SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Baclofen 5 mg/5 mL Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral solution contains 5 mg Baclofen.

Excipient(s) with known effect: liquid sorbitol, methyl paraben, propyl paraben
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution
Clear, very slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Baclofen 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution 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

Baclofen 5mg/5mL Oral Solution is given orally in 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 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution 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 mg daily, preferably in divided doses. The following gradually increasing dosage regimen is suggested, but should be adjusted to suit individual patient requirements.

5 mg three times a day for three days
10 mg three times a day for three days
15 mg three times a day for three days
20 mg three times a day for three days

Satisfactory control of symptoms is usually obtained with doses of up to 60 mg 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 100 mg 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 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution. 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 5 mg/5 mL Oral Solution should be selected i.e. approx. 5 mg daily. Baclofen 5mg/5mL Oral Solution 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 5mg/5mL Oral Solution therapy. The liver does not play a significant role in the metabolism of baclofen after oral administration of Baclofen 5mg/5mL Oral Solution (see section 5.2). However, Baclofen 5mg/5mL Oral
Solution has the potential of elevating liver enzymes. Baclofen 5mg/5mL Oral
Solution 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 very cautious dosage schedule be adopted and that patients be kept under appropriate surveillance.

Method of administration
Baclofen 5mg/5mL Oral Solution should be taken during meals with a little liquid.

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 5 mg/5 mL Oral Solution. Patients suffering from these conditions should therefore be treated cautiously and kept under close surveillance.

Epilepsy
Baclofen 5 mg/5 mL Oral Solution may also exacerbate epileptic manifestations but can be employed provided appropriate supervision and adequate anticonvulsive therapy are maintained.

Others

Baclofen 5 mg/5 mL Oral Solution should be used with extreme care in patients already receiving antihypertensive therapy, (see section 4.5). Baclofen 5 mg/5 mL Oral Solution should be used with caution in patients suffering from cerebrovascular accidents or from respiratory, hepatic or renal 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 5 mg/5 mL Oral Solution should be used with caution in patients with renal insufficiency and should only be administered to patients with end-stage renal failure (CKD stage 5, GFR < 15mL/min) when benefit outweighs risk (see Section 4.2). Cases of baclofen toxicity have been reported in patients with acute renal failure (see Section 4.9).
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.
Particular caution is required when combining Baclofen 5 mg/5 mL Oral Solution to drugs or medicinal products that can significantly affect renal function. Renal function should be closely monitored and Baclofen 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution 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.

Excipients
Baclofen 5mg/5mL Oral Solution syrup contains methyl para hydroxybenzoate and propyl para hydroxybenzoate, which may cause allergic reactions (possibly delayed). Baclofen Oral Solution syrup contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Baclofen 5mg/5mL Oral Solution syrup also contains 0.65 to 1.08 mg of sodium per 1 mL of syrup.

Abrupt withdrawal:
Anxiety and confusional states, hallucinations, psychotic, manic or paranoid states, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and as rebound phenomenon temporary aggravation of spasticity have been reported with abrupt withdrawal of baclofen, especially after long term medication.
Neonatal convulsions have been reported after intrauterine exposure to oral Baclofen 5 mg/5 mL Oral Solution (see Section 4.6).

Treatment should always, (unless serious adverse effects occur), therefore be gradually discontinued by successively reducing the dosage over a period of about 1-2 weeks.

Paediatric patients
There is very limited clinical data on the use of Baclofen 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution 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 interaction

Levodopa/dopa decarboxylase (DDC) inhibitor (Carbidopa)
In patients with Parkinson's disease receiving treatment with Baclofen 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution and levodopa/carbidopa.

Drugs causing Central Nervous System (CNS) depression
Increased sedation may occur when Baclofen 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution may be potentiated, resulting in pronounced muscular hypotonia.

Lithium
Concomitant use of oral Baclofen 5mg/5mL Oral Solution and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should be exercised when Baclofen 5 mg/5 mL Oral Solution is used concomitantly with lithium.

