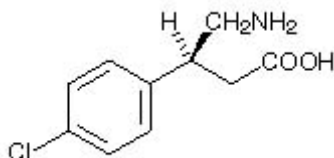


GenRx BACLOFEN TABLETS**NAME OF THE MEDICINE**

Baclofen

Chemical Name: (RS)-4 amino-3 (4-chlorophenyl)butyric acid.

Structural Formula:

Molecular Formula: $C_{10}H_{12}ClNO_2$

Molecular Weight: 213.7

CAS Registry Number: 1134-47-0

DESCRIPTION

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

Each tablet contains the following inactive ingredients: lactose, maize starch, microcrystalline cellulose and magnesium stearate.

PHARMACOLOGY**Pharmacokinetics**Absorption

Absorption from the gastrointestinal tract is rapid and complete. After an oral dose, peak plasma levels of unchanged drug are achieved in 1 to 2 hours. The bioavailability of oral baclofen is 70 to 80%.

Following oral administration of a single dose of 40mg baclofen, peak serum concentrations of 500 to 600 nanogram/mL are 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 is about 0.7 L/kg. In cerebrospinal fluid, the active substance attains concentrations approximately 8.5 times lower than in the plasma.

Baclofen is about 30% bound to plasma proteins.

Metabolism

About 15% of a dose of baclofen is metabolised in the liver. The main metabolite is β -chlorophenyl gamma hydroxybutyric acid, which is pharmacologically inactive.

Excretion

Baclofen is eliminated largely in unchanged form. The plasma elimination half-life of baclofen has been reported at between 2 and 6.8 hours. Approximately 75% of a single oral dose is excreted via the kidneys within 72 hours, with approximately 5% of this being excreted in the form of metabolites.

The remainder of the dose, including 5% as metabolites, is excreted in the faeces.

Pharmacodynamics

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

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 and general CNS depressant properties.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by various actions, including stimulation of GABA_B 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.

INDICATIONS

Suppression of voluntary muscle spasm in:

- Multiple sclerosis;
- Spinal lesions of traumatic, infectious, degenerative, neoplastic and unknown origin, causing skeletal hypertonus and spastic and dyssynergic bladder dysfunction.

Baclofen is not recommended in Parkinson's disease or spasticity arising from strokes, cerebral palsy or rheumatoid disorders.

CONTRAINDICATIONS

Known hypersensitivity to baclofen or the inactive ingredients.

PRECAUTIONS

Patients with Psychiatric Disorders

Baclofen should be used with caution in patients who suffer from spasticity together with psychotic disorders, schizophrenia, depressive or manic disorders or confusional states. These patients should be kept under careful surveillance, because treatment with baclofen may exacerbate these other conditions.

Patients with Potential Convulsive Conditions, including Epilepsy

Baclofen should be used with caution in patients with epilepsy or other convulsive conditions, cortical or subcortical brain damage or significant E.E.G abnormalities. In these patients baclofen may cause deterioration of seizure control and E.E.G changes and may precipitate convulsions. Baclofen can be used under appropriate supervision in patients with epilepsy provided adequate anticonvulsant therapy is continued.

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

Patients with Other Concomitant Conditions

Baclofen should be used with caution in patients with the following conditions:

- Peptic ulcer or with a history of peptic ulcers;
- Cerebrovascular disease 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 with Other Medicines**).

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 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.

Abrupt Withdrawal

Following abrupt withdrawal of baclofen, especially after long-term medication, anxiety, confusional states, delirium, hallucinations, psychotic, manic or paranoid states, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia and, as a rebound phenomenon, temporary aggravation of spasticity, have been reported. Therefore, except in overdose related emergencies, or where serious adverse effects have occurred, treatment should 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.

Postnatal convulsions have been reported after intrauterine exposure to oral Baclofen (See "Use in Pregnancy").

Switching from oral to intrathecal baclofen and vice versa:

An attempt should be made to discontinue concomitant antispastic medication to avoid possible overdose or adverse drug interactions. This should preferably be done before switching from oral to intrathecal baclofen or vice versa and requires careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispastics during chronic therapy with baclofen should be avoided.

