# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Baclofen 5mg/5ml oral solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is baclofen, a racemic mixture of the R, (-) and S, (+) isomers.

Each 5ml of oral solution contains 5mg baclofen.

*Excipients with known effect*:
Each 5ml of oral solution contains 7mg methyl parahydroxybenzoate (E218), 1925mg sorbitol (E420), 6.675mg propylene glycol and 8.1mg of sodium.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Oral Solution
Clear, pale yellow to yellow coloured oral solution with raspberry flavour.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Baclofen is indicated for the relief of spasticity of voluntary muscle resulting from such disorders as: multiple sclerosis, other spinal lesions, e.g. tumours of the spinal cord, syringomyelia, motor neurone disease, transverse myelitis, traumatic partial section of the cord.

Baclofen is also indicated in adults and children for the relief of spasticity of voluntary muscle arising from e.g. cerebrovascular accidents, cerebral palsy, meningitis, traumatic head injury.

Patient selection is important when initiating Baclofen therapy; it is likely to be of most benefit in patients whose spasticity constitutes a handicap to activities and/or physiotherapy. Treatment should not be commenced until the spastic state has become stabilised.

*Paediatric population*
Baclofen is indicated in patients 0 to <18 years for the symptomatic treatment of spasticity of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.
Baclofen is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

### 4.2 Posology and method of administration

Posology

Baclofen is given orally in either tablet or liquid form. The liquid may be particularly suitable for children or those adults who are unable to take tablets. Dosage titration can be more precisely managed with the liquid. The lowest dose compatible with an optimal response is recommended.

Before starting treatment with Baclofen it is prudent to realistically assess the overall extent of clinical improvement that the patient may be expected to achieve. Careful titration of dosage is essential (particularly in the elderly) until the patient is stabilised. If too high a dose is initiated or if the dosage is increased too rapidly side effects may occur. This is particularly

relevant if the patient is ambulant in order to minimise muscle weakness in the unaffected limbs or where spasticity is necessary for support.

Once the maximum recommended dose has been reached, if the therapeutic effect is not apparent within 6 weeks a decision whether to continue with Baclofen should be taken.

Discontinuation of the treatment should always be gradual by successively reducing the dosage over a period of approximately 1 to 2 weeks, except in overdose-related emergencies, or where serious adverse effects have occurred (see section 4.4).

*Adults*
Treatment should be started with a dosage of 15 ml (15mg) daily, preferably in divided doses. The following gradually increasing dosage regimen is suggested, but should be adjusted to suit individual patient requirements.

5ml (5mg) three times a day for three days

10ml (10mg) three times a day for three days

15ml (15mg) three times a day for three days

20ml (20mg) three times a day for three days

Satisfactory control of symptoms is usually obtained with doses of up to 60ml (60mg) daily, but a careful adjustment is often necessary to meet the requirements of each individual patient.

The dose may be increased slowly if required, but a maximum daily dose of more than 100ml (100mg) is not advised unless the patient is in hospital under careful medical supervision. Small frequent dosage may prove better in some cases than larger spaced doses.

Also some patients benefit from the use of Baclofen only at night to counteract painful flexor spasm. Similarly a single dose given approximately 1 hour prior to performance of specific tasks such as washing, dressing, shaving, physiotherapy, will often improve mobility.

Special populations
*Elderly patients (aged 65 years or above):*
Elderly patients may be more susceptible to side effects, particularly in the early stages of introducing Baclofen. Small doses should therefore be used at the start of treatment, the dose being titrated gradually against the response, under careful supervision. There is no evidence that the eventual average maximum dose differs from that in younger patients.

*Paediatric population (0 to < 18 years):*
Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), in 2-4 divided doses, preferably in 4 divided doses. The dosage should be cautiously raised at about 1 week intervals, until it becomes sufficient for the child's individual requirements.
The usual daily dosage for maintenance therapy ranges between 0.75 and 2mg/kg body weight. The total daily dose should not exceed a maximum of 40mg/day in children below 8 years of age. In children over 8 years of age, a maximum daily dosage of 60mg/day may be given.

