NEW ZEALAND DATA SHEET

PACIFEN
Baclofen Tablets 10 mg & 25 mg

Presentation

PACIFEN 10 mg tablets are white, round, flat bevelled edged marked ‘BN’ | ‘10’ on one side and ‘G’ on the other. Each tablet contains 10 mg of baclofen and has a diameter of 7 mm.

PACIFEN 25 mg tablets are white, round, flat bevelled edged marked ‘BN’ | ‘25’ on one side and ‘G’ on the other. Each tablet contains 25 mg of baclofen and has a diameter of 8 mm.

Uses

Antispastic agent. Baclofen is a derivative of gamma-aminobutyric acid (GABA) and is chemically unrelated to other antispastic agents.

Actions

Baclofen is an effective antispastic agent with a spinal site of action. Its mechanism of action and pharmacological properties are different from those of other antispastic agents.

Baclofen also has central sites of action given the adverse event profile and general CNS depressant properties.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by various actions, including stimulation of GABA\(_{\beta}\)-receptors. This stimulation in turn inhibits the release of excitatory amino acids (glutamate and aspartate). Neuromuscular transmission is not affected by baclofen.

Baclofen exerts an antinociceptive effect. The clinical significance of this awaits clarification. In neurological diseases associated with spasm of the skeletal muscles, the clinical effects of baclofen take the form of a beneficial action on reflex muscle contractions and of marked relief from painful spasm, automatism, and clonus. Baclofen, where indicated, improves the patient’s mobility, making for greater independence, and facilitating passive and active physiotherapy. Baclofen stimulates gastric acid secretion.

Pharmacokinetics

Absorption

Baclofen is rapidly and completely absorbed from the gastrointestinal tract. Maximum concentrations of unchanged drug are achieved in plasma in 2 to 4 hours after an oral dose. The bioavailability of oral baclofen is 70-80%.

Following oral administration of a single dose of 40 mg baclofen, a peak serum concentration between 500 to 600 nanogram/mL was reached. The serum concentration remains above 200 nanogram/mL for 8 hours. The onset of action is highly variable and may range from hours to weeks.

Distribution

The distribution volume of baclofen amounts to 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.
cerebrospinal fluid, the active substance attains concentrations approximately 8.5 times lower than in the plasma.

**Metabolism**

About 15% of the baclofen dose is metabolised in the liver. Deamination yields the main metabolite, \(\beta\)-(chlorophenyl)-\(\gamma\)-hydroxybutyric acid, which is pharmacologically inactive.

**Elimination**

Approximately 70% of baclofen is eliminated in the urine in the unchanged form. The plasma elimination half-life of baclofen averages 3 to 4 hours. Within 72 hours, approximately 75% of the dose is excreted via the kidneys, approximately 5% of this quantity being in the form of metabolites. The remainder of the dose, including 5% as metabolites, is excreted in the faeces.

**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 to 12 years), \(C_{\text{max}}\) of 62.8±28.7 nanogram/mL, and \(T_{\text{max}}\) 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 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.

**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.
Indications

Spasticity of the skeletal muscles in multiple sclerosis. Spastic conditions occurring in spinal-cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin: e.g. spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord; muscle spasm 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.

Dosage and Administration

Treatment should always be initiated with small, gradually increasing doses of PACIFEN. The optimum daily dosage should be individually adapted to the patient’s requirements in such a way that clonus, flexor and extensor spasms, and spasticity are reduced, but that adverse effects are as far as possible avoided.

In order to prevent excessive weakness and falling, PACIFEN should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion or whenever spasticity is used to maintain function. It may be important to maintain some degree of muscle tone and allow occasional spasms to help support circulatory function. PACIFEN should be taken during meals with a little liquid.

The daily dosage should be given in divided doses, preferably 3 in adults and 4 in children.

Adults

Treatment should as a rule be started with a dosage of 5 mg, 3 times daily, which, for the purpose of cautious dose titration, should subsequently be increased at 3-day intervals by 5 mg, 3 times daily until the requisite daily dosage has been attained. In certain patients reacting sensitively to medicines, it may be advisable to begin with a lower daily dosage (5 mg or 10 mg) and to raise this dosage more gradually. The optimum dosage generally ranges from 30 mg to 80 mg daily. Daily doses of 100 to 120 mg may be given to carefully supervised patients in hospital. Children Treatment should usually be started with a very low dose, e.g. 0.3 mg/kg a day, in divided doses. The dosage should be raised cautiously, at about 1 to 2 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. In children over 10 years of age, however, a maximum daily dosage of 2.5 mg/kg body weight may be given.