Impaired Hepatic Function

Baclofen is partially metabolised in the liver. Patients with impaired liver function should be periodically monitored with laboratory tests (**see DOSAGE AND ADMINISTRATION - Monitoring Advice**).

Impaired Renal Function

Since baclofen is largely eliminated by the kidneys, a dosage reduction is advised to avoid drug accumulation. Baclofen should be used with caution in patients with renal insufficiency and should only be administered to patients with end stage renal failure when benefit outweighs risk. (**see DOSAGE AND ADMINISTRATION – Patients with impaired renal function**).

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.

Effect on Ability to Drive or Use 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 effects should be advised to refrain from driving or using machines.

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

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"**).

Effects on Fertility

There are no data available on the effect of baclofen on fertility in humans.

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 20 mg/kg/day, which is maternotoxic. The relevance of this finding to humans is unknown. At the same dose the incidence of incomplete sternebral ossification in the foetuses was increased.

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, doses of up to 10 mg/kg/day were given orally. Maternotoxicity was 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 be used during pregnancy only if the expected benefit outweighs the potential risk to the foetus.

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

Use in Lactation

Studies in lactating women are limited to one patient. In this particular case, available evidence suggests that baclofen was found in quantities so small that undesirable effects in the infant would have been unlikely. However, given the limited information available, treatment of breast-feeding women with baclofen should be approached with caution.

Use in Children

Baclofen should be given with extreme caution to children under 16 years of age, as only limited data are available.

Use in the Elderly

See **DOSAGE AND ADMINISTRATION**.

Carcinogenicity and Mutagenicity

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.

INTERACTIONS WITH OTHER MEDICINES**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.

Drugs causing Central Nervous System (CNS) depression:

Increased sedation may occur when baclofen is taken concomitantly with other drugs acting on the central nervous system, including other muscle relaxants (such as tizanidine), with synthetic opiates or with alcohol (see **PRECAUTIONS**). 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:

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

Lithium:

Concurrent 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 antihypertensive agents is likely to potentiate 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 impact renal function may reduce baclofen excretion leading to toxic effects (see **PRECAUTIONS, Impaired renal function**).

Others:

Concurrent use of baclofen with monoamine oxidase (MAO) inhibitors 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.

There have been reports of mental confusion, hallucinations, headaches, nausea and agitation in patients with Parkinson's disease receiving treatment with levodopa plus carbidopa, who also required treatment with baclofen.

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

Effect on Laboratory Tests

No information is available on the effects of baclofen on laboratory tests.

ADVERSE EFFECTS

Adverse reactions mainly occur at the start of treatment (for example, somnolence and sedation), if the dosage is increased too quickly, if large doses are used, or if the patient is elderly. These are often transitory and can be alleviated or eliminated by reducing the dosage; however, they may necessitate withdrawal of the medication.

Elderly patients, and patients with a history of psychiatric illness, cortical or organic brain disorders, or with cerebrovascular disorders (such as stroke), may experience more serious adverse reactions.

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 **PRECAUTIONS**).

Certain patients have shown increased spasticity as a paradoxical reaction to the medication.

Frequency Estimate:

Very common $\geq 10\%$

Common 1% to < 10%

Uncommon 0.1% to < 1%

Rare 0.01% to < 0.1%

Very rare < 0.01%

Not known (cannot be estimated from the available data).

Cardiovascular System

Common: hypotension, diminished cardiovascular functions, cardiac output decreased

Rare: arrhythmias, dyspnoea, palpitations, chest pain, ankle oedema

Not known: bradycardia

Gastrointestinal disorders

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

Common: gastrointestinal disturbance, constipation, diarrhoea, retching, vomiting, dryness of the mouth

Rare: colicky abdominal pain, anorexia

Hepatobiliary disorders

Rare: disorders of hepatic function (e.g. increased AST and glucose)

Musculoskeletal System

Common: myalgia, muscular weakness

Nervous System

Very common: sedation, somnolence

Common: respiratory depression, lightheadedness, lassitude, exhaustion, confusional state, dizziness, personality changes, vertigo, headache, insomnia, euphoria, depressive states, ataxia, tremor, hallucinations, nightmares