*Patients with impaired renal function:*
In patients with impaired renal function or undergoing chronic haemodialysis, a particularly low dosage of Baclofen should be selected i.e. approx. 5ml (5mg) daily.

Baclofen should be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk. These patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy) (see section 4.4 and section 4.9).

*Patients with hepatic impairment:*

No studies have been performed in patients with hepatic impairment receiving baclofen therapy. The liver does not play a significant role in the metabolism of baclofen after oral administration of baclofen (see section 5.2). However, baclofen has the potential of elevating liver enzymes. Baclofen should be prescribed with caution in patients with hepatic impairment.

*Patients with spastic states of cerebral origin:*
Unwanted effects are more likely to occur in these patients. It is therefore recommended that a cautious dosage schedule be adopted and that patients be kept under appropriate surveillance.

**Method of administration:**
Baclofen should be taken during meals with a little liquid.

Baclofen should be taken using the provided oral syringe

**4.3 Contraindications**

- Hypersensitivity to baclofen or to any of the excipients listed in section 6.1
- Peptic ulceration

**4.4 Special warnings and precautions for use**

*Psychiatric and nervous system disorders*
Psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson's disease may be exacerbated by treatment with baclofen. Patients suffering from these conditions should therefore be treated cautiously and kept under close surveillance.

Suicide and suicide-related events have been reported in patients treated with baclofen. In most cases, the patients had additional risk factors associated with an increased risk of suicide including alcohol use disorder, depression and/or a history of previous suicide attempts. Close supervision of patients with additional risk factors for suicide should accompany drug therapy. 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.

Cases of misuse, abuse and dependence have been reported with baclofen. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of baclofen misuse, abuse or dependence e.g. dose escalation, drug-seeking behaviour, development of tolerance.

*Epilepsy*
Baclofen may also exacerbate epileptic manifestations but can be employed provided appropriate supervision and adequate anticonvulsive therapy are maintained.

*Others*
Baclofen should be used with extreme care in patients already receiving antihypertensive therapy, (see section 4.5).

Baclofen should be used with caution in patients suffering from cerebrovascular accidents or from respiratory or hepatic impairment.

Since unwanted effects are more likely to occur, a cautious dosage schedule should be adopted in elderly and patients with spasticity of cerebral origin (see section 4.2).

*Renal impairment*
Baclofen should be used with caution in patients with renal impairment and should be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk (see section 4.2). Neurological signs and symptoms of overdose including clinical manifestations of toxic encephalopathy (e.g. confusion, disorientation, somnolence and depressed level of consciousness) have been observed in patients with renal impairment taking oral baclofen at doses of more than 5mg per day and at doses of 5mg per day in patients with end-stage renal failure being treated with chronic haemodialysis. Patients with impaired renal function should be closely monitored for prompt diagnosis of early symptoms of toxicity (see section 4.9).

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.

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.

*Urinary disorders*
Under treatment with baclofen neurogenic disturbances affecting emptying of the bladder may show an improvement. In patients with pre-existing sphincter hypertonia, acute retention of urine may occur; the drug should be used with caution in such cases.

*Laboratory tests*
In rare instances elevated aspartate aminotransferase, blood alkaline phosphatase and blood glucose levels in serum have been recorded. Appropriate laboratory tests should be performed in patients with liver diseases or diabetes mellitus in order to ensure that no drug induced changes in these underlying diseases have occurred.

*Excipient(s) warning:*
Methyl parahydroxybenzoate (E218): May cause allergic reactions (possibly delayed). Sorbitol (E420): This medicinal product contains 1925mg sorbitol in each 5ml dose which is equivalent to 385mg/ml. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
Sodium: This medicinal product contains 8.1mg sodium per 5ml, equivalent to 0.41% of the WHO recommended maximum daily intake of 2g sodium for an adult.
Propylene glycol (E1520): This medicinal product contains 6.675mg propylene glycol in each 5ml dose which is equivalent to 1.335mg/ml. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

*Abrupt withdrawal:*
Treatment should always, (unless serious adverse effects occur), be gradually discontinued by successively reducing the dosage over a period of about 1-2 weeks. Anxiety and confusional state, delirium, hallucinations, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and temporary aggravation of spasticity as a rebound phenomenon have been reported with abrupt withdrawal of baclofen, especially after long term medication.

