PRODUCT MONOGRAPH

Pr APO-BACLOFEN

Baclofen Tablets USP

10 mg and 20 mg

Antispastic Agent

APOTEX INC.
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TABLE OF CONTENT

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NAME OF DRUG

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THERAPEUTIC CLASSIFICATION

Antispastic Agent

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

The precise mechanisms of action of baclofen are not fully known. It inhibits both monosynaptic and polysynaptic reflexes at the spinal level, probably by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory neurotransmitter γ-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects.

Peak plasma concentrations of baclofen are achieved within 2 hours and the plasma half-life is 2 to 4 hours.

Special populations

Geriatrics (aged 65 years or above)

Following a single oral dose, elderly patients have a slower rate of absorption and elimination, a slightly prolonged elimination half-life, but a similar systemic exposure of baclofen compared to young adults.

Hepatic impairment

No pharmacokinetic data is available in patients with hepatic impairment after administration of baclofen. However, as 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 in female patients under chronic hemodialysis or compensated renal failure indicate significantly decreased clearance and increased half-life of baclofen in these patients. Severe neurological outcomes have been reported in patients with renal impairment after oral administration, thus **baclofen** should be given with special care and caution in these patients (see WARNINGS, Renal Impairment).

A randomized, single dose, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 20 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of baclofen was measured and compared following a single oral dose (1 x 20 mg tablet) of Apo-Baclo (baclofen) 20 mg tablet (Apotex Inc.) and Lioresal® (baclofen) 20 mg tablet (Ciba-Geigy).

Baclofen (1 x 20 mg) From Measured Data Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference[†]	Ratio of Geometric[#] Means (%)	90% Confidence Interval (%)
AUCt (ng•h/mL)	836 883 (32)	826 856 (25)	101.3	89.2 – 115.0
AUCinf (ng•h/mL)	986 1034 (29)	1021 1038 (19)	96.6	87.5 – 106.6
C_{max} (ng/mL)	199 207 (26)	178 187 (28)	111.7	100.7 – 124.0
T_{max}[§] (h)	1.73 (41)	1.86 (47)		
Thalf[§] (h)	3.60 (37)	3.96 (39)		

* Apo–Baclo (baclofen) 20 mg tablets (Apotex Inc.)
[†] Lioresal® (baclofen) 20 mg tablets (Ciba-Geigy) were purchased in Canada.
[#] Results are based on Least Squares Means (LSM).
[§] Expressed as arithmetic means (CV%) only.

INDICATIONS

APO-BACLOFEN (baclofen) is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis.

APO-BACLOFEN may also be of some value in patients with spinal cord injuries and other spinal cord diseases.

CONTRAINDICATIONS

Hypersensitivity to APO-BACLOFEN (baclofen) or to any of the excipients.

WARNINGS

Abrupt Drug withdrawal

Following abrupt withdrawal of baclofen, delirium, visual and auditory hallucinations, convulsion (status epilepticus), dyskinesia, confusional state, psychotic disorder, mania or paranoia, anxiety with tachycardia and sweating, insomnia, rhabdomyolysis and worsening of spasticity have occurred. Therefore, except for serious adverse reactions, the dose of APO-BACLOFEN (baclofen) should be reduced slowly when the drug is discontinued (over a period of approximately 1 to 2 weeks).

For the intrathecal formulation of **baclofen**, it has been reported that clinical characteristics of withdrawal may resemble autonomic dysreflexia, malignant hyperthermia, neuroleptic-malignant syndrome, or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis.

Neonatal Withdrawal:

Drug withdrawal reactions including, irritability, high-pitched crying, tremor, hypertonicity, excessive sucking, disordered sleep, hyperthermia, mottling, and postnatal convulsions have been reported in neonates after intrauterine exposure to oral **baclofen.** Neonates with risk of intrauterine exposure to **baclofen** should be carefully monitored for the development of signs consistent with withdrawal. If clinical manifestations of withdrawal develop, non-pharmacologic measures should be considered (for instance, minimizing sensory or environmental stimulation, maintaining temperature stability, increasing the frequency of feeds). Initiation of pharmacotherapy may be

considered in neonates with moderate to severe signs of withdrawal to prevent further complications (See WARNINGS, Pregnancy and Lactation).

