SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Baclofen 5mg/5ml Oral Liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of Baclofen oral liquid contains 1mg baclofen (5mg/5ml).

Excipients with known effect

Sorbitol solution 70%: 2000 mg/5ml

Methyl parahydroxybenzoate: 6.6mg/5ml

Propyl parahydroxybenzoate: 0.66mg/5ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral liquid

A clear raspberry flavoured liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Baclofen oral liquid is indicated 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.

Baclofen oral liquid is also indicated in adults and children 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 baclofen 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, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

4.2 Posology and method of administration

Posology:

Before starting treatment with baclofen 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 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 6 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.

5mg three times a day for three days
10mg three times a day for three days
15mg three times a day for three days
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 1 hour prior to performance of specific tasks such as washing, dressing, shaving, physiotherapy, will often improve mobility.

Special Populations:

***Elderly (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.

***Patients with renal impairment*:**
In patients with impaired renal function or undergoing chronic haemodialysis, a particularly low dosage of baclofen should be selected i.e. approx. 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.

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

Method of administration
Baclofen should be taken during meals with a little liquid.

4.3 Contraindications

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

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

Encephalopathy
Cases of encephalopathy have been reported in patients receiving baclofen at therapeutic doses, which were reversible after treatment discontinuation. Symptoms included somnolence, depressed level of consciousness, confusion, myoclonus and coma.

If signs of encephalopathy are observed, baclofen should be discontinued.

***Others*:**
Baclofen should be used with extreme care in patients already receiving antihypertensive therapy (see section 4.5).

Baclofen should be used with caution in patients suffering from cerebrovascular accidents or from respiratory or hepatic impairment.

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*:**
Baclofen should be used with caution in patients with renal impairment and should only be administered to patients with end-stage renal failure 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 with end-stage renal failure being treated with chronic haemodialysis. Patients with impaired renal function should be closely monitored for prompt diagnosis of early symptoms of toxicity.

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.

Cases of baclofen toxicity have been reported in patients with acute renal failure (see section 4.9).

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.

***Laboratory tests*:**
In rare instances elevated AST, alkaline phosphatase and 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.

***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 states, delirium, hallucinations, psychotic disorder, mania or paranoia, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and temporary aggravation of spasticity 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 (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.

***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.

***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).

***Excipients*:**

- Sorbitol- This medicine contains 1400 mg sorbitol in each 5 ml dose and therefore patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
- Baclofen oral liquid also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).
- Propylene glycol- This medicine contains 150 mg propylene glycol in each 5 ml of solution which is equivalent to 30 mg per ml of solution. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

4.5 Interaction with other medicinal products and other forms of interaction

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.

***Drugs causing Central Nervous System (CNS) depression*:**
Increased sedation may occur where 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. In addition, hypotension has been reported with concomitant use of morphine and intrathecal baclofen. Careful monitoring of respiratory and cardiovascular functions is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

***Antidepressants*:**
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.

***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).

4.6 Fertility, pregnancy and lactation

Pregnancy:

During pregnancy, especially in the first 3 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.

Foetal/neonatal adverse reactions

Drug withdrawal reactions including postnatal convulsions in neonates have been reported after intra-uterine exposure to oral Baclofen (see section 4.4).

Breast-feeding:

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.

Fertility:

No data available

4.7 Effects on ability to drive and use machines

Baclofen may be associated with 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.

4.8 Undesirable effects

Adverse 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 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.

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 byre-adjusting the dosage (i.e. by reducing the doses given during the day and possibly increasing the evening dose).

Adverse reactions (Table 1) 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).

Table 1 Tabulated summary of adverse drug reactions

Nervous system disorders	
Very common:	Sedation, somnolence
Common:	Respiratory depression, confusional state, dizziness, headache, insomnia, euphoric mood, depression, muscular weakness, ataxia, tremor, hallucinations, nightmares, myalgia, nystagmus, dry mouth
Rare:	Paraesthesia, dysarthria, dysgeusia
Not known:	Sleep apnoea syndrome* Encephalopathy
Eye disorders	
Common:	Accommodation disorders, visual impairment
Cardiac disorders	
Common:	Cardiac output decreased
Not known:	Bradycardia
Vascular disorders	
Common:	Hypotension
Gastrointestinal disorders	
Very common:	Nausea
Common:	Gastrointestinal disturbance, retching, vomiting, constipation, diarrhoea
Rare:	Abdominal pain
Hepatobiliary disorders	
Rare:	Hepatic function abnormal
Skin and subcutaneous tissue disorders	
Common:	Hyperhidrosis, rash
Not known:	Urticaria
Renal and urinary disorders	
Common:	Polyuria, enuresis, dysuria
Rare:	Urinary retention
Reproductive system and breast disorders	
Rare:	Erectile dysfunction

General disorders and administration site conditions	
Common:	Fatigue
Very rare:	Hypothermia
Not known:	Drug withdrawal syndrome (see section 4.4)
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisations 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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

***Symptoms*:**

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

Also liable to occur are: confusion, hallucinations, agitation, convulsion, abnormal electroencephalogram (burst suppression pattern and triphasic waves, generalised slowing on EEG), accommodation disorder, impaired pupillary reflex; generalised muscular hypotonia, myoclonus, hyporeflexia or areflexia; peripheral vasodilatation, hypotension or hypertension, bradycardia or tachycardia, or cardiac arrhythmia; hypothermia; nausea, vomiting, diarrhoea, salivary hypersecretion; increased hepatic enzymes, SGOT and AP values, rhabdomyolysis, tinnitus.

Patients with renal impairment can develop signs of overdose even on low doses of oral baclofen (see section 4.2 and section 4.4).

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.

***Management*:**

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.

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antispastic with spinal site attack, ATC code: M03B X01

Mechanism of action:

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 beta 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_{max}, C_{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, β-(p-chlorophenyl)-4-hydroxybutyric acid, which is pharmacologically inactive.

Elimination:

The plasma elimination half-life of baclofen averages 3 to 4 hours.

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 (aged 65 years or above)*:**
The pharmacokinetics of baclofen in elderly 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_{max} of 62.8±28.7 nanogram/ml, and T_{max} in the range of 0.95-2h have been reported. Mean plasma clearance (Cl) of 315.9ml/h/kg; volume of distribution (Vd) of 2.58L/kg; and half-life (T1/2) of 5.10h 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 haemodialysis 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 haemodialysis 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

Sorbitol, liquid (non-crystallising)
Hydroxyethyl cellulose
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Raspberry flavour
Propylene glycol
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Once opened, use within 28 days.

Dilution: Baclofen oral liquid may be diluted with Purified Water and stored at room temperature for up to 28 days.

6.5 Nature and contents of container

300ml amber glass (Type 3) bottle with a child resistant tamper evident polypropylene lid.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Ltd
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8 MARKETING AUTHORISATION NUMBER(S)

PL 20046/0012

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