PACKAGE INSERT TEMPLATE FOR BACLOFEN TABLET

Brand or Product Name
[Product name] Tablet 10mg

Name and Strength of Active Substance(s)

Baclofen …..10mg

Product Description
[Visual description of the appearance of the product (eg colour, viscosity etc)
eg White, circular flat beveled edge film-coated tablets marked '10' on one side

Pharmacodynamics

Derivative of gamma aminobutyric acid (GABA); the precise mechanism of action of baclofen has not been fully determined. It acts mainly at the spinal cord level to inhibit the transmission of both monosynaptic and polysynaptic reflexes, possibly by hyperpolarization of primary afferent fiber terminals resulting in antagonism of the release of putative excitatory transmitters (i.e., glutamic and aspartic acids). Actions at supraspinal sites may also be involved.

Baclofen has general central nervous system (CNS)–depressant actions. Animal studies demonstrated that baclofen also may have antinociceptive effects, possibly by acting at spinal and supraspinal sites to decrease the responsiveness of nociceptive neurons, thereby resulting in analgesia.

Pharmacokinetics
Absorption
Baclofen is rapidly and almost completely absorbed from the gastrointestinal tract after an oral dose. Peak plasma concentrations occur about 0.5 to 3 hours after ingestion, but the rate and extent of absorption vary between patients, and may vary inversely with the dose

Metabolism
About 15% is metabolised in the liver
The main metabolite is β-(p-chlorophenyl)-γ-hydroxybutyric acid, which is pharmacologically inactive.

Distribution
The distribution volume of baclofen amounts to 0.7 L/kg.
Baclofen crosses the placenta and is distributed into breast milk.
After oral doses some baclofen crosses the blood-brain barrier, with concentrations in CSF about 12% of those in the plasma. About 30% of baclofen is bound to plasma proteins.

Elimination
The elimination half-life of baclofen is about 3 to 4 hours in plasma and about 1 to 5 hours in the CSF.
Baclofen is eliminated largely in unchanged form. Within 72 hours approx. 75% of the dose is excreted via the kidneys, approx. 5% of this quantity being in the form of metabolites. The remainder of the dose, 5% of which is in metabolite form, is excreted in the faeces.

Indication

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 myelitits, traumatic paraplegia or paraparesis, and compression of the spinal cord; muscle spasticity of cerebral origin, especially where due to infantile cerebral palsy. In spasticity due to cerebrovascular accident or degenerative or neoplastic brain disease, baclofen is less suitable owing to the likelihood of intolerance, but it may be tried if administered cautiously.

Recommended Dosage

Treatment should be initiated with small doses of baclofen, then gradually increased. It is recommended that the lowest effective dose be used. The optimum dosage must be individually adapted to the patient's requirements so that clonus, flexor and extensor spasms, and spasticity are reduced, while avoiding adverse effects as far as possible.

In order to prevent excessive weakness and falling, baclofen should be used with caution when spasticity is needed to maintain upright posture and balance in locomotion or other functions. It may be important to maintain a certain degree of muscle tone and allow occasional spasms to help support circulatory function and, possibly, prevent deep vein thrombosis.

Baclofen tablets should be taken at mealtimes with a small amount of liquid.

Close monitoring is required at the start of treatment so that potential adverse effects such as general muscle weakness, abrupt loss of muscle tone (risk of failing), fatigue or confusion can be rapidly detected, and the dosage adjusted as necessary.

If baclofen is to be withdrawn after prolonged administration (longer than 2-3 months), the dose should be reduced gradually over the course of about 3 weeks, since abrupt withdrawal may occasionally be associated with anxiety and confusional states, hallucinations, cerebral seizures, dyskinesia, tachycardia or hyperthermia. Withdrawal should also be gradual on account of the risk of a transient rebound effect involving increased spasm frequency and/or severity.

Treatment with baclofen should be re-evaluated if it has not proved successful within 6 to 8 weeks of the patient's reaching the maximum recommended dose.

