SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Baclofen 5mg/5ml Oral Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: Each 5ml contains 5mg baclofen.

Excipients:  Sodium methyl parahydroxybenzoate (E219)
                        Sodium propyl parahydroxybenzoate (E217)
                        Liquid maltitol (E965)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Oral solution.

A clear, almost colourless solution with a raspberry odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the relief of spasticity of voluntary muscle resulting from such disorders as:
multiple sclerosis, other spinal lesions, e.g. tumours of the spinal cord, syringomyelia,
motor neurone disease, transverse myelitis, traumatic partial section of the cord.

Also for the relief of spasticity of voluntary muscle arising from e.g. cerebrovascular
accidents, cerebral palsy, meningitis, traumatic head injury.

Patient selection is important when initiating therapy; it is likely to be of most benefit
in patients whose spasticity constitutes a handicap to activities and/or physiotherapy.
Treatment should not be commenced until the spastic state has become stabilised.
Paediatric population:

Baclofen is indicated in patients 0 to <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, tranverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

4.2 Posology and method of administration

Before starting treatment with Baclofen 5mg/5ml Oral Solution it is prudent to realistically assess the overall extent of clinical improvement that the patient may be expected to achieve. Careful titration of dosage is essential (particularly in the elderly) until the patient is stabilised. If too high a dose is initiated or if the dosage is increased too rapidly side effects may occur. This is particularly relevant if the patient is ambulant in order to minimise muscle weakness in the unaffected limbs or where spasticity is necessary for support.

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

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).

Adults

Treatment should be started with a dosage of 15mg daily, preferably in divided doses. The following gradually increasing dosage regimen is suggested, but should be adjusted to suit individual patient requirements.

One 5ml spoonful (5mg) three times a day for three days

Two 5ml spoonfuls (10mg) three times a day for three days

Three 5ml spoonfuls (15mg) three times a day for three days

Four 5ml spoonfuls (20mg) three times a day for three days

Satisfactory control of symptoms is usually obtained with doses of up to 60mg daily, but a careful adjustment is often necessary to meet the requirements of each individual patient.
The dose may be increased slowly if required, but a maximum daily dose of more than 100mg is not advised unless the patient is in hospital under careful medical supervision. 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 one hour prior to performance of specific tasks such as washing, dressing, shaving, physiotherapy will often improve mobility.

**Special populations**

**Elderly patients (aged 65 years or above):**
Elderly patients may be more susceptible to side effects, particularly in the early stages of introducing baclofen. Small doses should therefore be used at the start of treatment, the dose being titrated gradually against the response, under careful supervision. There is no evidence that the eventual average maximum dose differs from that in younger patients.

**Paediatric population (0 to <18 years)**
Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg/day), in 2-4 divided doses (preferably in 4 divided doses).
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. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

**Patients with impaired renal function**
In patients with impaired renal function or undergoing chronic haemodialysis, a particularly low dosage of baclofen should be selected i.e. approximately 5mg daily. 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 section 4.4 and section 4.9).

**Patients with hepatic impairment**
No studies have been performed in patients with hepatic impairment receiving baclofen therapy. The liver does not play a significant role in the metabolism of baclofen after oral administration of baclofen (see section 5.2). However, baclofen has the potential of elevating liver enzymes. Baclofen should be prescribed with caution in patients with hepatic impairment.

**Patients with spastic states of cerebral origin**
Unwanted effects are more likely to occur in these patients. It is therefore recommended that a very cautious dosage schedule be adopted and that patients be kept under appropriate surveillance.
Route of administration: Oral use
Baclofen should be taken during meals with a little liquid.

4.3 Contraindications
Hypersensitivity to baclofen or to any of the excipients, peptic ulceration.

4.4 Special warnings and precautions for use

Psychiatric and nervous system disorders
Psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson’s disease may be exacerbated by treatment with baclofen. Patients suffering from these conditions should therefore be treated cautiously and kept under close surveillance.

Epilepsy
Baclofen may also exacerbate epileptic manifestations but can be employed provided appropriate supervision and adequate anticonvulsive therapy are maintained.

Others
It should be used with extreme care in patients already receiving antihypertensive therapy, (see Section 4.5 Interactions).

Should be used with caution in patients suffering from diabetes, cerebrovascular accidents or from respiratory or hepatic impairment or with a history of peptic ulceration.

Should be used with caution in the elderly.

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).