If no benefit is apparent within 6 to 8 weeks of achieving the maximum dosage, a decision whether to continue with PACIFEN should be taken.

Impaired Renal Function

In patients with impaired renal function baclofen should be given with caution and in lower doses. In patients undergoing chronic haemodialysis, baclofen concentrations in plasma are elevated and therefore a particularly low dosage of PACIFEN should be selected, i.e. approx. 5 mg daily.

Elderly

Since unwanted effects are more likely to occur in elderly patients or in patients with spastic states of cerebral origin, it is recommended that a very cautious dosage schedule be adopted in such cases and that the patient be kept under appropriate surveillance.

Contraindications

- Known hypersensitivity to baclofen or any of the components of the formulation.
- Peptic ulceration.
**Warnings and Precautions**

**Monitoring Advice**

Since in rare instances elevated AST, alkaline phosphatase or glucose levels in the serum have been recorded, appropriate laboratory tests should be performed periodically in patients with liver diseases or diabetes mellitus, in order to ensure that no drug-induced changes in these underlying diseases have occurred.

Careful monitoring of respiratory and cardiovascular function is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

**Abrupt Discontinuation**

Anxiety and confusional states, hallucinations, psychotic, manic, or paranoid states, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia and, as a rebound phenomenon, temporary aggravation of spasticity, have been reported upon the abrupt withdrawal of baclofen, especially after long-term medication.

Postnatal convulsions have been reported after intrauterine exposure to oral baclofen (see ‘Use in Pregnancy’ section).

Except in overdose-related emergencies or where serious adverse effects have occurred, treatment should therefore always be gradually withdrawn by successive dosage reduction over a period of approximately 1 to 2 weeks.

If withdrawal symptoms occur, restarting baclofen therapy and withdrawing over a longer period may help to resolve withdrawal problems.

**Psychiatric and Nervous System Disorders**

Patients suffering not only from spasticity but also from psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson’s disease should be treated cautiously with baclofen and kept under careful surveillance, because exacerbations of these conditions may occur.

**Epilepsy or Other Potential Convulsive Conditions**

Caution is needed in patients with epilepsy or other convulsive conditions, cortical or subcortical brain damage or significant EEG abnormalities, since ingestion of baclofen may cause deterioration of seizure control and EEG changes, and may precipitate convulsions. In patients with epilepsy and muscle spasticity, baclofen can be used under appropriate supervision, provided adequate anticonvulsive therapy is continued.

Lowering of the convulsion threshold may occur and seizures have been reported occasionally after cessation of baclofen or with overdosage.

**Other Concomitant Conditions**

Baclofen should be used with caution in patients with:

- cerebrovascular diseases/accidents or respiratory or hepatic insufficiency
- porphyria
- a history of alcoholism
- diabetes mellitus (baclofen may increase blood glucose concentrations)
- hypertension (see 'Interactions' section).
Since unwanted effects are more likely to occur, a cautious dosage schedule should be adopted in elderly and patients with spasticity. Baclofen is not recommended in Parkinson’s disease or spasticity arising from strokes, cerebral palsy or rheumatoid disorders.

**Changes in Muscle Tone**

Baclofen should be used with caution in patients who use spasticity to maintain an upright posture and balance in moving. If an undesirable degree of muscular hypotonia occurs, making it more difficult for patients to walk or fend for themselves, this can usually be relieved by adjusting the dosage (i.e. by reducing the doses given during the day and possibly increasing the evening dose).

During treatment with baclofen, neurogenic disturbances affecting emptying of the bladder may improve, whereas in patients with pre-existing sphincter hypertonia, acute retention of urine may occur. The drug should, therefore, be used with caution in such cases.

**Renal Impairment**

Since baclofen is largely eliminated by the kidneys, a dosage reduction is advised to avoid drug accumulation. Signs of overdose have been observed in patients with renal impairment taking oral baclofen at doses of more than 5 mg per day. 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 <15 mL/min) 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 ‘Dosage and Administration – Impaired Renal Function’ and ‘Overdose’ section).

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.

**Hepatic Impairment**

Baclofen has the potential of elevating liver enzymes and should be prescribed with caution in patients with hepatic impairment.

Because baclofen is partially metabolised in the liver, patients with impaired hepatic function should be periodically monitored with laboratory tests (see ‘Monitoring Advice’ section).

**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.

**Posture and Balance**

Baclofen should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion (see ‘Dosage and Administration’ section).

**Use in Pregnancy (Category B3)**

*Australian categorisation definition of Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.*

In two teratogenic studies in pregnant rats, baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in foetuses, at a dose of 20 mg/kg/day, which is maternotoxic. The
relevance of this finding to humans is unknown. At the same dose there was also an increased incidence of incomplete sternebral ossification in the foetuses.

