PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1 NAME OF MEDICINE
SPASIFEN 10 (Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg baclofen.
Sugar free.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White, round (7 mm), flat, uncoated tablets having a break line on one side and plain on the other side.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
SPASIFEN is indicated for spasticity of the skeletal muscle due to multiple sclerosis; spastic conditions occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown aetiology – e.g., spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.Spasticity of cerebral origin, e.g., following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

4.2 Posology and method of administration
Posology
Treatment should always be initiated with small, gradually increasing doses of SPASIFEN. The optimum daily dosage should be individually adapted to the patient's requirements in such a way that clonus, flexor and extensor spasms, and spasticity are reduced, but that a sufficient degree of muscle tone is maintained to permit active movements and adverse effects are avoided as far as possible.

In order to prevent excessive weakness and falling, SPASIFEN should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion or whenever spasticity is used to maintain function. It may be important to maintain some degree of muscle tone and allow occasional spasms to help support circulatory function.

The daily dosage should be given in at least 3 divided doses in adults, and 3 to 4 in children.

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

Abrupt discontinuation of the treatment should be avoided. 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 as a rule be started with a dosage of 5 mg three times daily, which for the purpose of cautious dose titration should subsequently be increased at three-day intervals by 5 mg three times daily until the requisite daily dosage has been attained,
i.e.: 5 mg three times daily for 3 days
10 mg three times daily for 3 days
15 mg three times daily for 3 days
20 mg three times daily for 3 days

In certain patients reacting sensitively to medicines, it may be advisable to begin with a lower daily dosage (5 mg or 10 mg) and to raise this dosage more gradually. The optimum dosage generally ranges from 30 mg to 80 mg daily.

Doses of more than 80 mg to 100 mg daily are not generally recommended although higher doses have been given to carefully supervised patients in hospital.

Special Populations
Paediatric population
Treatment should usually be started with a very low dose, e.g., 0,3 mg/kg a day, in divided doses. The dosage should be raised cautiously, at about 1-to-2-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 mass. In children over 10 years of age, however, a maximum daily dosage of 2,5 mg/kg body mass may be given.

Patients with impaired renal function
In patients with impaired renal function SPASIFEN should be given with caution and at lower doses. These patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy). Patients undergoing chronic haemodialysis, baclofen concentrations in plasma are elevated and therefore a particularly low dosage of SPASIFEN should be selected, i.e. approximately 5 mg daily.

Elderly patients
Since unwanted effects are more likely to occur in elderly patients or in patients with spastic states of cerebral origin, in such cases it is recommended that a very cautious dosage schedule be adopted, and that the patient be kept under appropriate surveillance.

Patients with impaired hepatic function
No studies have been performed in patients with hepatic impairment under SPASIFEN therapy. Liver does not play significant role in the metabolism of baclofen after oral administration of SPASIFEN. However, SPASIFEN has the potential of elevating liver enzymes. SPASIFEN should be prescribed with caution in patients with hepatic impairment.

Method of administration
Oral route.
SPASIFEN should be taken during meals with a little liquid.

4.3 Contraindications
SPASIFEN is contraindicated in:
- Hypersensitivity to baclofen or to any of the excipients listed in section 6.1.
- Porphyria.

4.4 Special warnings and precautions for use
Alcohol or central nervous system depressants
SPASIFEN may be associated with dizziness, sedation, somnolence, visual disturbances and impaired concentration which may impair the patient's reaction and may be aggravated by the simultaneous intake of alcohol or central nervous system depressant agents.

Psychiatric and nervous system disorders
Psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson's disease may be exacerbated by treatment with SPASIFEN. 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 medicine 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 dose escalation, drug-seeking behaviour, development of tolerance.

Epilepsy
SPASIFEN may also exacerbate epileptic manifestations but can be employed provided appropriate supervision and adequate anticonvulsive therapy are maintained. Seizures have occasionally been reported in connection with the discontinuation of baclofen or with over-dosage. Adequate anticonvulsive therapy should be continued, and the patient adequately monitored.

Antihypertensive therapy
SPASIFEN should be used with extreme care in patients already receiving antihypertensive therapy (see section 4.5).

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

Peptic ulcers
SPASIFEN should be used with caution in patients suffering from, or with a history of peptic ulcers.

Elderly and patients with spasticity of cerebral origin
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 be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk (see section 4.2). 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 5 mg 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 SPASIFEN to medicines that can significantly affect renal function. Renal function should be closely monitored and SPASIFEN 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 SPASIFEN neurogenic disturbances affecting emptying of the bladder may show an improvement. Inpatients with pre-existing sphincter hypertonia, acute retention of urine may occur; the medicine should be used with caution in such cases.

Laboratory tests
In 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 medicine 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 state, delirium, hallucination, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and temporary aggravation of spasticity have been reported with abrupt withdrawal of SPASIFEN, especially after long term medication.

Medicine withdrawal reactions including postnatal convulsions in neonates have been reported after intrauterine exposure to oral SPASIFEN. As a precautionary measure, SPASIFEN administration to neonates with gradual tapering can help in controlling and preventing withdrawal reactions (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 patients
There is very limited clinical data on the use of SPASIFEN in children under the age of one year. Use in this patient population should be based on the medical practitioner's consideration of individual benefit and risk of therapy.

