SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Baclofen Thame 10mg/5ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral solution contains 10mg of Baclofen.

Excipients with known effect:
Each 5ml of oral solution contains 7mg methyl parahydroxybenzoate (E218), 1.925mg sorbitol (E420), 6.675mg propylene glycol (E1520) and 8.1mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution
Clear, pale yellow to yellow colour solution with raspberry odour
Sugar Free

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Baclofen 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,

Baclofen is also indicated in adults 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
Baclofen is given orally in either tablet or liquid form. These two formulations are bioequivalent. The liquid may be particularly suitable for children or those adults who

are unable to take tablets. Dosage titration can be more precisely managed with the liquid formulation.

Titration of dosage 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 Baclofen.

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).

Adults:
Treatment should be started with a dosage of 7.5 (15 mg) daily, preferably in 2 to 4 divided doses. Dose should be titrated upwards cautiously by 7.5 ml (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 mg or 10 mg) and to raise this dosage more gradually (*see Section 4.4 Special warnings and precautions* for use). The optimum dosage generally ranges from 15 to 40 ml (30 to 80 mg) daily.

Satisfactory control of symptoms is usually obtained with doses of up to 30 ml (60mg) daily, but a careful adjustment is often necessary to meet the requirements of each individual patient.

Maximum daily dose *(Adults)*
The dose may be increased slowly if required, but a maximum daily dose of more than 50 ml (100mg) is not advised unless the patient is in hospital under careful medical supervision. In such cases, 50 ml – 60 ml (100 mg-120 mg) may occasionally be necessary. The maximum daily dose of Baclofen oral solution should not exceed 100mg. 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.

<u>Special populations</u>
Once the maximum recommended dose has been reached, if the therapeutic effect is not apparent within 6-8 weeks a decision whether to continue with baclofen should be taken.

Elderly:
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 patients (below 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). Therefore, Baclofen tablets are not suitable for use in children with a body weight below 33kg. Baclofen oral solution may be used in 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 2mg/kg body weight. Baclofen tablets are not suitable for use in children below 33kg with a body weight.

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

Maximum daily dose
Paediatric patients (below 18 years)
The maximum daily dose should not exceed 2 mg/kg/day.

The maximum daily dose should not exceed 40 mg/day in children below 8 years old and 60 mg/day in children 8 years and older.

Renal Impairment
In patients with impaired renal function or undergoing chronic haemodialysis, a particularly low dosage of Baclofen should be selected i.e. approx. 2.5 ml (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 Special warnings and precautions for use and section 4.9 Overdose).

Hepatic impairment
No studies have been performed in patients with hepatic impairment receiving Baclofen therapy. Liver does not play a significant role in the metabolism of baclofen after oral administration of Baclofen (see section 5.2 Clinical Pharmacology). However, Baclofen has the potential of elevating liver enzymes. Baclofen should be prescribed with caution in patients with hepatic impairment. (see section 4.4 special warnings and precautions for use).

Geriatric patients (aged 65 years or above)
Since Unwanted effects are more likely to occur in elderly patients it is therefore recommended that a cautious dosage schedule be adopted and that the patient be kept under appropriate surveillance.
Patients with spastic states of cerebral origin
Since unwanted effects are more likely to occur in patients with spastic states of cerebral origin, it is recommended that a cautious dosage schedule be adopted in such cases and that the patient be kept under appropriate surveillance.

Method of administration

Baclofen should be taken orally during meals with a little liquid.
Baclofen should be taken using the provided oral syringe.

4.3 Contraindications

Hypersensitivity to baclofen or to any of the excipients

4.4 Special warnings and precautions for use

Psychiatric and nervous system disorders

Porphyria, history of alcoholism, hypertension, 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 should only be used with great caution in patients with a history of convulsions since exacerbation of such condition 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 Interactions).

Others

Baclofen should be used with caution in patients with a history of peptic ulcers cerebrovascular disease 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 posology and method of administration).

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 therapy.

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, somnolence hallucination) 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 renal impairment 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 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.

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.
Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Abrupt discontinuation:
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, hallucination, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and temporary aggravation of spasticity and hypertonia 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).

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.

Excipients warnings:
Methyl parahydroxybenzoate (E218): May cause allergic reactions (possibly delayed).
Sorbitol (E420): This medicinal product contains 1925mg sorbitol in each 5ml dose which is equivalent to 385mg/ml. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
Sodium: This medicinal product contains 8.1mg sodium per 5ml, equivalent to 0.41% of the WHO recommended maximum daily intake of 2g sodium for an adult.

