1.3.1.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Fampridine 10 mg Ascend Extended-release tablet

Fampridine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each extended release tablet contains 10 mg of fampridine.

Sugar-free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Extended-release tablet.

White to off white biconvex, oval shaped, bevelled edge, film coated tablets, debossed "D10" on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fampridine 10 mg Ascend is indicated for the improvement of walking in adult patients with multiple sclerosis (MS) with walking disability (Expanded Disability Status Scale [EDSS] 4-7).

4.2 Posology and method of administration

Treatment with **Fampridine 10 mg Ascend** is restricted to prescription and supervision by medical practitioners experienced in the management of MS.

Posology:

The recommended dose is one 10 mg tablet, twice daily, taken 12 hours apart (one tablet in the morning and one tablet in the evening).

Fampridine 10 mg Ascend should not be administered more frequently or at higher doses than recommended (see section 4.4).

The tablets should be taken without food (see section 5.2).

*Starting and evaluating **Fampridine 10 mg Ascend** treatment*

- Initial prescription should be limited to two to four weeks of therapy as clinical benefits should generally be identified within two to four weeks after starting **Fampridine 10 mg Ascend**.
- An assessment of walking ability, e.g. the Timed 25 Foot Walk (T25FW) or Twelve Item Multiple Sclerosis Walking Scale (MSWS-12), is recommended to evaluate improvement within two to four weeks. If no improvement is observed, **Fampridine 10 mg Ascend** should be discontinued.
- **Fampridine 10 mg Ascend** should be discontinued if benefit is not reported by patients.

*Re-evaluating **Fampridine 10 mg Ascend** treatment:*

If decline in walking ability is observed, medical practitioners should consider an interruption to treatment in order to reassess the benefits of **Fampridine 10 mg Ascend** (see above). The re-evaluation should include withdrawal of **Fampridine 10 mg Ascend** and performing an assessment of walking ability. **Fampridine 10 mg Ascend** should be discontinued if patients no longer receive walking benefit.

Missed dose:

The usual dosing regimen should always be followed. A double dose should not be taken if a dose is missed.

Special populations

Elderly:

Renal function should be checked in older people before starting treatment with **Fampridine 10 mg Ascend**. Monitoring renal function to detect any renal impairment is recommended in older people (see section 4.4).

Renal impairment:

Fampridine 10 mg Ascend is contraindicated in patients with mild, moderate, and severe renal impairment (creatinine clearances <80 ml/min) (see section 4.3).

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment.

Paediatric patients:

The safety and efficacy of **Fampridine 10 mg Ascend** in children under the age of 18 years have not been established. No data are available.

Method of administration:

Oral use.

The tablet must be swallowed whole. It must not be divided, crushed, dissolved, sucked, or chewed.

4.3 Contraindications

Fampridine 10 mg Ascend is contraindicated in:

- Patients with hypersensitivity to fampridine or to any of the excipients as listed in section 6.1.
- Concurrent treatment with other medicines containing fampridine (4-aminopyridine).
- Patients with prior history or current presentation of seizure.
- Patients with mild, moderate, or severe renal impairment (creatinine clearances < 80 ml/min).
- Concomitant use of **Fampridine 10 mg Ascend** with medicines that are inhibitors of Organic Cation Transporter 2 (OCT2) for example, cimetidine.

4.4 Special warnings and precautions for use

Seizure risk

Treatment with fampridine increases seizure risk (see section 4.8).

This medicine should be administered with caution in the presence of any factors which may lower seizure threshold.

Fampridine should be discontinued in patients who experience a seizure while on treatment.

Renal impairment

Fampridine is primarily excreted unchanged by the kidneys. Patients with renal impairment have higher plasma concentrations which are associated with increased adverse reactions, in particular neurological effects. Determining renal function before treatment and its regular monitoring during treatment is recommended in all patients (particularly in the elderly in whom renal function might be reduced). Creatinine clearance can be estimated using the Cockroft-Gault formula.

Caution is required when **Fampridine 10 mg Ascend** is prescribed in patients with mild renal impairment or in patients using medicines that are substrates of OCT2 for example, carvedilol, propranolol, and metformin.

Hypersensitivity reactions

Serious hypersensitivity reactions (including anaphylactic reaction) have been reported, the majority of these cases occurred within the first week of treatment. Particular attention should be given to patients with a previous history of allergic reactions. If an anaphylactic or other serious allergic reaction occurs, this medicine should be discontinued and not restarted.

Other warnings and precautions

Fampridine should be administered with caution to patients with cardiovascular symptoms of rhythm and sinoatrial or atrioventricular conduction cardiac disorders (these effects are seen in overdose). There is limited safety information in these patients.

The increased incidence of dizziness and balance disorder seen with fampridine may result in an increased risk of falls. Therefore, patients should use walking aids as needed.

Low white blood cell counts were observed in patients treated with fampridine as in **Fampridine 10 mg Ascend**. Infections were observed and increased infection rate and impairment of the immune response cannot be excluded.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Concurrent treatment with other medicines containing fampridine (4- aminopyridine) is contraindicated (see section 4.3).

Fampridine is eliminated mainly via the kidneys with active renal secretion accounting for about 60 % (see section 5.2). OCT2 is the transporter responsible for the active secretion of fampridine. Thus, the concomitant use of fampridine with medicines that are inhibitors of OCT2 for example, cimetidine is contraindicated (see section 4.3) and concomitant use of fampridine with medicines that are substrates of OCT2 for example, carvedilol, propranolol, and metformin is cautioned (see section 4.4.)