Neonatal convulsions have been reported after intrauterine exposure to oral baclofen (see section 4.6).

*Paediatric patients*
There is very limited clinical data on the use of baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.

*Posture and balance*
Baclofen should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion (see section 4.2).

**4.5 Interaction with other medicinal products and other forms of interactions**

*Levodopa/dopa decarboxylase (DDC) inhibitor (Carbidopa)*
In patients with Parkinson's disease receiving treatment with baclofen and levodopa (alone or in combination with DDC inhibitor, carbidopa), there have been reports of mental confusion, hallucinations, nausea and agitation. Worsening of the symptoms of Parkinsonism has also been reported. Hence, caution should be exercised during concomitant administration of Baclofen and levodopa/carbidopa.

*Drugs causing Central Nervous System (CNS) depression*
Increased sedation may occur when baclofen is taken concomitantly with other drugs causing CNS depression including other muscle relaxants (such as tizanidine), with synthetic opiates or with alcohol (see section 4.7).

The risk of respiratory depression is also increased. In addition, hypotension has been reported with concomitant use of morphine and intrathecal baclofen. Careful monitoring of respiratory and cardiovascular functions is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

*Antidepressants*
During concomitant treatment with tricyclic antidepressants, the effect of baclofen may be potentiated, resulting in pronounced muscular hypotonia.

*Lithium*
Concomitant use of oral Baclofen and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should be exercised when Baclofen is used concomitantly with lithium.

*Antihypertensives*
Since concomitant treatment with Baclofen and anti-hypertensives is likely to increase the fall in blood pressure, the dosage of antihypertensive medication should be adjusted accordingly.

*Agents reducing renal function*
Drugs or medicinal products that can significantly affect renal function may reduce baclofen excretion leading to toxic effects (see Section 4.4).

**4.6 Fertility, pregnancy and lactation**

During pregnancy, especially in the first 3 months, baclofen should only be employed if its use is of vital necessity. The benefits of the treatment for the mother must be carefully weighed against the possible risks for the child. Baclofen crosses the placental barrier.

One case of suspected withdrawal reaction (generalised convulsions) has been reported in a week-old infant whose mother had taken oral baclofen 80 mg daily throughout her pregnancy. The convulsions, which were refractory to standard anticonvulsant treatment, ceased within 30 minutes of giving baclofen to the infant.

In mothers taking 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.

**4.7 Effects on ability to drive and use machines**

Baclofen may be associated with adverse effects such as dizziness, sedation, somnolence and visual impairment (See section 4.8) which may impair the patient's reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines.

**4.8 Undesirable effects**

Adverse effects occur mainly at the start of treatment (e.g. sedation, somnolence and nausea), if the dosage is raised too rapidly, if large doses are employed, or in elderly patients. They are often transitory and can be attenuated or eliminated by reducing the dosage; they are seldom severe enough to necessitate withdrawal of the medication.

Should nausea persist following a reduction in dosage, it is recommended that baclofen be ingested with food or a milk beverage.

In patients with a history of psychiatric illness or with cerebrovascular disorders (e.g. stroke) as well as in elderly patients, adverse reactions may assume a more serious form.

Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients.

Certain patients have shown increased spasticity as a paradoxical reaction to the medication.

An undesirable degree of muscular hypotonia - making it more difficult for patients to walk or fend for themselves – may occur and can usually be relieved by re-adjusting the dosage (i.e. by reducing the doses given during the day and possibly increasing the evening dose).

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000) very rare (< 1/10,000) and Not known (cannot be estimated from the available data).