Antihypertensives
Since concomitant treatment with Baclofen 5 mg/5 mL Oral Solution and antihypertensives 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

Pregnancy

During pregnancy, especially in the first 3 months, Baclofen 5 mg/5 mL Oral Solution 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 5 mg/5 mL Oral Solution 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.

Breast-feeding
In mothers taking Baclofen 5 mg/5 mL Oral Solution in therapeutic doses, the active substance passes into the breast milk, but in quantities so small that no undesirable effects in the infant are to be expected.

4.7 Effects on ability to drive and use machines

Baclofen 5mg/5mL Oral Solution may be associated with adverse effects such as dizziness, sedation, somnolence and visual disturbances (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 5 mg/5 mL Oral Solution be ingested with food or a milk beverage. In patients with a case 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.
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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) very rare (< 1/10,000) and Not known (cannot be estimated from the available data).

Table 1 Tabulated summary of adverse drug reactions

Nervous system disorders	
Very common:	Sedation, somnolence
Common:	Respiratory depression, confusional state, dizziness, hallucination, depression, fatigue, insomnia, euphoric mood, muscular weakness, ataxia, tremor, nightmares, myalgia, headache, nystagmus, dry mouth.
Rare:	Paraesthesia, dysarthria, dysgeusia
Unknown	Sleep apnoea sundrome*

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 (more than or equal to 100 mg) in patients who are alcohol dependent.

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).

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

the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:

Prominent features are signs of central nervous depression: somnolence, depressed level of consciousness, respiratory depression, respiratory depression and coma. Also liable to occur are: confusion, hallucination, agitation, accommodation disorder, impaired pupillary reflex; generalised muscular hypotonia, myoclonus, hyporeflexia or areflexia; convulsion, abnormal electroencephalogram (burst suppression pattern and triphasic waves); peripheral vasodilatation, hypotension or hypertension, bradycardia, tachycardia or cardiac arrhythmia; hypothermia; nausea, vomiting, diarrhoea, salivary hypersecretion; increased hepatic enzymes and rhabdomyolysis. Patients with renal impairment can develop signs of overdose even on low doses of oral Baclofen 5 mg/5 mL Oral Solution (see section 4.2 and section 4.4)

A deterioration in the condition may occur if various substances or drugs acting on the central nervous system (e.g. alcohol, diazepam, 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, 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:
M03B X01

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 $GABA_B$ 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 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 solution and tablet formulations is observed in respect of t_{max}, C_{max} 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 and 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. The serum protein binding rate is approximately 30%.

Baclofen is eliminated largely in unchanged form. Within 72 hours, about 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 2.5mg Baclofen tablet in children (aged 2 to12 years), C_{max} of 62.8±28.7 nanogram/mL, and T_{max} in the range of 0.95-2 h have been reported. Mean plasma clearance (Cl) of 315.9mL/h/kg; volume of distribution (Vd) of 2.58 L/kg; and half-life ($T_{1/2}$) of 5.10 h have been reported.

Hepatic impairment

No pharmacokinetic data are available in patients with hepatic impairment after administration of Baclofen 5 mg/5 mL Oral Solution. 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 5 mg/5 mL Oral Solution. Baclofen is predominantly eliminated unchanged in urine. Sparse plasma concentration data collected only in female patients under chronic hemodialysis 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 hemodialysis 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

Liquid Sorbitol (Non-Crystallising) (E420)
Methyl Paraben (E218)
Propyl Paraben (E216)
Flavour raspberry
Carmellose Sodium (E466)
Purified Water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

Unopened bottles: 2 years
Opened bottles: 60 days

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. See section 6.3 for details of shelf life once opened. Protect from light. Do not refrigerate.

6.5 Nature and contents of container

Clear, very slightly yellow solution with a raspberry flavour
Type III Amber Glass bottles of 300ml with child resistant polypropylene closures containing tamper evident ring.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Strides Arcolab International Limited
Unit 4, Metro Centre,
Tolpits Lane,
Watford, Hertfordshire

WD 189 SS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 28176/0162

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/05/2015

10 DATE OF REVISION OF THE TEXT

04/07/2018