Renal impairment

After oral **baclofen** dosing, severe neurological outcomes and symptoms of overdose including clinical manifestations of toxic encephalopathy (e.g. confusion, hallucination, somnolence, depressed level of consciousness and coma) have been reported in patients with renal impairment. Patients with renal impairment should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy) (see SYMPTOMS AND TREATMENT OF OVERDOSAGE). Caution should be exercised while administering **baclofen** in patients with renal impairment because baclofen is primarily excreted unchanged through the kidneys. In patients dependent on dialysis, a particularly low dose of **baclofen** should be selected i.e. approximately 5 mg daily. Unscheduled hemodialysis may be considered a treatment option in cases of severe baclofen toxicity as hemodialysis has been reported to effectively remove baclofen from the body, alleviate clinical symptoms of overdose and shorten the recovery time in these patients.

End Stage Renal Failure: **baclofen** should be administered to end stage renal failure patients only if the expected benefits are considered acceptable, given potential risks.

Concomitant medications that may impact 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 (see PRECAUTIONS, Drug interactions).

Stroke

Baclofen has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug.

Pregnancy and Lactation

Safe use of baclofen during pregnancy or lactation has not been established. Baclofen crosses the placental barrier and passes into breast milk. High doses are associated with an increased incidence of abdominal hernias in the fetuses of rats and of ossification defects in those of rats

and rabbits. Therefore, the drug should be administered to pregnant patients, or women of child-bearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Infants exposed to **baclofen** through maternal oral dosing during pregnancy are at risk of experiencing baclofen withdrawal at birth; identification of this condition may be confounded due to delayed appearance of withdrawal symptoms in this population.

Epilepsy

Extreme caution should be exercised in patients with epilepsy or a history of convulsive disorders. In such patients, the clinical state and electroencephalogram should be monitored at regular intervals during therapy, as deterioration in seizure control and EEG has been reported occasionally in patients taking **baclofen.**

PRECAUTIONS

Use in Children

Safe use of **baclofen** in children under age 12 has not been established and APO-BACLOFEN is, therefore, not recommended for use in children.

Driving and Using Machines

APO-BACLOFEN (baclofen) may be associated with adverse effects such as dizziness, sedation, somnolence and visual impairment (see ADVERSE REACTIONS) which may impair the patient's reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines. Patients should also be cautioned that the central nervous system effects of baclofen may be additive to those of alcohol and other CNS depressants.

Posture and balance

APO-BACLOFEN should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

No studies have been performed in patients with hepatic impairment receiving **baclofen** therapy. As baclofen does not undergo predominant hepatic metabolism, its pharmacokinetics is unlikely to be altered to a clinically significant level in patients with hepatic impairment.
However, patients with severe hepatic impairment should be treated with caution, as they are in general more sensitive to therapeutic effects/adverse effects of drugs.

In rare instances, elevated SGOT, alkaline phosphatase and glucose levels in the serum have been recorded when using oral baclofen.

Others

Caution should also be used in treating the following populations: patients with peptic ulceration (or a history of); elderly patients with cerebrovascular disorders; and patients with respiratory impairment. **Regarding patients with renal failure, see WARNINGS, Impaired Renal function.**

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 DOSAGE and ADMINISTRATION).

Urinary disorders

APO-BACLOFEN should be used with caution in patients with underlying bladder sphincter hypertonia, since acute retention of urine may occur.

Psychiatric and Nervous System Disorders

Patients suffering from psychiatric disorders such as psychosis, schizophrenia, or confusional states should be treated cautiously with APO-BACLOFEN and kept under close surveillance, since exacerbation of these conditions may occur with baclofen treatment.

Laboratory tests

The following laboratory tests have been found to be abnormal in a few patients receiving baclofen: aspartate aminotransferase, blood alkaline phosphatase and blood sugar (all elevated). Therefore, in patients with liver diseases or diabetes mellitus, appropriate laboratory tests should be performed periodically in order to ensure that no drug-induced changes in these underlying diseases have occurred.

Drug Interactions

Anesthetics

Anesthetic agents may potentiate the CNS effects of baclofen.