**Table 1 Summary of adverse drug reactions**

| Organ Systems | Frequency | Adverse reactions |
|---|---|---|
| *Nervous system disorders* | Very common | Sedation, somnolence |
| | Common | Respiratory depression, confusional state, dizziness, hallucination, depression, fatigue, insomnia, euphoric mood, muscular weakness, ataxia, tremor, nightmare, myalgia, headache, nystagmus, dry mouth. |
| | Rare | Paraesthesia, dysarthria, dysgeusia. |
| | Not known | Sleep apnoea syndrome* |
| *Eye disorders* | Common | Visual impairment, accommodation disorder |
| *Cardiac disorders* | Common | Cardiac output decreased |
| | Not known | Bradycardia |
| *Vascular disorders* | Common | Hypotension |
| *Gastrointestinal disorders* | Very common | Nausea |
| | Common | Gastrointestinal disorder, constipation, diarrhoea, retching, vomiting |
| | Rare | Abdominal pain |
| *Hepatobiliary disorders* | Rare | Hepatic function abnormal |
| *Skin and subcutaneous tissue disorders* | Common | Rash, hyperhidrosis |
| | Not known | Urticaria |
| *Renal and urinary disorders* | Common | Pollakiuria, enuresis, dysuria |
| | Rare | Urinary retention |
| *Reproductive system and breast disorders* | Rare | Erectile dysfunction |
| *General disorders and administration site conditions* | Very rare | Hypothermia |
| | Not known | Drug withdrawal syndrome (see section 4.4) |
| *Investigations* | Not known | Blood glucose increased |

* Cases of central sleep apnoea syndrome have been observed with baclofen at high doses (≥ 100 mg) in patients who are alcohol dependent.

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 HPRA Pharmacovigilance Website: www.hpra.ie.

**4.9 Overdose**

Symptoms:
Prominent features are signs of central nervous depression: somnolence, depressed level of consciousness, coma and respiratory depression. Also liable to occur are: confusion, hallucinations, agitation, convulsion, abnormal electroencephalogram (burst suppression pattern and triphasic waves), tinnitus, accommodation disorder, impaired pupillary reflex; generalised muscular hypotonia, myoclonia, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension or hypertension, bradycardia or tachycardia, or cardiac arrhythmia; hypothermia; nausea, vomiting, diarrhoea, salivary hypersecretion; increased hepatic enzymes, SGOT and AP values, rhabdomyolysis. Patients with renal impairment can develop signs of overdose even on low doses of oral baclofen (see section 4.2 and section 4.4).

Deterioration in the condition may occur if various substances or drugs acting on the central nervous system (e.g. alcohol, diazepam, and tricyclic antidepressants) have been taken at the same time.

Treatment:
No specific antidote is known.

Supportive measures and symptomatic treatment should be given for complications such as hypotension, hypertension, convulsions, gastrointestinal disorders and respiratory or cardiovascular depression.

Since the drug is excreted chiefly via the kidneys, generous quantities of fluid should be given, possibly together with a diuretic. Haemodialysis (sometimes unscheduled) may be useful in severe poisoning associated with renal failure (see section 4.4).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antispastic with spinal site attack, ATC code: M03BX01.

Baclofen is an antispastic agent acting at the spinal level. A gamma-aminobutyric acid (GABA) derivative, baclofen is chemically unrelated to other antispastic agents.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating the GABAB receptors, this stimulation in turn inhibiting the release of the excitatory amino acids glutamate and aspartate. Neuromuscular transmission is unaffected by Baclofen.

The major benefits of Baclofen stem from its ability to reduce painful flexor spasms and spontaneous clonus thereby facilitating the mobility of the patient, increasing his independence and helping rehabilitation.

Baclofen also exerts an antinociceptive effect. General well being is often improved and sedation is less often a problem than with centrally acting drugs.

Baclofen stimulates gastric acid secretion.

### 5.2 Pharmacokinetic properties

*Absorption*: Baclofen is rapidly and completely absorbed from the gastro-intestinal tract. No significant difference between the liquid and tablet formulations is observed in respect of Tmax, Cmax and bioavailability. Following oral administration of single doses (10-30mg) peak plasma concentrations are recorded after 0.5 to 1.5 hours and areas under the serum concentration curves are proportional to the dose.

