PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

FENOZYD 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg baclofen.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white coloured, round shaped, biconvex, uncoated tablets with bevelled edges, a score line on one side and a “10” debossed on the other side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 FENOZYD. 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, FENOZYD 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.

FENOZYD should be taken during meals with a little liquid.
The daily dosage should be given in at least 3 divided doses in adults, and 3 to 4 in children.

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

Children

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.

If no benefit is apparent within 6 to 8 weeks of achieving the maximum dosage, a decision whether to continue with FENOZYD 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.
Abrupt discontinuation of the treatment should be avoided (see section 4.4).

Renal impairment

In patients with impaired renal function or undergoing chronic haemodialysis, a particularly low dosage of FENOZYD should be selected, i.e. approximately 5 mg daily. Signs and symptoms of overdosage have been reported with doses above 5 mg daily in this setting.

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.

Hepatic impairment

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to baclofen or to any of the excipients (see section 6.1).
- Porphyria.

4.4 Special warnings and precautions for use

Psychiatric and nervous system disorders

Porphyria (see section 4.3), history of alcoholism, hypertension, psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson's disease may be exacerbated by treatment with FENOZYD. 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, as in FENOZYD. 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 treatment with FENOZYD. 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, as in FENOZYD. 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

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

Others

FENOZYD should be used with extreme care in patients already receiving antihypertensive therapy (see section 4.5). FENOZYD should be used with caution in patients suffering from, or with a history of peptic ulcers as well as in those suffering from cerebrovascular accidents or from respiratory or hepatic impairment. Patients who suffered from stroke tolerate FENOZYD poorly. Since unwanted effects are more likely to occur, a cautious dosage schedule should be adopted in elderly patients and patients with spasticity of cerebral origin (see section 4.2).

Renal impairment

Signs of overdose have been observed in patients with renal impairment taking baclofen at doses of more than 5 mg per day.

FENOZYD should be used with caution in patients with renal impairment (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, as in FENOZYD, at doses of more than 5 mg per day. Patients with impaired renal function should be closely monitored for prompt diagnosis of early symptoms of toxicity.

Cases of baclofen toxicity have been reported in patients with acute renal failure (see section 4.9). Particular caution is required when combining FENOZYD with medicines or medicinal products that can significantly affect renal function. Renal function should be closely monitored, and FENOZYD 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 FENOZYD, neurogenic disturbances affecting emptying of the bladder may show an improvement. In patients with pre-existing sphincter hypertonia, acute retention of urine may occur; FENOZYD should be used with caution in such patients.

Abrupt withdrawal

Treatment with FENOZYD 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, hallucinations, psychotic disorder, mania or paranoia, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and temporary aggravation of spasticity as a rebound phenomenon have been reported with abrupt withdrawal of baclofen, as in FENOZYD, especially after long-term medication.

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

Laboratory tests

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

Posture and balance

FENOZYD should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion.

Paediatric patients

There is very limited clinical data on the use of FENOZYD 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.

4.5 Interaction with other medicines and other forms of interaction

Medicines causing central nervous system (CNS) depression

Increased sedation may occur when FENOZYD 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 muscles weakness.

Pretreatment with FENOZYD may prolong the duration of fentanyl-induced anaesthesia.

Lithium

Concomitant use of oral baclofen and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should be exercised when FENOZYD is used concomitantly with lithium.

Antidepressants

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

Antihypertensives

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

Medicines reducing renal function

Medicines or medicinal products that can significantly affect renal function may reduce FENOZYD excretion leading to toxic effects (see section 4.4).

Levodopa/dopa decarboxylase (DDC) inhibitor (carbidopa)

In patients with Parkinson's disease receiving treatment with baclofen and levodopa (alone or in combination with DDC inhibitor, carbidopa), there have been reports of mental confusion, hallucinations, nausea and agitation. Worsening of the symptoms of Parkinsonism have also been reported. Hence, caution should be exercised during concomitant administration of FENOZYD and levodopa/carbidopa.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. FENOZYD crosses the placental barrier and should not be used during pregnancy.

Fetal/neonatal adverse reactions

Drug withdrawal syndrome, including postnatal convulsions in neonates, has also been reported after intrauterine exposure to oral baclofen, as in FENOZYD (see section 4.4).

Breastfeeding

In mothers taking FENOZYD 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

FENOZYD may be associated with adverse effects such as dizziness, sedation, somnolence, visual impairment and impaired concentration (see section 4.8) which may impair the patient's reactions. Patients experiencing these adverse reactions should be advised to refrain from driving or operating machinery.

