1 Name of the Medicinal Product

BACLOFEN TABLETS BP 10mg

2 Qualitative and Quantitative Composition

Each tablet contains 10mg Baclofen PhEur.

Excipient with known effect: Lactose PhEur 89.50mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to off-white uncoated tablets.

White to off-white, circular, biconvex uncoated tablets impressed “C” on one face, and the identifying letters “B” “L” on either side of a central division line on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

2) Adults and children in the relief of spasticity of voluntary muscle arising from conditions such as cerebral palsy, cerebrovascular accidents, traumatic head injury and meningitis. Treatment with Baclofen should not be initiated until the spastic state has become stabilised and it should be administered selectively; it is most likely to be of benefit to patients whose spasticity constitutes a handicap to activities 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

Before commencing treatment the overall extent of clinical improvement that the patient may be expected to achieve must be realistically assessed. Careful titration of dosage is essential (particularly in the elderly) until the patient is stabilised. If the initial dosage is too high or if the dosage is increased too rapidly, side-effects may occur. This is particularly relevant if the patients 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 mg daily, preferably in divided doses. The following gradually increasing dosage regimen is suggested, but should be adjusted to suit individual patient requirements.5mg three times daily for three days.
10mg three times daily for three days.
15mg three times daily for three days.
20mg three times daily for three days.

Satisfactory control of symptoms is usually obtained with doses up to 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 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 raised cautiously, 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 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

Baclofen tablets are not suitable for use in children below 33 kg 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. approximately 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 very cautious dosage schedule be adopted and that patients be kept under appropriate surveillance.

Method of Administration
For oral administration.

Baclofen should be taken during meals with a little liquid.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in 6.1.
- Peptic ulceration.

4.4 Special warnings and precautions for use

Psychiatric and nervous system disorders
Porphyria, history of alcoholism, hypertension, 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.

Encephalopathy
Cases of encephalopathy have been reported in patients receiving baclofen at therapeutic doses, which were reversible after treatment discontinuation. Symptoms included somnolence, depressed level of consciousness, confusion, myoclonus and coma.
If signs of encephalopathy are observed, baclofen should be discontinued.

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, 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 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.

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

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.

Baclofen stimulates gastric acid secretion and should be used with caution in patients with a history of peptic ulceration.

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.

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 states, delirium, hallucinations, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and temporary aggravation of spasticity and hypertonia have been reported with abrupt withdrawal of Baclofen, especially after long term medication.

Drug withdrawal reactions including postnatal convulsions in neonates 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 1-2 weeks.

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).

Excipients
Patients with rare hereditary problems of galactose intolerance, total 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 concommitant 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

Pregnancy
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.

Foetal/neonatal adverse reactions
Drug withdrawal reactions including postnatal convulsions in neonates have been reported after intra-uterine exposure to oral Baclofen (see section 4.4).

Breast-feeding
In mothers taking Baclofen in therapeutic doses, the active substance passes into 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 Tabulated summary of adverse drug reactions

Immune system disorders	
Not known:	Hypersensitivity
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* Encephalopathy
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, alopecia
Renal and urinary disorders	
Common:	Pollakiuria, enuresis, dysuria
Rare:	Urinary retention
Reproductive system and breast disorders	
Rare:	Erectile dysfunction
Not known:	Sexual dysfunction
General disorders and administration site conditions	
Very rare	Hypothermia
Not known	Drug withdrawal syndrome** (see section 4.4), swelling face and peripheral oedema
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.

**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; website: 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 or encephalopathy: . somnolence, impairment of consciousness, respiratory depression, coma. Also liable to occur are confusion, hallucinations, agitation, convulsions, abnormal electroencephalogram (burst suppression pattern and triphasic waves, generalised slowing on EEG), accommodation disorders, impaired pupillary reflex; generalised muscular hypotonia, myoclonia, hyporeflexia or areflexia; convulsions; peripheral vasodilation, hypotension or hypertension, bradycardia or tachycardia, or cardiac arrhythmia; hypothermia; nausea, vomiting, diarrhoea, salivary hypersecretion; increased hepatic enzymes SGOT and AP values, rhabdomyolysis; tinnitus. 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 CNS *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, 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: Muscle relaxant, other centrally acting agent.
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 simulating the $GABA_B$-receptors, this simulation 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 wellbeing 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 gastrointestinal tract.
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
The plasma elimination half-life of baclofen is about 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 ($T_{1/2}$) 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 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. A dose related increase in the incidence of ovarian cysts, and less marked increase in enlarged and/or haemorrhagic adrenals have been observed in female rats treated for 2 years. No teratogenic effects have been noted in mice or rabbits. 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

Also contains: lactose, pregelatinised maize starch, maize starch, magnesium stearate, water.

6.2. Incompatibilities

None known.

6.3. Shelf -life

Shelf-life
Three years from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.

Shelf-life after first opening
Not applicable.

6.4. Special precautions for storage

Store below 25°C.
Protect from light.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene tablet containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass bottles with screw caps and polyfoam wad or cotton wool. An alternative closure for polyethylene containers is a polypropylene, twist on, push down and twist off child-resistant, tamper-evident lid.

The product may also be supplied in blister packs in cartons:
a) Carton: Printed carton manufactured from white folding box board.
b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil.

Pack sizes: 28s, 30s, 50s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s, 250s, 500s, 1000s.

Product may also be supplied in bulk packs for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Maximum size of bulk packs: 50,000.

6.6. Instruction for use and handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8. MARKETING AUTHORISATION NUMBER(S)

PL 00142/0344

9 Date of First Authorisation/Renewal of Authorisation

Date of first authorisation: 24th June 1993
Date of latest renewal: 27th January 2005

10 DATE OF REVISION OF THE TEXT

25/11/2024