Propylene glycol (E1520): This medicinal product contains 6.675mg propylene glycol in each 5ml dose which is equivalent to 1.335mg/ml. 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

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 combination 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
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 under Section 4.7 Effects on ability to drive and use machines).

The risk of respiratory depression is also increased. In addition, hypotension has been reported with concomitant use of morphine and intrathecal baclofen. Careful monitoring of respiratory and cardiovascular functions is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

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
During concomitant 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 and other drugs known to lower blood pressure
Since concomitant treatment with Baclofen and drugs that lower blood pressure is likely to increase the fall in blood pressure, the dosage of concomitant medication should be adjusted accordingly.

Agents reducing renal function
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 hypoglycaemic 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 foetuses of rats given approximately 13 times 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. Baclofen crosses the placental barrier. and should be used during pregnancy only if 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 oral baclofen.

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

Fertility
There are no data available on the effect of baclofen on fertility in humans. Baclofen did not impair male or female fertility in rats at dose levels not toxic to them.

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 be associated with adverse effects such as dizziness, sedation, somnolence and visual impairment (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.

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 posology and method of administration).

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.

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, < 1/10); uncommon (≥1/1,000, < 1/100); rare (≥1/10,000, <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: Encephalopathy, Sleep Apnoea syndrome*

Eyes disorders:
Common: Accommodation disorder, visual impairment.

Gastro-intestinal disorders:
Very common: Nausea.

Common: Gastro-intestinal disorder, constipation, diarrhoea, retching, vomiting.

Rare: Abdominal pain

Cardiac Disorders:
Common: Cardiac output decreased.

Not known: Bradycardia

Vascular disorders:
Common: Hypotension

Renal and urinary disorders:
Common: Pollakiuria, enuresis, dysuria.

Rare: Urinary retention

Reproductive system and breast disorders:
Rare: Erectile dysfunction

Not known: Sexual dysfunction

Hepatobiliary disorders:
Rare: Hepatic function abnormal.

Immune system disorders:
Not known: Hypersensitivity

Skin and subcutaneous tissue disorders:
Common: Hyperhidrosis, skin rash.

Not known: Urticaria, alopecia

General disorders and administration site conditions
Very rare: Hypothermia

Not known: Drug withdrawal syndrome, (see section 4.4 special warnings and precautions for use), swelling face and peripheral oedema (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 (≥ 100mg) 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 (ie. 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 ADR Reporting at www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

Symptoms:
Prominent features are signs of central nervous depression or encephalopathy: somnolence, depressed level of consciousness, respiratory depression, coma, tinnitus.

Also liable to occur are: confusion, hallucination, 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, tachycardia or cardiac arrhythmia, hypothermia, nausea, vomiting, diarrhoea, salivary hypersecretion, increased hepatic enzymes sleep apnea, rhabdomyolysis.

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 disturbances 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 Special warnings and precautions for use).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antispastic with spinal site of action, ATC code: M03B X01
Mechanism of action (MOA)

Baclofen is highly effective 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 $GABA_B$ receptors, this stimulation in turn inhibiting the release of the excitatory amino acids glutamate and aspartate. Neuromuscular transmission is unaffected by Baclofen.

Baclofen also exerts an antinociceptive effect. General wellbeing is often improved and sedation is less often a problem than with 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. 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. 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/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. 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 to12 years), C_{max} of 62.8 ± 28.7 nanogram/mL, and T_{max} in the range of 0.95-2 h have been reported. Mean plasma clearance (Cl) of 315.9 mL/h/kg; volume of distribution (V_d) 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

Reproductive toxicity

For information on reproductive toxicity, see Section 4.6 Fertility, pregnancy and lactation.

Oral baclofen was shown to not 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 mg/kg dose in adults. Baclofen given orally has been shown to increases 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

Methyl parahydroxybenzoate
Carmellose sodium
Liquid sorbitol (non-crystallising)
Raspberry flavor [contains propylene glycol (E1520)]
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months
Discard 90 days after first opening.

6.4 Special precautions for storage

Store below 25°C.
Store in the original packaging in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bottle: Type III amber glass bottle

Closure: Tamper evident, child resistant white plastic cap consists of polypropylene inner, polyethylene outer, expanded polyethylene (EPE) liner

Dosing device: 1ml oral syringe with 0.01ml graduation and 10ml syringe with 0.25ml graduation and a syringe adaptor

Pack size: 150ml

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Syri Pharma Limited t/a Thame Laboratories
Floor 0, 1 WML,
1 Windmill Lane,
Dublin 2, D02 F206

8. MARKETING AUTHORISATION NUMBER(S)

MA1296/02301

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