Antidepressants

The concomitant administration of baclofen and tricyclic antidepressants may potentiate the pharmacological effects of baclofen, resulting in pronounced muscular hypotonia. In addition, concomitant use of tricyclic antidepressants can cause sedation, drowsiness and potentiate the effects of **baclofen** resulting in pronounced muscular hypotonia.

Lithium

Concomitant use of oral **baclofen** and lithium resulted in aggravated hyperkinetic symptoms. Caution should be exercised when **baclofen** is used concomitantly with lithium.

MAO inhibitors

The concurrent use of MAO inhibitors and baclofen may result in increased CNS-depressant effects; therefore, caution is advised and the dosage of one or both agents should be adjusted accordingly.

Antihypertensives

Since combined treatment with baclofen and antihypertensives is likely to increase the fall in blood pressure, 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 a DDC inhibitor, carbidopa), there have been several reports of mental confusion, hallucinations, headache, 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.

Antidiabetic agents

Isolated cases of increased blood glucose concentrations have been reported with baclofen, dosage adjustments of antidiabetic agents (oral and insulin) may therefore be necessary with combined baclofen treatment.

Neuromuscular blocking agents

Caution should be exercised when administering baclofen and magnesium sulfate (or other neuromuscular blocking agents), since a synergistic effect may theoretically occur.

Agents reducing renal function

Drugs or medicinal products that can significantly impact renal function (ex: memantine, NSAIDS) may reduce baclofen excretion leading to toxic effects (see WARNINGS, Impaired Renal Function).

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), synthetic opiates, hypnotics, anxiolytics or alcohol (see PRECAUTIONS, Driving and using machines). 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.

Lactation

Baclofen is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug.

Infertility

There are no data available on the effect of baclofen on fertility in humans. Baclofen did not impair male or female fertility at non-maternally toxic doses in rats (see TERATOLOGY AND REPRODUCTION STUDIES).

ADVERSE REACTIONS

Adverse effects most frequently occur at the start of treatment (e.g. sedation, somnolence), particularly if the dosage is increased too rapidly, if large doses are administered, and in the elderly patient. However, these effects are often transient and can be alleviated or eliminated by decreasing the dosage; they are seldom severe enough to warrant withdrawal of the medication.

Should persistent nausea occur following a reduction in dosage, it is recommended that **baclofen** be ingested with food or a milk beverage.

Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients.

In elderly patients or those patients with cerebrovascular disorder or a history of psychiatric illness, more serious adverse reactions may occur, such as hallucinations and confusion.

Muscular hypotonia of a degree sufficient to make walking or movement difficult may occur, but is usually relieved by readjusting the dosage. For this purpose, the overall dose of **baclofen** may be reduced, or the daytime dose reduced and the evening dose increased.

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

Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

Adverse reactions listed below are ranked 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).

The most common adverse reactions associated with baclofen are transient somnolence, , sedation, dizziness, weakness and fatigue. Other adverse reactions reported were:

Nervous System Disorders

Common: Headache, insomnia, muscular weakness, tremor, ataxia, respiratory depression, euphoric mood, depression, confusional state, hallucinations, nightmare, myalgia, nystagmus, and dry mouth.

Rare: Excitement, paresthesia, tinnitus, slurred speech, coordination disorder, rigidity, dystonia, dysarthria, epileptic seizures, lowered convulsion threshold, and dysgeusia.

Eye disorders

Common: Accommodation disorders, visual impairment.

Rare: Blurred vision, strabismus, miosis, mydriasis, diplopia.

Cardiac disorders

Common: Cardiac output decreased.

Rare: dyspnea, palpitation, chest pain, syncope.

Not known: Bradycardia.

Vascular disorders

Common: Hypotension.

Gastrointestinal disorders

Very common: Nausea.

Common: Constipation, gastrointestinal disorders, retching, vomiting, diarrhea.

Rare: Anorexia, abdominal pain, and positive test for occult blood in stool.

Hepatobiliary disorders

Rare: Hepatic function abnormal.

Skin and subcutaneous tissue disorders

Common: Instances of rash, hyperhidrosis, pruritus.

Not known: Urticaria.

Renal and urinary disorders

Common: Pollakiuria, enuresis, dysuria.