*Distribution*: The volume of distribution of baclofen is 0.7 l/kg. The protein binding rate is approximately 30% and is constant in the concentration range of 10 nanogram/mL to 300 microgram/mL. In cerebrospinal fluid active substance concentrations are approximately 8.5 times lower than in the plasma.

*Biotransformation*: Baclofen is metabolised to only a minor extent. Deamination yields the main metabolite, β-(p-chlorophenyl)-4-hydroxybutyric acid, which is pharmacologically inactive.

*Elimination/excretion*: The plasma elimination half-life of baclofen averages 3 to 4 hours.

Baclofen is eliminated largely in unchanged form. Within 72 hours, approximately 75% of the dose is excreted via the kidneys with about 5% of this amount as metabolites.

Special populations

*Elderly patients (aged 65 years or above)*
The pharmacokinetics of baclofen in elderly patients are virtually the same as in patients below 65 years of age. Following a single oral dose, elderly patients have slower elimination but a similar systemic exposure of baclofen compared to adults below 65 years of age. Extrapolation of these results to multi-dose treatment suggests no significant pharmacokinetic difference between patients below 65 years of age and elderly patients.

*Paediatric patients*
Following oral administration of 2.5 mg baclofen tablet in children (aged 2 to12 years), Cmax of 62.8±28.7 nanogram/mL, and Tmax in the range of 0.95-2 h have been reported. Mean plasma clearance (Cl) of 315.9 mL/h/kg; volume of distribution (Vd) of 2.58 L/kg; and half-life (T1⁄2) of 5.10 h have been reported.

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

*Renal impairment*
No controlled clinical pharmacokinetic study is available in patients with renal impairment after administration of baclofen. Baclofen is predominantly eliminated unchanged in urine. Sparse plasma concentration data collected only in female patients under chronic haemodialysis or compensated renal failure indicate significantly decreased clearance and increased half-life of baclofen in these patients. Dosage adjustment of baclofen based on its systemic levels should be considered in renal impairment patients, and prompt haemodialysis is an effective means of reversing excess baclofen in systemic circulation.

**5.3 Preclinical safety data**

Baclofen increases the incidence of omphaloceles (ventral hernias) in the foetuses of rats given approximately 13 times the maximum oral dose (on a mg/kg basis) recommended for human use. This was not seen in mice or rabbits.

An apparently dose related increase in the incidence of ovarian cysts, and a less marked increase in enlarged and/or haemorrhagic adrenals have been observed in female rats treated for 2 years. The clinical relevance of these findings is not known.

Experimental evidence to date suggests that baclofen does not possess either carcinogenic or mutagenic properties.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Methyl parahydroxybenzoate (E218)
Sorbitol, liquid (non-crystallising) (E420)
Carmellose Sodium (E466)
Raspberry flavour (contains propylene glycol (E1520))
Purified water

**6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

**6.3 Shelf life**

24 months
Discard 60 days after first opening.

**6.4 Special precautions for storage**

Do not store above 30°C. Do not refrigerate. Store in the original packaging in order to protect from light.

**6.5 Nature and contents of container**

Bottle: Ph. Eur. Type III amber glass bottles

Closure: Tamper evident, child resistant white plastic cap consists of polypropylene inner, polyethylene outer, expanded polyethylene (EPE) liner

Dosing Device: 1 ml oral syringe with 0.01 ml graduation and 10 ml oral syringe with 0.25 ml graduation along with a syringe adaptor.

Pack size: 300ml

**6.6 Special precautions for disposal**

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

**7 MARKETING AUTHORISATION HOLDER**

Syri Pharma Limited t/a Thame Laboratories
Floor 0
1 WML
1 Windmill Lane
Dublin 2
D02 F206
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA22697/005/001

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

Date of First Authorisation: 12th February 2016
Date of Last Renewal: 12th January 2021

**10 DATE OF REVISION OF THE TEXT**

October 2021