Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lioresal 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg baclofen.
Each tablet also contains wheat starch.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Product imported from France and Spain:
Circular flat, beveled edge white tablet with the letters ‘CG’ on one surface and K and J on either side of a breakline on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lioresal is indicated for the relief of spasticity of voluntary muscle resulting from such disorders as: multiple sclerosis, other spinal lesions, e.g. syringomyelia, motor neurone disease, transverse myelitis.

Lioresal 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 Lioresal 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.

4.2 Posology and method of administration

Lioresal is given orally in either tablet or liquid form.

Lioresal should be taken with meals with a little liquid.

The daily dose should be given in divided doses, preferably 3 in adults and 4 in children.

Titration of the dosage is necessary to meet individual patients requirements while avoiding adverse effects or interference with function depending on the activity of voluntary muscles e.g. bladder, central posture support.

Adults:
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 requirement 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.

In such cases 100mg - 120mg may occasionally be necessary. Small frequent dosage may prove better in some cases than larger spaced doses. Also some patient benefit from the use of Lioresal 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 Lioresal should be taken.

***Elderly*:**
Elderly patients may be more susceptible to side effects, particularly in the early stages of introducing Lioresal. 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.

Children:
A dosage range of 0.75-2mg/kg body weight should be used. In children over 10 years of age a maximum daily dosage of 2.5mgkg body weight may be given. Treatment is usually started with 2.5mg given four times daily. The dosage should be cautiously raised at about 3 day intervals, until it becomes sufficient for the child's requirements... The recommended daily dosages for maintenance therapy are:

Children aged:	12 months - 2 years	10 - 20 mg
	2 years - 6 years	20 - 30 mg
	6 years – 10 years	30 - 60mg

Patients with impaired renal function:
In patients with impaired renal function or undergoing chronic haemodialysis, a particularly low dosage of Lioresal should be selected, i.e., approximately 5mg daily. Signs and symptoms of over dosage have been reported with doses above 5mg daily in this setting (section 4.9 Overdose).

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 should be adopted and patients kept under appropriate surveillance.

4.3 Contraindications

Hypersensitivity to baclofen, use in patients with pulmonary insufficiency

4.4 Special warnings and precautions for use

Porphyria, history of alcoholism, hypertension, psychotic disorders, schizophrenia depressive or manic disorders, confusional states or Parkinson's disease may be exacerbated by treatment with Lioresal. Patients suffering from these conditions should therefore be treated cautiously and kept under close surveillance.

Lioresal should only be used with great caution in patients with a history of convulsions since exacerbation of such condition may occur.

Lioresal should be used with extreme care in patients already receiving antihypertensive therapy, (see Interactions).

Lioresal should be used with caution in patients with or with a history of peptic ulcers, cerebrovascular disease or from respiratory, hepatic or renal impairment. Under treatment with Lioresal, neurogenic disturbances affecting emptying of the bladder may show improvement. In patients with pre-exidting sphincter hypertonia acute retention of urine may occur, the drug should be used with caution in such cases.

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

Since in rare instances elevated SGOT, alkaline phosphate and glucose levels in serum have been recorded, appropriate laboratory tests should be performed in patients with liver disease or diabetes mellitus in order to ensure that no drug-induced changes in these underlying diseases have occurred.

4.5 Interaction with other medicinal products and other forms of interaction

Where Lioresal is taken concomitantly with other drugs acting on the CN with synthetic opiates or with alcohol, increased sedation may occur.

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.

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.

During concurrent treatment with tricyclic antidepressants, the effect of Lioresal may be potentiated, resulting in pronounced muscular hypotonia.

Since concomitant treatment with Lioresal and anti-hypertensives is likely to increase the fall in blood pressure, the dosage of antihypertensive medication should be adjusted accordingly. Hypotension has been reported in one patient receiving morphine and intrathecal baclofen.

Drugs which may produce renal insufficiency, for example, ibuprofen may reduce baclofen excretion leading to toxic effects. In patients with Parkinson's disease receiving treatment with Lioresal and levodopa plus carbidopa, there have been reports of mental confusion, hallucinations and agitation.

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

Aggravation of hyperkinetic symptoms may possibly occur in patients taking lithium.

