Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Baclopar 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of baclofen.

Excipient with known effect: Each tablet contains 40 mg of lactose monohydrate and 20 mg of Sodium starch glycolate (Type A).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White flat bevel-edge tablet, marked "BN" breakline "10" on one side with "G" logo on the reverse.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Baclopar is indicated for the relief of voluntary muscle spasticity as occurs in conditions such as multiple sclerosis and spinal cord lesions including syringomyelia, transverse myelitis and motor neurone disease.
Baclopar is also indicated in adults for the management of spasticity of cerebral origin including meningitis, cerebral palsy, traumatic head injury, cerebrovascular accident.

Patient selection is important when initiating Baclopar therapy. It is of most benefit in relief of spasticity which is seriously interfering with activity. Treatment should not be commenced until the spastic state has been stabilised.

Paediatric Population
Baclofen is indicated in patients below 18 years for the symptomatic treatment of spasticity 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.

Baclofen is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

4.2 Posology and method of administration

Posology
Titration of the dose is necessary to meet the individual patients requirements while avoiding adverse effects or interference with function depending on the activity of voluntary muscles e.g. bladder, central posture support. The lowest dose compatible with an optimal response is recommended.

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

Treatment should always, (unless serious adverse effects occur), be gradually discontinued by successively reducing the dosage over a period of about 1-2 weeks.

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 section 4.4 Special

warnings and precautions for use). In some cases, mobility is improved with small frequent doses, especially if given 1 hour prior to performing manual tasks, rather than larger spaced doses. Some patients benefit from only taking baclofen at night to reduce painful muscle spasms.

Adults: Treatment should be started with a dosage of 15 mg daily, preferably in 2 to 4 divided doses. Dose should be titrated upwards cautiously by 15 mg /day increments at 3-day intervals until the requisite daily dosage has been attained. In certain patients reacting sensitively to drugs, it may be advisable to begin with a lower daily dosage (5 or 10 mg) and to raise the dosage more gradually (see section 4.4 Special warnings and precautions for use). The optimum dosage generally ranges from 30 to 80 mg daily.

Satisfactory control of symptoms is usually obtained with doses of up to 60 mg daily, but a careful adjustment is often necessary to meet the requirement of each individual patient. The dose may be increased slowly if required, but a maximum daily dose of more than 100 mg is not advised unless the patient is in hospital under careful medical supervision. In such cases 100 mg – 120 mg may occasionally be necessary. Small frequent dosage may prove better in some cases than larger spaced doses. Also, some patients benefit from the use of baclofen only at night to counteract painful flexor spasm. Similarly, a single dose given approximately 1 hour prior to performance of specific tasks such as washing, dressing, shaving, physiotherapy, will often improve mobility.

Once the maximum recommended dose has been reached, if the therapeutic effect is not apparent within 6 weeks a decision whether to continue with baclofen should be taken.

Elderly (aged 65 years or above): Side effects are more common in elderly and are noticed most particularly at the beginning of baclofen therapy. Elderly patients should be treated under careful medical supervision and initially receive a low dose of baclofen which can gradually be titrated upwards according to the therapeutic response. There is no evidence that the eventual average maximum dose differs from that in younger patients.

Paediatric population (below 18 years): Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), in 2-4 divided doses (preferably in 4 divided doses). Baclofen tablets are not suitable for use in children below 33 kg body weight. Other pharmaceutical forms of baclofen may be more suitable for this population. For children above 33kg body weight, the most suitable formulation should be considered.

The dosage should be raised cautiously, at about 1 week intervals, until it becomes sufficient for the child's individual requirements.
The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight.

Patients with renal impairment: A particularly low dosage of baclofen should be used, i.e. 5 mg daily, in patients with impaired renal function or those undergoing haemodialysis.

Baclofen should be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk. These patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy) (see sections 4.4 Special warnings and precautions for use and 4.9 Overdose).

Patients with hepatic impairment: No studies havebeen performed in patients with hepatic impairment under Baclopar therapy. Liver does not play a significant role in the metabolism of baclofen after oral administration of Baclopar (see section 5.2 Pharmacokinetic properties). However, Baclopar has the potential of elevating liver enzymes, Baclopar should be prescribed with caution in patients with hepatic impairment (see section 4.4 Special warnings and precautions for use).

Patients with spastic states of cerebral origin: Such patients are more likely to experience unwanted side effects and should be kept under close surveillance. Therapy and subsequent dosage changes should be initiated with caution.

