateral sclerosis (ALS) may also cause spasticity in a minor portion of patients; ALS affects 5.2 per 100 000 subjects.

VI.2.2 Summary of treatment benefits

The active ingredient of Gablofen® is baclofen. Baclofen can be administered orally or intrathecally into the spinal canal. The intrathecal system can deliver baclofen directly into the spinal cord where spasticity can be treated, while from oral baclofen treatment only a small amount reaches the spinal fluid. Intrathecal treatment is performed with an implanted pump which continuously delivers a constant amount of baclofen. Baclofen decreases symptoms of severe spasticity and leads to increased quality of life in chronic spasticity patients, who are unresponsive to oral baclofen or other orally administered agents to treat spasticity. Spasticity results from injury or neurological diseases such as cerebral palsy, multiple sclerosis, and stroke and cannot be cured completely. The disease leads to immobility and pain which massively affects the patients' daily life and comfort. Baclofen helps to increase muscle function and relieve discomfort and pain. In non-ambulatory patients intrathecal baclofen treatment may stabilise the patients' legs and improve mobility. The implanted pumps need periodical refills depending on the flow and the concentration of baclofen in the pump. Higher concentrations can decrease the number of pump refills, which are associated with risks due to the invasiveness of the procedure, and with discomfort for the patient.

VI.2.3 Unknowns relating to treatment benefits

Intrathecal baclofen is of well-established use but the treatment and dosing is required to be individualised to optimise benefits. Around 5% of patients, receiving long term therapy may become refractory to dose increase. This has occasionally been treated with a "drug holiday". Thereafter, the effect of Gablofen® may be re-established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
1. Overdose (including CNS depression) 2. Drug withdrawal	Handling errors or failure of the pump or catheter may lead to overdose of baclofen or withdrawal with recurrence of spasticity, respectively. Symptoms of overdose include decreased muscle activity, drowsiness, loss of consciousness, nausea and vomiting or seizures. Pump failure may result from decreased battery life while catheter failure may result from dislocation, kinking or rupture. Symptoms of lack of effect/withdrawal include the symptoms of the underlying spasticity like increased muscle activity, decreased perception or low blood pressure. In serious cases seizures, muscle destruction, organ failure or death may occur.	Intrathecal baclofen therapy is used in a specialised healthcare setting that ensures a high standard of care for patients, to minimize handling errors of the pump. Monitoring of the patient after implantation of the pump and after changing the delivery rate of the pump allow for early detection and treatment of signs of overdose and withdrawal. All persons participating in the treatment or care given to the patient should be clearly informed about the symptoms of under- and overdosing.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
1. Formation of inflammatory granuloma	Inflammatory granuloma at the catheter tip were reported in rare cases for patients receiving intrathecal therapy for pain. Usually high concentrations of pain medication were used in these cases. Such a mass may lead to decreased drug effects, local pain or neurologic deficits. There is no clear information in clinical trials, published literature, or 18 years of commercial use of intrathecal baclofen therapy that inflammatory granuloma formation is a clinical risk. Therefore, the formation of inflammatory masses at the catheter tip is considered a potential risk for baclofen therapy. The company is conducting a study to assess the occurrence of inflammatory granuloma under intrathecal baclofen therapy using a 3 mg/ml Gablofen® concentration.

Missing information

Risk	What is known

Risk	What is known
1. Use in pregnant and lactating women	There are no adequate and sufficiently controlled studies in pregnant and lactating women. Therefore, the patient information leaflet advises patients to talk to their doctor if they are pregnant or breast-feeding. In mothers taking oral baclofen in therapeutic doses the active substance passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected. It is not known whether detectable levels of drug are present in the breast milk of nursing mothers receiving intrathecal baclofen. Possible effects on the fertility in humans have not been investigated.
2. Use in children younger than 4 years of age	There are no adequate and sufficiently controlled studies in children younger than 4 years of age. Therefore, the Summary of Product Characteristics as well as the patient information leaflet make doctors and patients aware that the product is not recommended for use in these patients.

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 minimising 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.

The Summary of Product Characteristics and the Package leaflet for Gablofen® can be found in the Gablofen®'s EPAR page.

No additional risk minimisation measures are necessary.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Not applicable.