4.8 Undesirable effects

Adverse effects (e.g. sedation, somnolence, fatigue and nausea) 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 FENOZYD.

Should nausea persist following a reduction in dosage, it is recommended that FENOZYD be ingested with food or a milk beverage. Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients. In patients with a 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.

Certain patients have shown increased spasticity as a paradoxical reaction to FENOZYD.

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

Many of the adverse CNS and genitourinary effects reported are known to occur in association with the underlying conditions being treated.

Tabulated list of adverse events

System organ class	Frequency	Adverse reaction
Nervous system disorders	*Frequent*	sedation, somnolence, dry mouth, respiratory depression, light-headedness, fatigue, confusional state, dizziness, headache, insomnia, depression, euphoric mood, myalgia, muscular weakness, ataxia, tremor, nystagmus, hallucinations, nightmare, mental confusion, exhaustion and depressive states
	Less frequent	paraesthesia, dysarthria, dysgeusia
	Frequency unknown	sleep apnoea syndrome (Cases of central sleep apnoea syndrome have been observed with baclofen, as in FENOZYD, at high doses [≥ 100 mg] in patients who are alcohol dependent.)
Eye disorders	*Frequent*	accommodation disorder, visual impairment
	Less frequent	tinnitus
Cardiac disorders	*Frequent*	decreased cardiac output
	Frequency unknown	bradycardia
Vascular disorders	*Frequent*	hypotension
Gastrointestinal disorders	*Frequent*	nausea, gastrointestinal disorder, retching, vomiting, constipation, diarrhoea
	Less frequent	abdominal pain

Hepatobiliary disorders	*Less frequent*	abnormal hepatic function
Skin and subcutaneous tissue disorders	*Frequent*	hyperhidrosis, rash
	Frequency unknown	urticaria
Renal and urinary disorders	*Frequent*	dysuria, pollakiuria, enuresis
	Less frequent	urinary retention
Reproductive system and breast disorders	*Less frequent*	erectile dysfunction
General disorders and administration site conditions	*Less frequent*	hypothermia
	Frequency unknown	drug withdrawal syndrome (see section 4.4) (Drug withdrawal syndrome including postnatal convulsions in neonates has also been reported after intrauterine exposure to oral baclofen, as in FENOZYD.)
Investigations	*Frequency unknown*	increased blood glucose

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of FENOZYD is important. It allows continued monitoring of the benefit/risk balance of FENOZYD. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

Prominent features that are signs of central nervous depression: somnolence, depressed level of consciousness, respiratory depression, coma. Also liable to occur are: confusion, hallucinations,

agitation, accommodation disorder, impaired/absent pupillary reflex, generalised muscular hypotonia, myoclonus, hyporeflexia or areflexia, convulsions, abnormal electroencephalogram (burst suppression pattern and triphasic waves), peripheral vasodilation, hypotension or hypertension, bradycardia, tachycardia or cardiac dysrhythmia, hypothermia, nausea, vomiting, diarrhoea, salivary hypersecretion, increased hepatic enzymes lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (SGOT) and alkaline phosphatase (AP) values, rhabdomyolysis. Patients with renal impairment can develop signs of overdose even on low doses of FENOZYD (see sections 4.2 and 4.4).

A deterioration in the condition may occur if various substances or 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 disorders and respiratory or cardiovascular depression. Since the medicine is excreted mainly 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

Category and class: A 2.10 Centrally active muscle relaxants.

Pharmacotherapeutic group: Antispastic with spinal site of attack.

ATC code: M03B X01.

Baclofen is an antispastic medicine acting at the spinal level. It is a gamma-aminobutyric acid

(GABA) derivative, chemically unrelated to other antispastic medicines.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating the $GABA_B$ receptors.

This stimulation in turn inhibits 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 their 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 medicines.

Baclofen stimulates gastric acid secretion.

5.2 Pharmacokinetic properties

Absorption

Baclofen is rapidly and completely absorbed from the gastrointestinal tract. 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 ng/mL to 300 µg/mL. In cerebrospinal fluid active substance concentrations are approximately 8,5 times lower than in the plasma.

Biotransformation

Baclofen is metabolised only to 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 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 multidose 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 ng/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 ($T_{½}$) 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

Anhydrous calcium hydrogen phosphate

Magnesium stearate

Microcrystalline cellulose

Povidone

Pregelatinised starch

Sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Protect from light.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Clear transparent PVC/PVDC aluminium blister strips containing 10 tablets.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park, Building B, Ground Floor

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Centurion

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Tel: 012 748 6400

8. REGISTRATION NUMBER

57/2.10/0182

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

04 January 2025

10. DATE OF REVISION OF THE TEXT

Not applicable.