Method of administration
For oral administration only.
Baclofen should be taken with meals and a little liquid.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Psychiatric and nervous system disorders
Baclofen should only be used with great caution in patients with porphyria, history of alcoholism, hypertension, psychotic disorders, schizophrenia depressive or manic disorders, confusional states or Parkinson's disease since exacerbation of such conditions may occur. Patients should be kept under close surveillance.

Suicide and suicide-related events have been reported in patients treated with baclofen. In most cases, the patients had additional risk factors associated with an increased risk of suicide including alcohol use disorder, depression and/or a history of previous suicide attempts. Close supervision of patients with additional risk factors for suicide should accompany drug therapy. Patients (and caregivers of patients) should be alerted about the need to monitor for clinical worsening, suicidal behaviour or thoughts or unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Cases of misuse, abuse and dependence have been reported with baclofen. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of baclofen misuse, abuse or dependence e.g. dose escalation, drug-seeking behaviour, development of tolerance.

Epilepsy
Baclofen should only be used with great caution in patients with a history of convulsions since exacerbation of such conditions may occur and seizures have occasionally been reported in connection with the discontinuation of baclofen or with overdosage. Adequate anticonvulsive therapy should be continued and the patient carefully monitored.

Baclofen should be used with extreme care in patients already receiving antihypertensive therapy (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Others
Patients with cerebrovascular disease, a history of/or existent peptic ulcers, or those with respiratory or hepatic impairment should receive baclofen only under careful supervision. 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 section 4.2 Posology and method of administration).

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

Abrupt withdrawal
Treatment should always, (unless serious adverse effects occur), be gradually discontinued by successively reducing the dosage over a period of about 1-2 weeks. Anxiety and confusional state, delirium, hallucinations, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and temporary aggravation of spasticity as a rebound phenomenon have been reported with abrupt withdrawal of baclofen, especially after long-term medication.

Drug withdrawal reactions including postnatal convulsions in neonates have been reported after intrauterine exposure to oral baclofen. As a precautionary measure, Baclofen administration to neonates with gradual tapering can help in controlling and preventing the withdrawal reactions. This recommendation is based on a limited number of case reports in the literature.
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.

Except in overdose-related emergencies or where serious adverse effects have occurred, the treatment should always be gradually discontinued by successively reducing the dosage (over a period of approximately 1 to 2 weeks).

Renal impairment
Baclofen should be used with caution in patients with renal impairment and should be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk (see section 4.2 Posology and method of administration). Neurological signs and symptoms of overdose including clinical manifestations of toxic encephalopathy (e.g. confusion, disorientation, somnolence and depressed level of consciousness) have been observed in patients with renal impairment taking oral baclofen at doses of more than 5mg per day and at doses of 5mg per day in patients withend-stage renal failure being

treated with chronic haemodialysis.Patients with impaired renal function should be closely monitored for prompt diagnosis of early signs and symptoms of toxicity (See section 4.9 Overdose).

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.

Urinary disorders
Patients with neurogenic disturbances affecting emptying may show improvement. In patients with pre-existing sphincter hypertonia may experience acute urinary retention, baclofen should be used with caution in such cases.

Laboratory tests
Elevated aspartate aminotransferase, blood alkaline phosphatase and blood glucose levels in serum have been recorded in rare instances. Appropriate tests should be performed in patients with liver disease or diabetes mellitus to ensure that no underlying drug induced changes have occurred in these diseases.

Paediatric population
There is very limited clinical data on the use of baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Observed Interactions to be considered

Levodopa/Dopa Decarboxylase (DDC) inhibitor (Carbidopa)
In patients with Parkinson's disease receiving treatment with baclofen and levodopa (alone or in combinations 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
In concomitant administration with other drugs acting on the CNS including other muscle relaxants (such as tizanidine) with synthetic opiates or with alcohol, increased sedation may occur (see section 4.4 Special warnings and precautions for use).

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.

Concurrent use of baclofen with MAO inhibitors may result in increased CNS-depressant and hypotensive effects; caution is recommended and dosage of one or both agents may require reduction.

Antidepressants
The effect of baclofen may be prolonged if co-administered with tricyclic anti-depressants resulting in marked muscle hypotonia.

Lithium
Concomitant use of oral baclofen and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should be exercised when baclofen is used concomitantly with lithium.

Antihypertensives
The risk of hypotension occurring is increased in patients receiving both baclofen and anti-hypertensive therapy. Adjustments to the dosage of anti-hypertensive medication should be made accordingly.