Renal impairment
Signs of overdose have been observed in patients with renal impairment taking more than 5mg baclofen per day. Baclofen should be used with caution in patients with renal insufficiency and should be administered to patients with end-stage renal failure (CKD stage 5, GFR < 15mL/min) only if the expected benefit outweighs the potential risk (see section 4.2).

Cases of baclofen toxicity have been reported in patients with acute renal failure (see section 4.9).
Particular caution is required when combining Baclofen to drugs or medicinal products that can significantly affect renal function. Renal function should 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**

Under treatment with baclofen neurogenic disturbances affecting emptying of the bladder may show an improvement. In patients with pre-existing sphincter hypertonia, acute retention of urine may occur; the drug should be used with caution in such cases.

**Excipients**

This medicine contains sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate. Parahydroxybenzoates may cause allergic reactions (possibly delayed allergic reactions). It also contains maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

**Paediatric patients**

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 therapy.

**Abrupt Withdrawal:**

Anxiety and confusional states, delirium, hallucinations, psychotic disorder, manic or paranoid states, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia and as rebound phenomenon temporary aggravation of spasticity have been reported with abrupt withdrawal of baclofen, especially after long term medication.

Neonatal convulsions have been reported after intrauterine exposure to oral Baclofen (see section 4.6).

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

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

**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)

4.5 **Interaction with other medicinal products and other forms of interaction**

**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), with synthetic opiates or with alcohol (see section 4.7).

The risk of respiratory depression is also increased. Careful monitoring of respiratory and cardiovascular functions is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

**Antidepressants**

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

Since concomitant treatment with baclofen and anti-hypertensives is likely to increase the fall in blood pressure, the dosage of antihypertensive medication should be adjusted accordingly.

Enhanced hypotensive effect when baclofen given with nitrates and diuretics.

The effects of baclofen are possibly modified by memantine.

Excretion of baclofen is possibly reduced by Ibuprofen and other NSAIDs (increased risk of toxicity).

**Agents reducing renal function**

Drugs or medicinal products that can significantly affect renal function may reduce baclofen excretion leading to toxic effects (see Section 4.4).
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, 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.

4.6 Fertility, pregnancy and lactation

During pregnancy, especially in the first three months, baclofen should only be employed if its use is of vital necessity. The benefits of the treatment for the mother must be carefully weighed against the possible risks for the child. Baclofen crosses the placental barrier.

One case of suspected withdrawal reaction (generalised convulsions) has been reported in a week-old infant whose mother had taken oral baclofen 80 mg daily throughout her pregnancy. The convulsions, which were refractory to standard anticonvulsant treatment, ceased within 30 minutes of giving baclofen to the infant.

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.

4.7 Effects on ability to drive and use machines

Baclofen may be associated with dizziness, sedation, somnolence and visual disturbances (see section 4.8 Undesirable effects) which may impair the patient’s reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines.

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), and Not known (cannot be estimated from the available data).

Unwanted effects occur mainly at the start of treatment (e.g. sedation, somnolence and nausea) 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 5mg/5ml Oral Solution be ingested with food or a milk beverage.

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.

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

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Hallucinations, agitation, anxiety, confusional state, insomnia, euphoria, depression, nightmares</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Very common:</td>
<td>Sedation, somnolence.</td>
</tr>
<tr>
<td>Common:</td>
<td>Convulsions, dizziness, headache, ataxia, tremor, nystagmus, dry mouth.</td>
</tr>
<tr>
<td>Rare:</td>
<td>Paraesthesia, dysarthria, dyseusia.</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Accommodation disorders, visual disturbances.</td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac output decreased.</td>
</tr>
<tr>
<td>Not known:</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td>Hypotension.</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Very common:</td>
<td>Nausea.</td>
</tr>
<tr>
<td>Common:</td>
<td>Gastro-intestinal disorder, retching, vomiting, constipation, diarrhoea.</td>
</tr>
<tr>
<td>Rare:</td>
<td>Abdominal pain.</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Hepatic function abnormal.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td>Rash, hyperhidrosis.</td>
</tr>
<tr>
<td>Not known:</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Muscular weakness, myalgia, muscular hypotonia</td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td>Pollakiuria, enuresis, dysuria.</td>
</tr>
<tr>
<td>Rare:</td>
<td>Urinary retention.</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td>Erectile dysfunction.</td>
</tr>
</tbody>
</table>
**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>Common:</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare:</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Not known</td>
<td>Drug withdrawal syndrome (see section 4.4)</td>
</tr>
</tbody>
</table>