Posture and balance
SPASIFEN 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 medicines 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 SPASIFEN and levodopa/carbidopa.

Medicines causing Central Nervous System (CNS) depression
Increased sedation may occur when SPASIFEN is taken concomitantly with other medicines 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 concomitant treatment with tricyclic antidepressants, the effect of SPASIFEN 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 SPASIFEN is used concomitantly with lithium.

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

Medicines reducing renal function
Medicines 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
Safety during pregnancy has not been established. Baclofen crosses the placental barrier and should not be used during pregnancy.

Foetal/neonatal adverse reactions
Medicine withdrawal reactions including postnatal convulsions in neonates have been reported after intra-uterine exposure to oral baclofen (see section 4.4).

Breastfeeding
In mothers taking SPASIFEN 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
There are no data available on the effect of baclofen on fertility in humans.

4.7 Effects on ability to drive and use machines
SPASIFEN may be associated with adverse effects such as 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. SPASIFEN can have a major influence on the ability to drive and use machines.

4.8 Undesirable effects
Unwanted effects occur mainly at the start of treatment (e.g., sedation, somnolence, drowsiness, fatigue and nausea), if the dose is raised too rapidly, if large doses are employed, or if the patient is an elderly person. 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 attacks of convulsions may possibly occur, particularly in epileptic patients.Certain patients have shown increased muscle spasticity as a paradoxical reaction to the medication.

Many of the adverse CNS and genitourinary effects reported are known to occur in association with the underlying conditions being treated.An undesirable degree of muscular hypotonia - making it more difficult for patients to walk or fend for themselves - may occur and may be relieved by re-adjusting the dosage (i.e., by reducing the doses given during the day and possibly increasing the evening dose).

a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Nervous system disorders	*Frequent*	Sedation, somnolence, drowsiness, fatigue and nausea, dryness of the mouth, respiratory depression, light-headedness, lassitude, exhaustion, mental confusion, dizziness, headache, insomnia, euphoria, depressive states, myalgia, muscular weakness, ataxia, tremor, nystagmus, hallucinations, nightmares.
	Less frequent	Paraesthesia, dysarthria, dysgeusia, hypothermia.
	Frequency unknown	Sleep apnoea syndrome.
Eye disorders	*Less frequent*	Visual impairment, accommodation disorder.
Ear and labyrinth disorders	*Less frequent*	Tinnitus.
Cardiac disorders	*Frequent*	Cardiac output decreased.
	Frequency unknown	Bradycardia.
Vascular disorders	*Frequent*	Hypotension.
Gastrointestinal disorders	*Frequent*	Nausea, gastrointestinal disorder, constipation, diarrhoea, retching, vomiting.
	Less frequent	Abdominal pain.
Hepatobiliary disorders	*Less frequent*	Abnormal hepatic function.
Skin and subcutaneous tissue disorders	*Frequent*	Rash, hyperhidrosis.
	Frequency unknown	Urticaria.
Renal and urinary disorders	*Frequent*	Pollakiuria, enuresis, dysuria.
	Less frequent	Urinary retention.
Reproductive system and breast disorders	*Less frequent*	Erectile dysfunction.
General disorders and administration site conditions	*Less frequent*	Hypothermia.
	Frequency unknown	Medicine withdrawal syndrome.
Investigations	*Frequency unknown*	Blood glucose increased.

b. Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
Signs and symptoms
Prominent features are signs of central nervous depression: drowsiness, impairment of consciousness, respiratory depression, 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 or hypertension, bradycardia or tachycardia; hypothermia; nausea, vomiting, diarrhoea, hypersalivation; elevated LDH, AST, and AP values, sleep apnoea, rhabdomyolysis. A deterioration in the condition may occur if various medicines 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.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A 2.10 Centrally active muscle relaxants
Pharmacotherapeutic group: Antispastic with spinal site attack
ATC code: M03B X01

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

Baclofen displays pronounced muscle-relaxing activity. It acts on the motor system of the spinal cord in a distinctive segmental fashion. Baclofen inhibits both mono- and polysynaptic reflex transmission and reduces the activity of the gamma motor neurones. It does not, however influence neuromuscular impulse transmission in the motor endplates. In neurological diseases associated with skeletal muscle spasm baclofen reduces spasticity. It also markedly relieves the associated pain, rigidity, automatism and clonus, with consequent improvement in the patient's mobility. Active and passive physiotherapy are thereby facilitated.

Baclofen stimulates gastric acid secretion.

5.2 Pharmacokinetic properties
Absorption
Baclofen is rapidly and completely absorbed from the gastrointestinal 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. 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, approximately 75 % of the dose is excreted via the kidneys with about 5 % of this amount as metabolites. The remainder of the dose, including 5 % as metabolites, is excreted in the faeces.

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 2,5 mg baclofen 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 (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 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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Microcrystalline cellulose
Pregelatinized starch (1500)
Maize starch
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 25 ºC.
Store in the original package.
KEEP OUT OF SIGHT AND REACH OF CHILDREN.

6.5 Nature and contents of container
Available in PVC/PVdC and aluminium blister packs of 28, 30, 56, 60, 84, 90 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION
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