Agents reducing renal insufficiency
Drugs which may produce renal insufficiency e.g. ibuprofen may reduce baclofen excretion leading to toxic effects (see section 4.4 Special warnings and precautions for use).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Baclofen given orally has been shown to increase the incidence of omphaloceles (ventral hernias) in the foetuses of rats given approximately 13 times the maximum oral dose (on a mg/kg basis) recommended for human use. This abnormality was not seen in mice or rabbits (see section 5.3 Preclinical safety data).

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

Drug withdrawal reactions including postnatal convulsions in neonates have been reported after intra-uterine exposure to baclofen.

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

Fertility
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.

Women of child-bearing potential
There are no data supporting any special recommendations in women of child-bearing potential.

4.7 Effects on ability to drive and use machines

Baclofen may induce dizziness, sedation, somnolence and visual impairment (see section 4.8) which may impair the patient's reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines.

Posture and balance
Baclofen should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion (see section 4.2).

4.8 Undesirable effects

Side-effects: Unwanted effects occur mainly at the start of treatment, if the dosage is raised too rapidly, if large doses are employed, or in elderly patients. 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.

Should nausea persist following a reduction in dosage, it is recommended that baclofen be ingested with food or a milk beverage (see section 4.2).

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.

In patients with a case 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.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (1/≥10); common (≥1/100, to < 1/10); uncommon (≥1/1,000, to <1/100); rare (≥1/10,000, to < 1/1,000); very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Nervous system disorders:

Very common: Sedation, somnolence.
Common: Respiratory depression, fatigue, confusional state, dizziness, headache, insomnia, euphoria mood, depression, muscular weakness, ataxia, tremor, hallucination, nightmare, myalgia, nystagmus, dry mouth.
Rare: Paraesthesia, dysarthria, dysgeusia. Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients.
Unknown: Sleep apnoea syndrome*

Eye disorders:
Common: Accommodation disorder, visual impairment.

Cardiac disorders:
Common: Cardiac output decreased
Not known: Bradycardia.

Vascular disorders:
Common: Hypotension

Gastro-intestinal disorders:
Very common: Nausea.
Common: Gastro-intestinal disorder, constipation, diarrhoea, retching and vomiting.
Rare: Abdominal pain

Hepatobiliary disorders:
Rare: Hepatic function abnormal

Skin and subcutaneous tissue disorders:
Common: Hyperhidrosis, skin rash.
Not known: Urticaria

Renal and urinary disorders:
Common: Pollakiuria, enuresis, dysuria
Rare: Urinary retention

Reproductive system and breast disorders:
Rare: Erectile dysfunction

General disorders and administration site disorders:
Very rare: Hypothermia
Not known: Drug withdrawal syndrome (see section 4.4 Special warnings and precautions for use).

Investigations
Not known: Blood glucose increased

** Cases of central sleep apnoea syndrome have been observed with baclofen at high doses (≥ 100 mg) in patients who are alcohol dependent*

Certain patients have shown increased spasticity as a paradoxical reaction to the medication. An undesirable degree of muscular hypotonia – making it more difficult for patients to walk or fend for themselves – may occur and can usually be relieved by re-adjusting the dosage (i.e. by reducing the doses given during the day and possibly increasing the evening dose).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance,Website: www.hpra.ie.

4.9 Overdose

Symptoms: Tinnitus, Central nervous depression: drowsiness, somnolence, depressed level of consciousness, respiratory depression, coma,tinnitus.

Also liable to occur are: confusion, hallucinations, agitation, convulsion, abnormal electroencephalogram (burst suppression pattern and triphasic waves), accommodation disorders, impaired pupillary reflex; generalised muscular hypotonia, myoclonia, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension or hypertension, bradycardia or tachycardia, or cardiac arrhythmia; hypothermia; nausea, vomiting, diarrhoea, salivary hypersecretion; increased hepatic enzymes, sleep apnoea syndrome, rhabdomyolysis.

The condition may be aggravated if various substances or drugs acting on the central nervous system (e.g. alcohol, diazepam, tricyclic antidepressants) were taken at the same time.

Treatment: There is no specific antidote.

Supportive measures and symptomatic treatment should be given for complications such as hypotension, hypertension, convulsions, gastro-intestinal disturbances and respiratory or cardiovascular depression.
Excretion is chiefly via the kidneys so 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 (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, centrally acting agents, other centrally acting agents, ATC code M03BX01

Mechanism of action
Baclofen is a highly effective antispastic agent acting at the spinal level. A gamma-aminobutyric acid (GABA) derivative, and chemically unrelated to other antispastic agent.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, most probably by stimulating the GABAß receptors. This, in turn inhibits the release of the excitatory amino acids (glutamate and aspartate). Baclofen does not affect neuromuscular transmission.