**Investigations**

| Not known                  | Blood glucose increased |

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

### 4.9 Overdose

**Symptoms**

Prominent features are signs of central nervous depression: somnolence, depressed level of consciousness, respiratory depression, coma. Also liable to occur are: confusion, hallucinations, agitation, accommodation disorders, impaired pupillary reflex; generalised muscular hypotonia, myoclonus, hyporeflexia or areflexia; convulsions, abnormal electroencephalogram (burst suppression pattern and triphasic waves); peripheral vasodilatation, hypotension or hypertension, bradycardia, tachycardia or cardiac arrhythmia; hypothermia; nausea, vomiting, diarrhoea, hypersalivation; increased hepatic enzymes.

Patients with renal impairment can develop signs of overdose even on low doses of baclofen (see Section 4.2 Posology and method of administration and 4.4 Special warnings and special precautions for use.)

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.

**Treatment**

No specific antidote is known.

Supportive measures and symptomatic treatment should be given for complications such as hypotension, hypertension, convulsions, gastrointestinal disorders and respiratory or cardiovascular depression.
After ingestion of a potentially toxic amount, activated charcoal should be considered. In the early period after ingestion charcoal should be considered in adults who ingested more than 100mg baclofen within 1 hour, and in children who have ingested more than 5mg/kg baclofen within 1 hour. 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 (see section 4.4). In the event of convulsions diazepam should be administered cautiously i.v.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Muscle relaxants, other centrally acting agents, ATC code: M03BX01

Baclofen is an antispastic agent acting at the spinal level. A gamma-aminobutyric acid (GABA) derivative, baclofen is chemically unrelated to other antispastic agents.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating the GABA\textsubscript{\text{A}} receptors, this stimulation in turn inhibiting the release of the excitatory amino acids glutamate and aspartate. Neuromuscular transmission is unaffected by baclofen.

The major benefits of baclofen stem from its ability to reduce painful flexor spasms and spontaneous clonus thereby facilitating the mobility of the patient, increasing his independence and helping rehabilitation.

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

Baclofen stimulates gastric acid secretion.

5.2 Pharmacokinetic properties
Absorption
Baclofen is rapidly and completely absorbed from the gastro-intestinal tract. No significant difference between the liquid and tablet formulations is
observed in respect of $t_{\text{max}}$, $c_{\text{max}}$ and bioavailability. Following oral administration of single doses (10-30mg) 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, $\beta$-(p-chlorophenyl)-4-hydroxybutyric acid, which is pharmacologically inactive.

**Elimination/excretion**

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 elderly patients are virtually the same as in patients below 65 years of age. Following a single oral dose, elderly patients have slower elimination but a similar systemic 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 patients**

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

**Hepatic impairment**

No pharmacokinetic data are available in patients with hepatic impairment after administration of baclofen. However, as the 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 only in female patients under chronic hemodialysis or compensated renal failure indicate significantly decreased clearance and increased half-life of baclofen in these patients. Dosage adjustment of baclofen based on its systemic levels should be considered in renal impairment patients, and prompt hemodialysis is an effective means of reversing excess baclofen in systemic circulation.

5.3 Preclinical safety data
Baclofen increases 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 was not seen in mice or rabbits.

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
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)
Raspberry flavour (contains nature identical flavouring substances, propylene glycol and maltol)
Carmellose sodium
Liquid maltitol (E965)
Citric acid monohydrate
Sodium citrate dihydrate
Purified water

6.2 Incompatibilities
None known
6.3 **Shelf life**

- Unopened: Three years.
- Opened: One month

6.4 **Special precautions for storage**

Store in the original container. Do not store above 25°C. Do not refrigerate or freeze.

6.5 **Nature and contents of container**

Amber glass bottle and tamper evident HDPE child resistant closure with EPE saranex faced liner.

Pack size 300 ml.

6.6 **Special precautions for disposal**

There is no specific instruction for use/handling.

7 **MARKETING AUTHORISATION HOLDER**

Crescent Pharma Limited
Units 3 & 4
Quidhampton Business Units
Polhampton Lane
Overton
Hants
RG25 3ED

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 20416/0193
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/10/2014

10 DATE OF REVISION OF THE TEXT

27/04/2017