

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Baclofen Tablets BP 10mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Baclofen 10 mg.

Excipient(s) with known effect: Lactose monohydrate: 40 mg per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

7mm flat bevelled edge tablet marked “BN” breakline “10” on one side and plain on the reverse.

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 for the relief of spasticity of voluntary muscle arising from e.g. cerebrovascular accidents, cerebral palsy, meningitis, traumatic head injury.

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 symptomatic treatment of muscle spasms occurring in spinal cord disease 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.

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.

4.2 Posology and method of administration

Adults

The following gradually increasing dosage regime is suggested but should be adjusted to suit individual patient requirements.

5 mg 3 times a day for 3 days
10 mg 3 times a day for 3 days
15 mg 3 times a day for 3 days
20 mg 3 times a day for 3 days

Satisfactory control of symptoms is usually obtained with doses 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 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 only at night to counteract painful flexor spasm. Similarly a single dose given approximately one hour prior to the performance of specific tasks such as washing, dressing, shaving, physiotherapy, will often improve mobility.

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

Elderly

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 the 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-<18 years)

Treatment should usually be started with a very low dose (corresponding to approximately 0.3mg/kg a day), in 2-4 divided doses (preferably in 4 divided doses). The dosage should be raised cautiously, at about 1 week intervals, until it becomes sufficient for the child's individual requirements. The usual daily dose for maintenance therapy ranges between 0.75 and 2mg/kg body weight. The total daily dosage 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 dose of 60mg/day may be given. Baclofen tablets are not suitable for the use in children below 33kg body weight.

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. 5 mg daily. Signs of overdose have been observed in patients with renal impairment treated with more than 5 mg oral baclofen per day.

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 the patients be kept under appropriate surveillance.

Method of administration
Baclofen is given orally.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Psychiatric and nervous system disorders

Psychotic disorders, manic or depressive disorders, schizophrenia or 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.

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 anti-hypertensive 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

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 treated with more than 5 mg oral baclofen per day. Patients with impaired renal function should be closely monitored for prompt diagnosis of early symptoms of toxicity.

Baclofen should be used with caution in patients with renal insufficiency and should be administered to patients with end-stage renal failure (CKD stage 5, GFR <15mL/min) only if the expected benefit outweighs the potential risk (see section 4.2).

Cases of baclofen toxicity have been reported in patients with acute renal failure (see section 4.9).

Particular caution is required when combining baclofen to drugs or medicinal products that can significantly affect renal function. Renal function should 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 (AST), 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.

Abrupt withdrawal

Anxiety and confusional state, delirium, hallucination, psychotic disorder delusions, mania or paranoia, 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 (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 one to two weeks.

Paediatric patients

There is very limited clinical data on the use of Baclofen in children under the age of one year. Use in the patient population should be based on the physician's consideration of individual benefit and risk 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).

Excipients

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 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 concurrent 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 anti-hypertensive 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 three 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 80mg daily throughout her pregnancy. The convulsions, which were refractory to standard anticonvulsant treatment, ceased within 30 minutes of giving baclofen to the infant.

Lactation

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 effects 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 attacks of 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 dose (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 ($\geq 1/10$); 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 (frequency cannot be determined from available data).

Table 1 Tabulated summary of adverse drug reactions

<p><i>Nervous system disorders</i> Very common: Somnolence, sedation Common: Respiratory depression, confusional state, dizziness, hallucinations, depression, fatigue, insomnia, euphoric mood, muscular weakness, headache, ataxia, tremor, nightmares, myalgia, nystagmus, dry mouth Rare: Paraesthesia, dysarthria, dysgeusia Unknown: Sleep apnoea syndrome*</p>
<p><i>Eye disorders</i> Common: Accommodation disorders, visual impairment</p>
<p><i>Cardiac disorders</i> Common: Cardiac output decreased Not known: Bradycardia</p>
<p><i>Vascular disorders</i> Common: Hypotension</p>
<p><i>Gastrointestinal disorders</i> Very common: Nausea, Common: Gastrointestinal disorder, retching, vomiting, constipation, diarrhoea Rare: Abdominal pain</p>

Hepatobiliary disorders

Rare: Hepatic function abnormal

Skin and subcutaneous tissue disorders

Common: Hyperhidrosis, rash

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

* Drug withdrawal syndrome including postnatal convulsions in neonates has also been reported after intra-uterine exposure to oral baclofen.

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 such as somnolence, impairment of consciousness, respiratory depression, acute respiratory failure and coma. Also liable to occur are confusion, hallucinations, agitation, abnormal electroencephalogram (burst suppression pattern and triphasic waves), psychosis, accommodation disorders, impaired pupillary reflex; generalised muscular hypotonia, myoclonia, hyporeflexia or areflexia, convulsions, peripheral vasodilation, hypotension, hypertension, bradycardia, tachycardia or cardiac arrhythmia, hypothermia, nausea, vomiting, diarrhoea, hypersalivation, elevated LDH, AST, ALP and blood creatine phosphokinase values and 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).

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 a gamma-aminobutyric acid (GABA) derivative, chemically unrelated to other antispastic agents.

Baclofen acts at the spinal level depressing monosynaptic and polysynaptic reflex transmission, probably by stimulating the GABA_B receptors. This stimulation in turn inhibits 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 their 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 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. 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 \pm 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.

Paediatric patients

Following oral administration of 2.5mg baclofen tablet in children (aged 2 to 12 years), C_{max} of 62.8 \pm 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. 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 predominately 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 two 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

Microcrystalline cellulose
Lactose Monohydrate
Calcium Hydrogen Phosphate Anhydrous
Colloidal Anhydrous Silica
Magnesium Stearate
Sodium Starch Glycollate (Type A)

6.2 Incompatibilities

None known

6.3 Shelf life

Blister packs: 48 months
Polypropylene containers: 36 months

6.4 Special precautions for storage

Do not store above 25°C. Keep the container tightly closed. Store in the original container

6.5 Nature and contents of container

Polypropylene containers with polyethylene caps (with optional polyethylene ullage filler)

Pack sizes: 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250, 500

Blister packs: unplastised 285µm PVdC and 30µm aluminium foil

Pack sizes: 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 180

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

No specific instructions for use/handling.

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS
Trading as: Co-pharma

8. MARKETING AUTHORISATION NUMBER(S)

PL 13606/0066

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 June 1998

10. DATE OF REVISION OF THE TEXT

11/10/2018