Rare: Nocturia, hematuria, urinary retention.

Reproductive system and breast disorders

Rare: Erectile dysfunction, inability to ejaculate.

General disorders and administration site conditions

Common: Fatigue, ankle edema.

Very rare: Hypothermia.

Not known: Drug withdrawal syndrome.

Investigation

Not known: Blood glucose increased.

Other

Weight gain, nasal congestion.

*Drug withdrawal syndrome including, irritability, high-pitched crying, tremor, hypertonicity, excessive sucking, disordered sleep, hyperthermia, mottling, and postnatal convulsions has also been reported after intra-uterine exposure to oral baclofen

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre

Signs and Symptoms

Symptoms of overdosage are predominantly those of central nervous system depression and include somnolence, depressed level of consciousness, respiratory depression, coma, seizures, confusion, hallucinations, agitation, abnormal electroencephalogram (burst suppression pattern and triphasic waves), accommodation disorder, impaired pupillary reflexes, muscular hypotonia, myoclonus, hyporeflexia or areflexia, hypotension or hypertension, bradycardia, tachycardia or cardiac arrhythmia, hypothermia, peripheral vasodilatation, nausea, vomiting, diarrhea, increased salivation, elevated LDH, AST, alkaline phosphatase blood glucose values, sleep apnea and rhabdomyolysis.

The signs and symptoms may be further aggravated by co-administration of a variety of other agents including alcohol, diazepam, and tricyclic antidepressants.

Treatment

There is no specific antidote. 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. A high urinary output should be maintained since APO-BACLOFEN (baclofen) is excreted mainly by the kidneys. For this purpose, generous quantities of fluid should be administered, possibly together with a diuretic. Hemodialysis (sometimes unscheduled) is indicated in severe poisoning associated with renal failure (see WARNINGS, Impaired Renal Function). In the event of convulsions, administer diazepam i.v. with caution.

DOSAGE AND ADMINISTRATION

The determination of optimal dosage of APO-BACLOFEN (baclofen) requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40 to 80 mg daily).

Treatment should be started with a dosage of 15 mg daily, preferably in divided doses.

The following dosage titration schedule is suggested:

5 mg t.i.d. for 3 days

10 mg t.i.d. for 3 days

15 mg t.i.d. for 3 days

20 mg t.i.d. for 3 days

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d).

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see WARNINGS).

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 WARNINGS).

Special populations

Renal impairment

Because **baclofen** is primarily excreted unchanged through the kidneys, it should be given with caution in patients with renal insufficiency, and generally with a reduced dose. In patients dependent on dialysis, a particularly low dose of **baclofen** should be selected i.e. approximately 5 mg daily (see WARNINGS, Impaired Renal Function).

Baclofen should only be administered to end stage renal failure patients when benefit outweighs risk. These patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (see WARNINGS, Renal Impairment).

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 should be kept under appropriate surveillance. Patients should be monitored for signs of overdose, central nervous system depression and toxic encephalopathy such as drowsiness, impairment of consciousness, coma, respiratory depression, hallucinations, agitation, and convulsions (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

Hepatic impairment

No studies have been performed in patients with hepatic impairment under **baclofen** therapy. Liver does not play significant role in the metabolism of baclofen after oral administration of **baclofen** (see CLINICAL PHARMACOLOGY). However, **baclofen** has the potential of elevating liver enzymes. **Baclofen** should be prescribed with caution in patients with hepatic impairment, although no dosage adjustment is needed (see PRECAUTIONS, Hepatic Impairment).

Geriatrics (aged 65 years or above)

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

Patients with spastic states of cerebral origin

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

AVAILABILITY

APO-BACLOFEN (baclofen) 10 mg Tablets are oval, white, scored tablets imprinted with "APO B10".

APO-BACLOFEN (baclofen) 20 mg Tablets are capsule-shaped, white, scored tablets imprinted with "APO B20".

APO-BACLOFEN 10 mg and 20 mg Tablets are available in bottles of 100, 250, 500 and 1000 tablets.

APO-BACLOFEN must be kept out of the reach and sight of children.