Baclofen also exerts an antinociceptive effect. General well-being is often improved and sedation is less often a problem than the centrally acting drugs.

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 marked relief from painful spasm, automatism, and clonus. Baclofen improves the patient's mobility, facilitating management of daily activities (including catheterisation) and physiotherapy. Prevention and healing of decubitus ulcers, and improvement in sleep patterns (due to elimination of painful muscle spasms) and in bladder and sphincter function, have also been observed as indirect effects of treatment with baclofen.

Baclofen stimulates gastric acid secretion.

5.2 Pharmacokinetic properties

Absorption
Baclofen is rapidly and completely absorbed from the gastro-intestinal tract. Following oral administration of single doses (10 - 30 mg) peak plasma concentrations are recorded after 0.5 to 1.5 hours and areas under the serum concentration curves are proportional to the dose.

Distribution
The volume of distribution of baclofen is 0.7 l/kg and the protein binding rate is approximately 30% and is constant in the concentration range of 10 nanogram/mL to 300 microgram/mL. In cerebrospinal fluid active substance concentrations are approximately 8.5 times lower than in the plasma.

Biotransformation
Baclofen is metabolised to only a minor extent. Deamination yields the main metabolite, β-(p-chlorophenyl)-4-hydroxybutyric acid, which is pharmacologically inactive.

Elimination

The plasma elimination half-life of baclofen averages 3 to 4 hours. The serum protein binding rate is approximately 30%. Baclofen is eliminated largely in unchanged form. Within 72 hours, about 75% of the dose is excreted via the kidneys with about 5% of this amount as metabolites.

Special populations

Elderly patients (aged 65 years or above)

The pharmacokinetics of baclofen in eldery patients aged 65 years or above are virtually the same as in young subjects below 65 years of age. Following a single oral dose, elderly patients have slower elimination but with a similar systematic exposure of baclofen compared to adults below 65 years of age. Extrapolation of these results to multi-dose treatment suggests no significant pharmacokinetic difference between patients below 65 years of age and elderly patients.

Paediatric population

Following oral administration of 2.5 mg baclofen tablet in children (aged 2 to 12 years), C_{max} of 62.8±28.7 nanogram/mL, and T_{max} in the range of 0.95 to 2 hours have been reported. Mean plasma clearance (CL) of 315.9 mL/h/kg; volume of distribution (Vd) of 2.58 L/kg; and half-life ($T_{1/2}$) of 5.10 hours have been reported.

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 study is available in patients with renal impairment after administration of baclofen. Baclofen is predominantly eliminated unchanged in the urine. Sparse plasma concentration data collected only in female patients under chronic haemodialysis or compensated renal failure indicate significantly decreased clearance and increased half-life of baclofen in these patients. Dosage adjustments of baclofen based on its systemic levels should be considered in renal impairment patients, and prompt haemodialysis is an effective means of reversing excess baclofen in systemic circulation.

5.3 Preclinical safety data

Reproductive toxicity

Oral baclofen was shown not to have adverse effects on fertility or postnatal development at non-maternally toxic dose levels in rats. Baclofen is not teratogenic in mice, rats, and rabbits at doses at least 2.1-times the maximum oral dose levels in adults. Baclofen given orally has been shown to increase the incidence of omphaloceles (ventral hernias) in the foetuses of rats given approximately 8.3- times the maximum oral adult dose expressed as a mg/kg dose. This abnormality was not seen in mice or rabbits. Baclofen dosed orally has been shown to cause delayed foetal growth (ossification of bones) at doses that also caused maternal toxicity in rats and rabbits.

Mutagenicity and Carcinogenicity

Baclofen was negative for mutagenic and genotoxic potential in tests in bacteria, mammalian cells, yeast, and Chinese hamsters. The evidence suggests that baclofen is unlikely to have mutagenic potential.
Baclofen showed no carcinogenic potential in a 2-year study in rats. An apparently dose-related increase in the incidence of ovarian cysts, and a less marked increase in enlarged and/or haemorrhagic adrenals have been observed in female rats treated for 2 years. The clinical relevance of these findings is not known.

Experimental evidence to date suggests that baclofen does not possess either carcinogenic or mutagenic properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline
Calcium hydrogen phosphate, anhydrous
Sodium starch glycolate (Type A)
Silica colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

6.5.1 HDPE bottles
HDPE (High Density Polyethylene) bottle with polypropylene cap. Pack contents of 50 or 100 tablets.

6.5.2 Blister strips
Polyvinylchloride blisters sealed onto aluminium foil. Pack contents of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd., T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
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8 MARKETING AUTHORISATION NUMBER

PA0577/195/001

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