4.6 Fertility, pregnancy and lactation

During pregnancy, Lioresal should be employed if its use is considered essential by the physician. The benefits of the treatment for the mother must be carefully weighed against the possible risks for the child. Baclofen crosses the placental barrier.

In mothers taking Lioresal 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

The patient’s reactions may be adversely affected by Lioresal induced sedation or decreased alertness, patients should therefore exercise due caution. Operating equipment or machinery may be hazardous.

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 Lioresal 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.

Frequency estimates: frequent > 10%, occasional > 1% - 10%, rare > 0.001% - 1%, isolated cases < 0.001%.

Central nervous system:
Frequent: particularly at the start of treatment, daytime sedation, drowsiness, and nausea may frequently occur.
Occasional: respiratory depression, light-headedness, lassitude, exhaustion, mental confusion, dizziness, headache, insomnia, euphoria, depression, muscular weakness, ataxia, tremor, hallucinations, nightmares, myalgia, nystagmus, dry mouth.
Rare: paraesthesia, dysarthria. Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients.

***Sense organs*:**
Occasional: accommodation disorders, visual disturbance.
Rare: dysgeusia.

Gastro-intestinal tract:
Frequent: nausea
Occasionally, mild gastro-intestinal disturbances constipation, diarrhoea, retching and vomiting
Rare: abdominal pain

Cardiovascular system:
Occasional: hypotension, diminished cardiovascular functions.

Urogenital system:
Occasional: frequency of micturition, enuresis, dysuria.
Rare: urinary retention, impotence.

***Liver*:**
Rare: disorders of hepatic function.

***Skin*:**
Occasional: hyperhidrosis, skin rash

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).

4.9 Overdose

Symptoms: Prominent features are signs of central nervous depression: drowsiness, impairment of consciousness, respiratory depression, and coma. Also liable to occur are: confusion, hallucinations, agitation, accommodation disorders, absent pupillary reflex; generalised muscular hypotonia, myoclonia, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension, bradycardia; hypothermia; nausea, vomiting, diarrhoea, hypersalivation; elevated LDH, SGOT and AP values.

A deterioration in the condition may occur if various substances or drugs acting on the central nervous system (for example, alcohol, diazepam, tricycle antidepressants) have been taken at the same time.

Treatment: No specific antidote is known.

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

After ingestion of a potentionally toxic amount, activated charcoal should be considered, especially during the early period after ingestion. Gastric decontamination 9e.g. vomiting, gastric lavage) should be considered in individual cases, especially in the early period (60 minutes) after ingestion of a potential life-threatening overdose. Comatose or convulsing patients should be intubated prior to the initiation of gastric decontamination.

Elimination of the drug from the gastro-intestinal tract (induction of vomiting, gastric lavage; comatose patients should be intubated prior to gastric lavage), administration of activated charcoal; if necessary, saline aperient; in respiratory depression, administration of artificial respiration, also measures in support of cardiovascular functions. Since the drug is excreted chiefly via the kidneys, generous quantities of fluid should be given, possibly together with a diuretic. In the event of convulsions, diazepam should be administered cautiously i.v.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Lioresal depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating the GABA beta-receptors. This stimulation in turn inhibits the release of the excitatory amino acids glutamate and aspartate. Neuromuscular transmission is unaffected by Lioresal.

Lioresal 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: Lioresal (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 (10-30 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%. In cerebrospinal fluid active substance concentrations are approximately 8.5 times lower than in plasma.

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

Elimination/excretion: The plasma elimination half-life of Lioresal averages 3-4 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.

Elderly: The pharmacokinetics of baclofen in elderly patients is virtually the same as in young subjects. The peak plasma concentrations of baclofen in elderly patients are slightly lower and occur later than in healthy young subjects but the AUCs are similar in the two groups.

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

Wheat starch
Colloidal anhydrous silica
Microcrystalline cellulose
Magnesium stearate
Povidone.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date for this product shall be the date on the blister strips and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
Do not store above 25°C.

6.5 Nature and contents of container

Blister packs of 30 or 50 tablets contained in an outer cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

PCO Manufacturing Limited
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Ashbourne
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8 MARKETING AUTHORISATION NUMBER

PPA 0465/054/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of 1st Authorisation : 13th March 1994

Date of Next Renewal: 13th March 2009

10 DATE OF REVISION OF THE TEXT

December 2011