CHEMISTRY AND PHARMACOLOGY

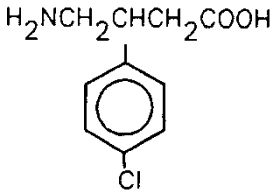
Drug Substance

Common Name: Baclofen

Chemical Name(s): 1) Butanoic acid, 4-amino-3-(4-chlorophenyl)

2) 2) β- (Aminomethyl) -p-chlorohydrocinnamic acid

Structural Formula:



Molecular Formula: $C_{10}H_{12}ClN0_2$

Molecular Weight: 213.66 g/mol

Description:

A white to off-white, odourless or practically odourless, crystalline powder. Slightly soluble in water; very slightly soluble in methanol; insoluble in chloroform.

pKa values: 3.9 and 9.6

Composition

Each APO-BACLOFEN tablet contains baclofen, U.S.P. Each tablet also contains the following non-medicinal ingredients: lactose, magnesium stearate, microcrystalline cellulose and starch.

Stability and Storage Recommendations

APO-BACLOFEN Tablets should be stored in tight containers between 15°C to 30°C.

PHARMACOLOGY

Baclofen exerted a pronounced muscle-relaxant effect in the non-anesthetized mouse, rabbit, cat, and dog. Doses of up to 10 mg/kg p.o. did not affect coordination in mice. Intravenous doses of 1 or 2 mg/kg decreased polysynaptic (flexor) spinal reflexes in anesthetized rabbits or cats respectively by 50%. A similar reduction was found in decerebrated, or spinal cats. The monosynaptic (extensor) spinal reflex was reduced 50% by a dose of 0.5 mg/kg i.v. in spinalized, decerebrate or anesthetized cats. Baclofen had no direct effect on the alpha-motor nerve fibres, neuromuscular transmission, or contraction of extrafusal muscle fibres in anesthetized cats. An intravenous dose of 0.8 mg/kg diminished the tonic activity of gamma motoneurons in decerebrate cats by 50%. Baclofen diminished or abolished decerebrate rigidity in cats in doses of 1-3 mg/kg. It had no effect on the de-efferented muscle spindle or the slowly-adapting pulmonary stretch receptors in anesthetized cats.

Baclofen had anticonvulsive effects against thiosemicarbazide and pentetrazole-induced convulsions in mice but had no effect against electroshock or strychnine-induced convulsions.

An intravenous dose of 3 to 6 mg/kg exerted a hypnotic effect in the unanesthetized dog.

Large doses impaired respiration in mice, rabbits, and dogs. Doses of 1 mg/kg i.v. produced a fall in the blood pressure of anesthetized rabbits or cats, but 3 mg/kg i.v. had no effect on the blood pressure, heart rate, ECG, or respiration of unanesthetized dogs.

In man a single oral dose of 10 mg of baclofen is rapidly and almost completely absorbed whereas absorption of 20 mg and 40 mg doses is less complete. Animal studies indicate rapid distribution throughout the body except to the CNS where concentrations are lower than average. The decay in CNS concentration is, however, slower than the decay from other tissues.
About 85% of a single oral dose is excreted unchanged in the urine. The remaining 15% is mainly deaminated to β-(p-chlorophenyl)- γ-hydroxybutyric acid within 24 hours. Baclofen is about 30% bound to serum proteins.

TOXICOLOGY

Acute Toxicity

Species	Route	LD_{50} (mg/kg)
Mouse	i.v.	26 ± 6
Mouse	p.o.	75 ± 22
Rat	i.v.	112 ± 14
Rat	p.o.	150 ± 18
Rat	s.c.	137 ± 17

The toxic symptoms in mice and rats included ataxia, clonic-tonic convulsions and respiratory paralysis.

