

# Data Sheet

## PACIFEN

**10mg & 25mg tablets**

**Baclofen**

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### Presentation

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

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

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### Uses

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Antispastic agent. Baclofen is a derivative of gamma-aminobutyric acid (GABA).

#### **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<sub>β</sub>-receptors. This stimulation in turn inhibits the release of excitatory amino acids (glutamate and aspartate) in guinea pig preparations. 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 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. In cerebrospinal fluid, the active substance attains concentrations approximately 8.5 times lower than in the plasma.

Baclofen is bound to plasma proteins to the extent of approximately 30%.

##### **Metabolism**

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

## **Excretion**

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.

## **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.

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## **Dosage and Administration**

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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 5mg, 3 times daily, which, for the purpose of cautious dose titration, should subsequently be increased at 3-day intervals by 5mg, 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 (5mg or 10mg) and to raise this dosage more gradually. The optimum dosage generally ranges from 30mg to 80mg daily. Daily doses of 100 to 120mg may be given to carefully supervised patients in hospital.

### **Children**

Treatment should usually be started with a very low dose, e.g. 0.3mg/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 2mg/kg body weight. In children over 10 years of age, however, a maximum daily dosage of 2.5mg/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. 5mg 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.

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## Contraindications

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Known hypersensitivity to baclofen or any of the components of the formulation.

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## Warnings and Precautions

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### ***Mental disorders***

Patients suffering not only from spasticity but also from psychotic disorders, schizophrenia, depressive or manic disorders or confusional states 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:

- peptic ulcers or with a history of peptic ulcers
- cerebrovascular diseases or respiratory, hepatic or renal failure (due to increased risk of central nervous system, respiratory and cardiovascular depression)
- porphyria
- a history of alcoholism
- diabetes mellitus (baclofen may increase blood glucose concentrations)
- hypertension (see '**Interactions**' section).

### ***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 (ie. 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.

### ***Impaired Renal Function***

Since baclofen is largely eliminated by the kidneys, a dosage reduction is advised to avoid drug accumulation (see '**Dosage and Administration**' section).

### ***Impaired Hepatic Function***

Because baclofen is partially metabolised in the liver, patients with impaired hepatic function should be periodically monitored with laboratory tests.

### ***Use in the Elderly***

See '**Dosage and Administration**' section.

### ***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.

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.

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

Baclofen may be associated with dizziness, sedation, somnolence and visual disturbance (see Adverse Effects) 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.

### ***Mutagenicity, Carcinogenicity and Reproduction Toxicity***

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.

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.

### ***Use in Pregnancy (Category B3)***

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 20mg/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 studies in pregnant women.

### ***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.

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## **Adverse Effects**

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Unwanted effects mainly occur at the start of treatment, 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.

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 spasticity as a paradoxical reaction to the medication.

Frequency estimate:

Classification	Frequency (%)
Very common	≥ 10%
Common	≥ 1% to < 10%
Uncommon	≥ 0.1% to <1%
Rare	≥ 0.01% to < 0.1%
Very rare	< 0.01%

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### ***Cardiac disorders***

Common: cardiac output decreased.

Rare: arrhythmias, palpitations, chest pain.

#### ***Vascular disorders***

Common: hypotension.

Rare: dyspnoea, ankle oedema.

#### ***Gastrointestinal disorders***

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

Common: gastrointestinal disturbance, 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, lightheadedness, lassitude, exhaustion, confusional state, dizziness, personality changes, vertigo, headache, insomnia, euphoric mood, depression, muscular weakness, ataxia, tremor, hallucinations, nightmares, myalgia, nystagmus, dry mouth, tinnitus.

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

Very rare: hypothermia.

#### ***Eye disorders***

Common: accommodation disorders, visual disturbances.

#### ***Skin and subcutaneous tissue disorders***

Common: hyperhidrosis, rash, pruritus.

#### ***Renal and urinary disorders***

Common: pollakiuria, dysuria, enuresis.

Rare: urinary retention, nocturia, haematuria.

#### ***Reproductive system and breast disorders***

Rare: erectile dysfunction, inability to ejaculate.

#### ***Miscellaneous***

Rare: nasal congestion, weight gain.

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## **Interactions**

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Where baclofen is taken concomitantly with other agents acting on the central nervous system, or with alcohol, increased sedation may occur (see also under '**Warnings and Precautions**' section). The risk of respiratory depression is also increased.

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

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.

Aggravation of hyperkinetic symptoms may possibly occur in patients taking lithium.

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

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.

In patients with Parkinson's disease receiving treatment with levodopa plus carbidopa, who additionally required use of baclofen, there have been reports of mental confusion, hallucinations, headaches, nausea and agitation.

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

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## Overdosage

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### ***Signs and Symptoms***

Prominent features are signs of central nervous depression: drowsiness impairment of consciousness, coma, respiratory depression due to absent respiratory movement, coma.

Also liable to occur are: confusion, hallucinations, agitation, accommodation disorders, absent pupillary reflex; generalised muscular hypotonia, myoclonia, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension or hypertension, bradycardia or tachycardia; hypothermia; nausea, vomiting, diarrhoea, hypersalivation; elevated lactate dehydrogenase (LDH), aspartate transaminase (AST) and alkaline phosphatase (ALP) values.

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.

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## Pharmaceutical Precautions

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Store below 25°C.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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

PACIFEN 25mg tablets: Bottles of 100's.

Not all strengths or pack sizes may be marketed.

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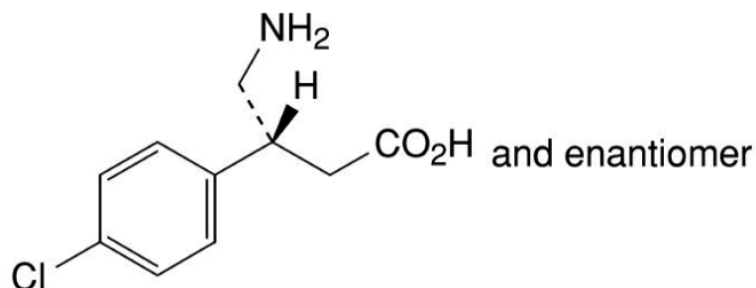
## Further Information

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Active ingredient: Baclofen

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

Structural formula:



Molecular formula: C<sub>10</sub>H<sub>12</sub>ClNO<sub>2</sub>

Molecular weight: 213.7

CAS Registry No.: 1134-47-0

## Excipients

Each Pacifen 10mg tablet contains baclofen 10 mg as the active ingredient.

Each Pacifen 25mg 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.

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## Name and Address

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## **Date of Preparation**

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7 September 2009