In mice, no teratogenic effects were observed at a dose of 81.5 mg/kg/day given via the diet or up to 40 mg/kg/day given by gavage. At 40 mg/kg/day by gavage, a delay in foetal growth was associated with maternal anorexia. The lack of maternotoxicity seen in the dietary study suggests that the dose used was inadequate.

In pregnant rabbits, oral doses up to 10 mg/kg/day were manifested as a sedative effect. Skeletal examination of foetuses revealed a marked increase in the absence of ossification of the phalangeal nuclei of fore limbs and hind limbs.

There are no adequate and well-controlled studies in pregnant women. Baclofen crosses the placental barrier and should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

One case of suspected withdrawal reaction (generalized convulsions) has been reported in a week-old infant whose mother had taken baclofen during pregnancy. The convulsions, which were refractory to standard anticonvulsant treatment, ceased within 30 minutes of giving baclofen to infant.

**Use in Lactation**

Studies in lactating women are limited to one (1) patient. In this particular case, available evidence suggests that baclofen is found in quantities so small that undesirable effects in the infant would have been unlikely.

**Paediatric Use**

Baclofen should be given with extreme caution to children under 16 years, as only limited data are available. Baclofen tablets are not suitable for use in children below 33 kg body weight.

**Use in the Elderly**

Small doses should 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. (See 'Dosage and Administration' section).

**Effects on Ability to Drive or Operate Machinery**

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

The patient’s ability to react may be adversely affected by sedation and decreased alertness caused by baclofen; patients should therefore exercise due caution when driving a vehicle or operating machinery.

**Carcinogenicity**

A two year carcinogenicity study in rats found no evidence that baclofen had carcinogenic potential at oral doses up to 100 mg/kg/day. An apparently dose related increase in the incidence of ovarian cysts and of enlarged and/or haemorrhagic adrenals at the highest two doses (50 and 100 mg/kg/day) was observed in female rats. The clinical relevance of these findings is not known.

Ovarian cysts have been found by palpation in about 5% of the multiple sclerosis patients who were treated with oral baclofen for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are known to occur spontaneously in a proportion of the normal female population.
**Genotoxicity**

Baclofen did not induce mutations in bacterial or mammalian cells *in vitro*, lacked DNA damaging activity in the sister chromatid exchange assay, and had no clastogenic activity in the nuclear anomaly test.

**Adverse Effects**

Unwanted effects mainly occur at the start of treatment (e.g. sedation, somnolence, nausea), if the dosage is increased too quickly, if large doses are used, or if the patient is elderly. They are often transitory and can be attenuated or eliminated by reducing the dosage. They may 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, cortical or organic brain disorders, or with cerebrovascular disorders (such as stroke), as well as elderly patients, adverse reactions may be more serious.

It is often difficult to distinguish whether some of these are drug effects or manifestations of the diseases under treatment. Psychiatric manifestations can occur in acute or chronic toxicity due to baclofen.

Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients (see 'Warnings and Precautions' section).

Certain patients have shown increased muscle 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 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), not known (cannot be estimated from the available data).

**Cardiac disorders**

Common: cardiac output decreased.

Rare: arrhythmias, palpitations, chest pain.

Not known: bradycardia.

**Vascular disorders**

Common: hypotension.

Rare: dyspnoea, ankle oedema.

**Gastrointestinal disorders**

Very common: nausea (particularly at the start of treatment).

Common: gastrointestinal disorder, constipation, diarrhoea, retching, vomiting.

Rare: colicky abdominal pain, anorexia.
**Hepatobiliary disorders**
Rare: hepatic function abnormal.

**Nervous system disorders**
Very common: sedation, somnolence.

Common: respiratory depression, fatigue, confusional state, dizziness, personality changes, vertigo, headache, insomnia, euphoric mood, depression, muscular weakness, ataxia, tremor, hallucination, nightmare, myalgia, nystagmus, dry mouth, tinnitus.

Rare: paresthesiae, dysarthria, dysgeusia, syncope, dyskinesia, coma, taste disturbances.

Very rare: hypothermia.

**Eye disorders**
Common: accommodation disorders, visual impairment.

**Skin and subcutaneous tissue disorders**
Common: hyperhidrosis, rash, pruritus.

Not known: urticaria.

**Renal and urinary disorders**
Common: pollakiuria, dysuria, enuresis.

Rare: urinary retention, nocturia, haematuria.