Species	Sex		No. of Groups	No. of Animals per Group	Dose mg/kg/day	Route	Duration of Study	Toxic Effects
	M	F						
Rat	20	20	4	5M 5F	0,5,10; 20-80 (weekly increases of 10 mg/kg/day)	p.o.	30 D	Slight adrenal enlargement
Rat	10	10	5	2M 2F	Baclofen + diazepam: 0 + 0, 4 + 2, 20 + 10, 0 + 10, 20 + 0	p.o.	30 D	None
Dog	8	8	4	2M 2F	0,1,2, 4-8 (doubled in last week)	p.o.	30 D	Emesis at all dose levels, anorexia, salivation, ataxia, sedation, weight loss
Rat	80	80	4	20M 20F	0,5, 20-160, 40-500	p.o.	1 Y	Weight loss, mild alopecia, urinary incontinence at intermediate and high doses. Elevated mean neutrophil/ lymphocyte ratios and SGPT at intermediate and high doses.
Rat	280	280	1 3	Control: 100M 100F Test: 60M 60F	0,5, 25-50, 50-100	p.o.	1 Y	Reduced weight gain. Dose-related urinary frequency. Dose-related increase in incidence of ovarian cysts.
Dog	12	12	4	3M 3F	0, 2-4, 3-8, 4-12	p.o.	1 Y	Transient emesis, sedation, convulsions and cardiovascular collapse (single animal), possible slight adrenal enlargement, hind limb weakness or paralysis.

TERATOLOGY AND REPRODUCTION STUDIES

Reproductive toxicity

Oral baclofen showed no significant adverse effects on fertility or postnatal development at non-maternally toxic dose levels in rats (approximately 2.1-times the maximum oral mg/kg dose in adults). At maternally toxic dose levels (8.3-times the maximum oral mg/kg dose in adults), baclofen increased the incidence of omphalocoeles (ventral hernias) in rats, an effect not seen in mice or rabbits. Delayed fetal growth (ossification of bones) in the fetuses of rats and rabbits was also observed at maternotoxic doses.

Rat: Doses of 4.4 to 5 and 17.7 to 21.3 mg/kg/day were administered orally to two groups of female rats during pre-mating, mating, gestation, and lactation. The only significant effect was a reduction in litter size and survivability of offspring (possibly due to agalactia) in the high-dose group. In another rat study, doses of 5 and 10 mg/kg/day were administered by gavage during the last trimester of pregnancy and throughout the lactation period. Five of 31 dams in the high-dose group showed severe weight loss from days 15 to 21 of gestation as well as agalactia and the entire litter of each of these dams died by day 2 post-partum. In a third study, baclofen doses of 30 mg/kg/day produced symptoms of ataxia and drowsiness in dams and the death of 4 of 24 dams dosed from gestation Days 1 to 12. At this high dose level, there was a slight increase in the resorption rate; however, the number and size of the fetuses remained normal and no malformations were reported.

Rat and Mouse: Doses of 5 and 20 mg/kg/day were administered by gavage to two groups of pregnant rats on days 6 to 15 of gestation. The only significant finding was the presence of abdominal hernias in 4/160 fetuses in the high-dose group. In a second similar study, 1/229 control fetuses and 6/293 fetuses from dams receiving 20 mg/kg/day had abdominal hernias. Comparable lesions did not occur in a similar mouse study.

The average number of stillbirths or viable newborns did not differ significantly between control and medicated groups. The average weight of neonates from the high-dose group was significantly reduced.

Rabbit: Doses of 1, 5 and 10 mg/kg/day were administered by gavage to groups of rabbits from the 6th to 18th day of gestation. There was an increased incidence of unossified phalangeal nuclei of forelimbs and hind-limbs in the fetuses from the high-dose group. In another study, a

slight increase in resorption rates and the number of rabbits that were non-gravid was observed in rabbits receiving 10 and 15 mg/kg/day of oral baclofen.

Mutagenicity and Carcinogenicity

Baclofen was negative for mutagenic and genotoxic potential in tests in bacteria, mammalian cells, yeast, and Chinese hamsters.

A 2-year rat study (oral administration of baclofen) found no evidence of carcinogenesis. An apparently dose related increase in the incidence of ovarian cysts and of enlarged and/or haemorrhagic adrenals at the maximum dose used (50 to 100 mg/kg) were observed in female rats treated with baclofen for two years. The clinical relevance of these findings is not known.

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PART III: CONSUMER INFORMATION

Pr APO-BACLOFEN
Baclofen Tablets

This leaflet is part III of a three-part -"Product Monograph" published when APO-BACLOFEN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-BACLOFEN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for

APO-BACLOFEN is used to reduce and relieve the excessive stiffness and/or spasms in your muscles occurring in various conditions such as multiple sclerosis and diseases or injuries of the spinal cord.