Rare: paresthesia, dysarthria, syncope, dyskinesia, coma

Very rare: hypothermia

Sense Organs

Common: tinnitus, nystagmus, accommodation disorders, visual disturbances

Rare: dysgeusia / taste disturbances

Skin and subcutaneous tissue disorders

Common: hyperhidrosis, rash, pruritus

Not known: Urticaria

Urogenital System

Common: dysuria, frequency of micturition (pollakiuria), enuresis

Rare: retention of urine, impotence (erectile dysfunction), inability to ejaculate, nocturia, haematuria

General disorders and administration site conditions

Very rare: Hypothermia

Not known: Drug withdrawal syndrome

Investigations

Not known: Blood glucose increase

Other

Rare: nasal congestion, weight gain

DOSAGE AND ADMINISTRATION

Treatment with baclofen should always be started in hospital using small doses, which are then gradually increased stepwise. The optimum daily dosage should be individually adapted to each patient's requirements, so that clonus, flexor and extensor spasms, and spasticity are reduced, while at the same time retaining enough muscle tone to permit active movements, and avoiding adverse effects as far as possible.

Abrupt discontinuation of treatment should be avoided (see **PRECAUTIONS**).

Baclofen should be taken during meals with a glass of water.

In adults, baclofen should be given in at least three divided doses daily.

Dosage regimen

As a rule, treatment should be started with a dose of 5 mg three times daily, which should subsequently be increased at three day intervals by 5 mg three times daily (i.e. the dosage regimen is 5 mg three times a day for 3 days, then 10 mg three times a day for 3 days, etc) until an optimum response is attained. In certain patients who react sensitively to drugs, it may be advisable to begin with a lower daily dose (5 or 10 mg), increased by smaller steps at longer intervals. The optimum dosage generally ranges from 30 to 75 mg daily, although occasionally in hospitalised patients doses up to 100 mg daily may be necessary.

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

Impaired Liver Function

Baclofen is partially metabolised in the liver. Patient with impaired liver function should be periodically monitored with laboratory tests (see **Monitoring Advice**).

Impaired Renal Function

Since baclofen is largely eliminated by the kidneys, a dosage reduction is advised to avoid drug accumulation. In patients with impaired renal function or undergoing chronic haemodialysis, low doses (i.e. approximately 5 mg daily) should be used. Signs and symptoms of overdosage have been reported with doses at and above 5mg daily in this setting (see **OVERDOSAGE**).

Baclofen should only be administered to patients with end stage renal failure when benefit outweighs risk. These patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy) (See **OVERDOSAGE**)

Use in the Elderly

Since unwanted effects are more likely to occur in elderly patients (due to increased risk of renal function impairment and CNS toxicity), a very cautious dosage schedule should be adopted and the patient kept under appropriate surveillance.

Toxicity due to baclofen may be mistaken for uraemic encephalopathy.

Use in Children

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

Monitoring Advice

In rare instances elevated serum levels of aspartate transaminase (AST), alkaline phosphatase, or glucose 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 have occurred.

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

OVERDOSAGE

Signs and Symptoms

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

Other signs and symptoms which are 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 1125 mg of baclofen and survived. Ingestion of 1250 to 2500 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 or administration of saline laxatives if necessary
- administration of artificial respiration in cases of respiratory muscle weakness
- measures in support of cardiovascular functions
- since the drug is excreted chiefly via the kidneys, generous quantities of fluid should be given, possibly together with a diuretic.
- 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 **PRECAUTIONS**)

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdose.

PRESENTATIONS AND STORAGE CONDITIONS

GenRx Baclofen 10 mg tablets

White, oval, flat-faced, bevel-edged tablets, scored and engraved “APO B10” on one side.
100 tablets per bottle.

AUST R 77577

GenRx Baclofen 25 mg tablets

White, round, flat-faced, bevel-edged tablets, scored on one side.
100 tablets per bottle.

AUST R 77576

GenRx Baclofen 10mg and 25mg tablets are intended for oral administration.
Each tablet contains 10mg or 25mg of baclofen.

Store below 25°C. Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia

GenRx is a registered trade mark of Apotex Pty Ltd.

POISONS SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

Date of First inclusion on the Australian Register of Therapeutic Goods (The ARTG): 9 January 2008

Date of most recent amendment: 17 September 2013