Adults

Treatment should be started with a dosage of 5 mg three times daily, given in 3 divided doses, then gradually increased. Depending on the response, each of the divided doses should subsequently be increased by 5 mg every three days. 30-80 mg per day is considered the standard daily dose, but 100 to 120 mg may be given in isolated cases (patients under medical supervision in hospitals).

Children

Experience with baclofen tablets is limited in children and adolescents. The minimum age for treatment is 12 months.

Treatment usually starts with very low amounts, e.g. 0.3 mg/kg/day, given in 4 divided doses.

The dosage should be cautiously raised, at intervals of about 1-2 weeks, until it becomes sufficient for the individual patient's requirements. The daily dosage for maintenance therapy is 0.75-2 mg/kg. However, in patients over 10 years of age, a maximum daily dose of 2.5 mg/kg may be given.

The dose should not exceed 40 mg/day in children below 8 years of age, but a maximum dose of 60 mg/day may be given in children over 8 years of age.

Use in patients with renal impairment

Baclofen should be used with caution in patients with renal impairment. Plasma concentrations of baclofen are elevated in patients undergoing chronic haemodialysis, and a particularly low dose of

baclofen (about 5 mg/day) should therefore be selected. Signs and symptoms of overdosage have been reported with doses of over 5 mg per day in this clinical situation.
Baclofen should not be used in patients with end stage renal failure unless the potential benefit outweighs risk of further treatment. Such patients must be closely monitored for early signs and symptoms of overdosage (e.g. drowsiness, lethargy).

Elderly patients and patients with spasticity of cerebral origin
The dosage should be increased particularly slowly elderly and weak patients suffering from organic brain disorders, cardiovascular disease, respiratory failure, or hepatic or renal impairment, and also in patients with spasticity of cerebral origin.

Mode of Administration
Oral

Contraindications
Known hypersensitivity to baclofen or to any of the excipients

Warnings and Precautions

Psychiatric disorders and Epilepsy
It should also be used with caution in patients with severe psychiatric disorders or epilepsy or convulsive disorders since these disorders may be exacerbated by baclofen. Patient should be carefully monitored

Abrupt discontinuation/Withdrawal
Abrupt withdrawal of baclofen may result in a withdrawal syndrome and exacerbation of spasticity; dosage should be reduced gradually over at least 1 to 2 weeks, or longer if symptoms occur.

Psychiatric reactions including hallucinations, paranoia, delusions, psychosis, anxiety, confusion, and agitation have been reported on abrupt withdrawal of oral baclofen; symptoms generally resolved on restarting. Convulsions have also been reported.

Renal impairment
Baclofen should be used with caution in patients with renal impairment; dose adjustments may be necessary. Caution is also required when Baclofen is combined with drugs that can significantly impact renal function. Renal function should closely monitored and baclofen daily dosage adjusted accordingly to prevent baclofen toxicity.

Urinary disorders
Urine retention may be exacerbated in patients with hypertonic bladder sphincters.
Under treatment with Baclofen, neurogenic disturbances affecting emptying of the bladder may show an improvement.

Others
Baclofen stimulates gastric acid secretion and should be used with caution in patients with a history of peptic ulcer and avoided in those with active peptic ulcer disease.

Liver function should be monitored in patients with liver disease.

Baclofen should also be used with caution in patients with respiratory impairment.

Care is also required in the elderly, in whom adverse effects may be more common, and in patients with cerebrovascular disease (who tolerate baclofen poorly).

Observations of increased blood sugar concentrations suggest caution in patients with diabetes mellitus.

Appropriate laboratory tests should therefore be performed periodically in order to ensure that no drug-induced changes in these underlying diseases have occurred.

It should be used with caution in patients who use their spasticity to maintain posture or to increase function.

Effects on the ability to drive and use machines
Baclofen may cause drowsiness; patients affected should not drive or operate machinery.

Interactions with Other Medicaments
Alcohol and other CNS depressants may exacerbate the CNS effects of baclofen and should be avoided; severe aggravation of hyperkinetic symptoms may possibly occur in patients taking lithium.