**Reproductive system and breast disorders**
Rare: erectile dysfunction, inability to ejaculate.

**General disorders and administration site conditions**
Very rare: hypothermia.

Not known: drug withdrawal syndrome (see ‘Warnings and Precautions’ section).

Not known: blood glucose increase.

**Miscellaneous**
Rare: nasal congestion, weight gain.

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**Interactions**

**Drugs Causing Central Nervous System (CNS) Depression**

Increased sedation may occur when baclofen is taken concomitantly with other agents causing CNS depression including other muscle relaxants (such as tizanidine), synthetic opiates or with alcohol (see 'Warnings and Precautions' section). 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
Concurrent use of baclofen and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should be exercised when baclofen is used concomitantly with lithium.

Others
The concurrent use of baclofen with monoamine oxidase inhibitors (MAOIs) may result in increased CNS-depressant and hypotensive effects. Caution is recommended and dosage of one or both agents may require reduction.

Since baclofen may increase blood glucose concentrations, dosage adjustments of insulin and/or oral hypoglycaemic agents may be necessary during and after concurrent therapy.

Studies in rats indicate that the agonistic effects of baclofen on gastric acid secretion are potentiated by diazepam.

Antihypertensives
Since concomitant treatment with baclofen and antihypertensive agents is likely to increase the risk of hypotension, the dosage of antihypertensive medication should be adjusted accordingly.

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, headaches, 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.

Agents Reducing Renal Function
Drugs or medical products that can significantly impact renal function may reduce baclofen excretion leading to toxic effects (see ‘Warnings and Precautions – Renal Impairment’ section).

Overdosage

Signs and Symptoms
Prominent features are signs of central nervous depression: somnolence, impairment of consciousness, respiratory depression due to absent respiratory movement, coma.

Also liable to occur are: confusion, hallucinations, agitation, EEG changes (burst suppression pattern and triphasic waves), accommodation disorders, impaired pupillary reflex; generalised muscular hypotonia, myoclonus, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension or hypertension, bradycardia or tachycardia or cardiac arrhythmias; hypothermia; nausea, vomiting, diarrhoea, hypersalivation; increased hepatic enzymes. Patients with renal impairment can develop signs of overdose even on low doses of oral baclofen (see ‘Dosage and Administration’ and ‘Warnings and Precautions’ section).

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.
Adult patients have ingested up to 1,125 mg of baclofen and survived. Ingestion of 1,250 to 2,500 mg by one patient was fatal. Serious poisoning has occurred with doses of 150 and 300 mg in adults.

**Treatment**

No specific antidote is known.

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

Symptomatic treatment should include the following:

- elimination of the drug from the gastrointestinal tract e.g. administration of activated charcoal; if necessary, saline laxatives
- since the drug is excreted chiefly via the kidneys, generous quantities of fluid should be given, possibly together with a diuretic
- measures in support of cardiovascular functions
- in the case of respiratory muscle weakness, administration of artificial respiration
- in the event of convulsions, diazepam should be administered cautiously intravenously, paying attention to increased muscle relaxation, and possible respiratory insufficiency, if the patient is not already being artificially ventilated
- haemodialysis (sometimes unscheduled) may be useful in severe poisoning associated with renal failure (see ‘Warnings and Precautions’ section).

Contact the Poisons Information Centre on 0800 764 766 or 0800 POISON for advice on management of overdosage.

**Pharmaceutical Precautions**

Store below 25°C.

**Medicine Classification**

Prescription Medicine.

**Package Quantities**

PACIFEN 10 mg tablets: Bottles of 50’s, 100’s and 250’s.

PACIFEN 25 mg tablets: Bottles of 100’s.

Not all strengths or pack sizes may be marketed.

**Further Information**

Active ingredient: Baclofen

Chemical name: (3RS)-4-amino-3-(4-chlorophenyl)butanoic acid

Structural formula:
Molecular formula: C10H12ClNO2  Molecular weight: 213.7

CAS Registry No.: 1134-47-0

Baclofen is a white or almost white powder, slightly soluble in water, very slightly soluble in ethanol (96%), practically insoluble in acetone and in ether. It dissolves in dilute mineral acids and in dilute alkali hydroxides.

**Excipients**

Each PACIFEN 10 mg tablet contains baclofen 10 mg as the active ingredient.
Each PACIFEN 25 mg tablet contains baclofen 25 mg as the active ingredient.

The tablets also contain the following inactive ingredients: lactose, cellulose – microcrystalline, calcium hydrogen phosphate anhydrous, sodium starch glycollate, silica – colloidal anhydrous, magnesium stearate.

PACIFEN tablets are gluten free.

**Name and Address**

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**Date of Preparation**

09 May 2016