What it does

Due to the relaxation of muscle and the consequent relief from pain, APO-BACLOFEN improves your ability to move, makes it easier for you to manage your daily activities and facilitates physiotherapy.

If you have any questions about how APO-BACLOFEN works or why this medicine has been prescribed for you, ask your doctor.

When it should not be used

Do not take APO-BACLOFEN

If you are allergic (hypersensitive) to baclofen or any of the other ingredients listed in "**What the nonmedicinal ingredients are**".

If this applies to you, tell your doctor without taking APO-BACLOFEN. If you think you may be allergic, ask your doctor for advice.

What the medicinal ingredient is

The active substance of APO-BACLOFEN is baclofen.

What the non-medicinal ingredients are

The non-medicinal ingredients are: microcrystalline cellulose, starch, magnesium stearate and lactose.

What dosage forms it comes in:

APO-BACLOFEN is available in 10 mg and 20 mg tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use APO-BACLOFEN talk to your doctor or pharmacist if you:

- Have kidney disease. Your doctor will decide whether or not APO-BACLOFEN is the appropriate treatment for you;
- Are suffering from epilepsy (seizures);
- Have acute pain in your stomach (ulcer) or intestines, breathing problems, liver disease, or a disturbance of blood circulation in your brain;
- Are taking medicines for arthritis or pain (see section: "**Interactions with this medication**");
- Have difficulty urinating;
- Have Parkinson's disease or certain mental illnesses accompanied by confusion or depression;
- Are diabetic.

Older people (aged 65 years or above) or people with a disturbance of circulation in the brain

If you are in one of these groups, you may experience more side effects. Therefore, your doctor will keep you under appropriate surveillance and may adapt the dose of APO-BACLOFEN you take.

Children and adolescents

Safe use of baclofen in children under age 12 has not been established and APO-BACLOFEN is therefore not recommended for use in children.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

You should not use APO-BACLOFEN during pregnancy unless your doctor advises you to do so. Tell your doctor if you are pregnant, planning to become pregnant, or breast-feeding. He or she will discuss with you the potential risk of taking APO-BACLOFEN during pregnancy or if you are breast-feeding. Use of APO-BACLOFEN during pregnancy may result in the newborn experiencing withdrawal from the drug including, irritability, high-pitched crying, trembling, increased muscle tone, excessive sucking, disordered sleep, increase in body temperature, uneven discolored patches on the skin, and convulsions and other symptoms related to sudden stop of treatment sometime after delivery. Your doctor may need to treat your newborn for withdrawal reactions.

Driving and using machines

In some people, APO-BACLOFEN may be associated with dizziness, sleepiness or visual disturbance. If this happens to you, do not drive a car, use a machine, or do other things that need your full attention.

Further safety measures

Before having any kind of surgery (including by the dentist), or emergency treatment, tell the doctor in charge that you are taking APO-BACLOFEN.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with APO-BACLOFEN include:

- Alcohol;
- Sedative drugs;
- Medicines used to treat mood disorders such as antidepressants and lithium;
- Medicines used to treat high blood pressure;
- Medicines used to treat Parkinson's disease;
- Medicines for arthritis or pain.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not drink alcohol during your treatment with APO-BACLOFEN.

PROPER USE OF THIS MEDICATION

Usual dose:
Follow your doctor's instructions carefully. Do not exceed the recommended dose.

How much APO-BACLOFEN **to take**

Treatment usually starts with 15 mg daily, preferably taken in divided doses. The dose is then gradually increased until the best results are obtained; this may be between 40 mg to 80 mg per day, taken in divided doses.

The dose prescribed by your doctor may be different from that written here. If this is the case, follow the doctor's instructions.

Your doctor will tell you exactly how many tablets of APO-BACLOFEN to take.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

When to take APO-BACLOFEN

Taking APO-BACLOFEN at the same time each day will help you to remember when to take your medicine.

How to take APO-BACLOFEN

Be sure to take this medicine regularly, and exactly as your doctor tells you. This will help you to get the best results and reduce the risk of side effects.
How long to take APO-BACLOFEN

Continue taking APO-BACLOFEN as your doctor tells you.