Concomitant use of CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of respiratory depression, hypotension, oversedation, and syncope. If CNS depressants are used concurrently, consider a dose reduction of the CNS depressant and use with caution.

Baclofen when administered with antidepressants, specifically imipramine, amitriptyline, and clomipramine, has induced short term memory loss. In addition, concomitant imipramine and baclofen may result in additive muscle relaxant effects.

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

In patients with Parkinson's disease receiving treatment with Baclofen and levadopa, there have been reports of mental confusion, hallucinations, headaches, nausea and agitation.
There may be increased weakness (muscular hypotonia) if baclofen is given to patients taking a tricyclic antidepressant and there may be an increased hypotensive effect if it is given to patients receiving antihypertensive therapy.

Ibuprofen and other drugs that produce renal insufficiency may reduce baclofen excretion leading to toxicity.

Adverse Effects / Undesirable Effects
Unwanted effects occur mainly at the start of treatment (e.g. sedation, somnolence), if the dose is increased too rapidly, or if large doses are employed. 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. 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 muscle spasticity as a paradoxical reaction to the medication.

Many of the side effects reported are known to occur in association with the underlying conditions being treated.

Adverse effects associated with baclofen such as sedation, somnolence, and nausea are often transient and dose-related. They may be minimised by increasing doses gradually or controlled by a reduction in dosage.

Cardiovascular disorders: Hypotension

Gastrointestinal disorders: Constipation, Nausea, Vomiting, Gastrointestinal disturbance, diarrhoea, Abdominal pain.

Renal and urinary disorders: Pollakiuria, enuresis, dysuria., urinary retention, urinary complications

Respiratory disorders: Pneumonia

Skin and subcutaneous tissue disorders: Hyperhidrosis, rash, Urticaria

Eye disorders: visual disturbances

Reproductive system and breast disorders: Erectile dysfunction.
Hepatobiliary disorders: Hepatic function abnormal, alterations in liver function values

Nervous system disorders: Sedation, Respiratory depression, light-headedness, lassitude, fatigue confusional state, dizziness, headache, insomnia, euphoric mood, depression, muscular weakness, ataxia, tremor, hallucinations, nightmares, myalgia, nystagmus, dry mouth, somnolence. Hypothermia. Paraesthesia, dysarthria, dysgeusia.

Other adverse effects include tinnitus, convulsions, slurred speech, blood sugar changes, and a paradoxical increase in spasticity. Abrupt withdrawal of baclofen can result in increased spasticity, hallucinations and seizures. Baclofen should be withdrawn gradually in patients)

Statement on Usage During Pregnancy and Lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Lactation

In mothers taking baclofen in therapeutic doses, the active substance passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected.

Overdose and Treatment
Symptoms

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

Also liable to occur are : confusion, hallucinations, agitation, convulsion, EEG changes (burst suppression pattern and triphasic waves), accommodation disorders, absent pupillary reflex; generalized

muscular hypotonia, myoclonia, hyporeflexia or areflexia, peripheral vasodilation, hypotension or hypertension, bradycardia, tachycardia or cardiac arrhythmias, hypothermia, nausea, vomiting, diarrhoea, hypersalivation, elevated liver enzymes.

A deterioration of the overdose syndrome may occur if various substances or drugs acting on the central nervous system (e.g. alcohol, diazepam, tricyclic antidepressants) have been taken at the same time.

Treatment

No specific antidote is known.

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

After ingestion of a potentially toxic amount, activated charcoal should be considered, especially during the early period after ingestion. Gastric decontamination (e.g. gastric lavage) should be considered in individual cases, especially in the early period (60 minutes) after ingestion of a potentially life-threatening overdose. Comatose or convulsing patients should be intubated prior to the initiation of gastric decontamination.

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. In the event of convulsions, diazepam should be administered cautiously i.v..
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

Storage Conditions

[eg Store below…. °C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]