If you have questions about how long to take APO-BACLOFEN talk to your doctor or your pharmacist.

Do not suddenly stop taking APO-BACLOFEN **without first checking with your doctor.** He or she will tell you when and how you can stop taking this medicine; stopping suddenly can make your condition worse.

If you stop your treatment suddenly, you may experience: nervousness, feeling confused, hallucinations, abnormal thinking or behaviour, convulsions, uncontrollable twitching, jerking or writhing movements, fast heart beat, high body temperature. The excessive stiffness (spasms) in your muscles may also worsen.

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you have accidentally taken many more tablets than your doctor has prescribed, seek immediate emergency medical treatment, even though you do not feel sick.

The main symptoms of overdose are drowsiness, breathing difficulties, trouble of consciousness and being unconscious (coma).

Other symptoms may include: feeling confused, hallucinations, agitation, convulsions, blurred vision, unusual muscle weakness, sudden contraction of the muscles, poor or absent reflexes, high or low blood pressure, slow, fast or irregular heart beat, low body temperature, nausea, vomiting, diarrhea or excessive salivation, trouble breathing during sleep (sleep apnoea), pain in muscles, fever and dark urine (rhabdomyolysis).

If you have kidney disease and have accidentally taken more tablets or more syrup than your doctor has prescribed, you may experience neurological symptoms of overdose (e.g. drowsiness, feeling confused, hallucinations).

Missed Dose
If you have forgotten to take one of your schedule doses, take it as soon as you remember. However, if it is almost time for your next dose, do not take the missed one at the same time as the scheduled one, otherwise you will be doubling the dose. Just go back to your regular dosing

timetable. If you have forgotten to take several doses you should contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, APO-BACLOFEN can have some side effects, although not everybody gets them. These are often mild and are usually at the start of treatment; they normally wear off after a few days.

Very common side effects
These side effects may affect more than 1 in 10 patients:

- Drowsiness, sleepiness;
- Nausea.

If any of these affects you severely, **tell your doctor.**

Common side effects
These side effects may affect between 1 and 10 in every 100 patients:

- Feeling faint, tiredness, dizziness, headache, inability to sleep, weakness in arms and legs, pain in muscles, uncontrollable eye movements, dry mouth;
- Disturbance of the digestive tract, retching, vomiting, constipation, diarrhea;
- Sweating a lot;
- Passing more urine than normal, bedwetting.

If any of these affects you severely, **tell your doctor**.

Rare side effects
These side effects may affect between 1 and 10 in every 10,000 patients:

- Tingling or numbness of the hands and/or feet, difficulty in speaking, taste disturbance;
- Abdominal pain;
- Sudden decrease in urine;
- Inability to get or to maintain an erection (impotence).

Side effect also reported (frequency unknown)
Increased blood sugar

If any of these affects you severely, **tell your doctor**.

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical treatment
		Only if severe	In all cases	
Common	Breathing problems		√	
	Feeling of confusion		√	
	Feeling of extreme happiness		√	
	Sad mood (depression)		√	
	Loss of coordination affecting balance and walking, limb and eye movements and/or speech (signs of ataxia)		√	
	Trembling		√	
	Hallucinations		√	
	Nightmares		√	
Common	Blurred vision/visual disturbance		√	
	Shortness of breath at rest or with activity, swelling in the legs and tiredness (signs of decreased cardiac output)		√	
	Low blood pressure (hypotension)		√	
	Skin rash and hives		√	
	Difficulty passing urine, pain when passing urine or a sudden decrease in urine		√	
Rare	Abdominal pain, yellowing of the skin or eyes and tiredness (signs of liver disturbance)			√
	Convulsions			√
Very rare	Low body temperature		√	
Not known	Symptoms following sudden discontinuation of the medicine (drug withdrawal syndrome)		√	
	Slow heart beat		√	

This is not a complete list of side effects. For any unexpected effects while taking APO-BACLOFEN, contact your doctor or pharmacist.

HOW TO STORE IT

APO-BACLOFEN Tablets should be stored in tight containers between 15°C to 30°C.

Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about APO-BACLOFEN:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

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