Interferon: fampridine has been administered concomitantly with interferon-beta and no pharmacokinetic medicine interactions were observed.

Baclofen: fampridine has been administered concomitantly with baclofen and no pharmacokinetic medicine interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There is limited amount of data from the use of fampridine in pregnant women.

As a precautionary measure it is preferable to avoid the use of **Fampridine 10 mg Ascend** in pregnancy.

Breastfeeding:

It is unknown whether fampridine is excreted in human or animal milk. **Fampridine 10 mg Ascend** is not recommended during breastfeeding.

Fertility:

No effects on fertility were seen in animal studies.

4.7 Effects on ability to drive and use machines

Fampridine 10 mg Ascend has a moderate influence on the ability to drive and use machines (see section 4.8). **Fampridine 10 mg Ascend** can cause dizziness.

4.8 Undesirable effects

Summary of the safety profile:

Adverse reactions identified are mostly neurological and include seizure,
insomnia, anxiety, balance disorder, dizziness, paraesthesia, tremor, headache, and asthenia. This is consistent with fampridine's pharmacological activity. The highest incidence of adverse reactions is urinary tract infection.

Tabulated list of adverse reactions:

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Frequent, less frequent, frequency unknown.

System organ class	***Frequent***	***Less Frequent***
Infections and infestations	Urinary tract infection[1], influenza[1], nasopharyngitis[1], viral infection[1]	
Immune system disorders		Anaphylaxis, Angioedema, Hypersensitivity
Psychiatric disorders	Insomnia, anxiety	
Nervous system disorders	Dizziness, headache, balance disorder, paraesthesia, tremor	Seizure[2], exacerbation of trigeminal neuralgia
Cardiac disorders	Palpitations	Tachycardia
Vascular disorders		Hypotension[3]
Respiratory, thoracic and mediastinal disorders	Dyspnoea, pharyngo-laryngeal pain	Nasopharyngitis
Gastrointestinal system disorders	Nausea, vomiting, constipation, dyspepsia	
Skin and subcutaneous tissue disorders		Rash, urticaria
Musculoskeletal and connective tissue disorders	Back pain	
General disorders and administrative site conditions	Asthenia	Chest discomfort[3]

1. See section 4.4.
2. See section 4.3 and 4.4
3. These symptoms were observed in the context of hypersensitivity.

Description of selected adverse reactions:

Seizure:

In post-marketing experience, there have been reports of seizure, the frequency is not known (cannot be estimated from the available data). For further information on seizure risk, please refer to sections 4.3 and 4.4.

Hypersensitivity:

In post-marketing experience, there have been reports of hypersensitivity reactions (including anaphylaxis) which have occurred with one or more of the following: dyspnoea, chest discomfort, hypotension, angioedema, rash and urticaria. For further information on hypersensitivity reactions, please refer to sections 4.3 and 4.4.

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. Healthcare professionals are asked 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. Alternatively all adverse events can be reported to Ascend Laboratories via the e-mail: pharmacist.rsa@alkem.com.

4.9 Overdose

Symptoms:

Acute symptoms of overdose with fampridine were consistent with central nervous system excitation and included confusion, tremulousness, diaphoresis, seizure, and amnesia.

Central nervous system adverse reactions at high doses of 4-aminopyridine include dizziness, confusion, seizures, status epilepticus, involuntary and choreoathetoid movements. Other side effects at high doses include cases of cardiac dysrhythmias (for example, supraventricular tachycardia and bradycardia) and ventricular tachycardia as a consequence of potential QT prolongation. Reports of hypertension have also been received.

Treatment:

Patients who overdose should be provided supportive care. Repeated seizure activity should be treated with benzodiazepine, phenytoin, or other appropriate acute antiseizure therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 1.6 Other central nervous system stimulant.

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX07.

Fampridine is a potassium channel blocker. By blocking potassium channels, fampridine reduces the leakage of ionic current through these channels, thereby prolonging repolarization and thus enhancing action potential formation in demyelinated axons and neurological function. Presumably, by enhancing action potential formation, more impulses might be conducted in the central nervous system.

5.2 Pharmacokinetic properties

Absorption:

Orally administered fampridine is rapidly and completely absorbed from the gastrointestinal tract. Fampridine has a narrow therapeutic index. Absolute bioavailability of fampridine prolonged-release tablets has not been assessed, but relative bioavailability (as compared to an aqueous oral solution) is 95 %. The fampridine prolonged-release tablet has a delay in the absorption of fampridine manifested by slower rise to a lower peak concentration, without any effect on the extent of absorption.

When fampridine tablets are taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of fampridine is approximately 2 – 7 % (10 mg dose). The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. However, C_{max} increases by 15 – 23 %. Since there is a clear relationship between C_{max} and dose related adverse reactions, it is recommended to take fampridine without food (see section 4.2).

Distribution:

Fampridine is a lipid-soluble medicine which readily crosses the blood-brain barrier. Fampridine is largely unbound to plasma proteins (bound fraction varied between 3 - 7 % in human plasma). Fampridine has a volume of distribution of approximately 2,6 l/kg. Fampridine is not a substrate for P-glycoprotein.

Biotransformation:

Fampridine is metabolised in humans by oxidation to 3-hydroxy-4-aminopyridine and further conjugated to the 3-hydroxy-4-aminopyridine sulfate. No pharmacological activity was found for the fampridine metabolites against selected potassium channels *in vitro*.

The 3-hydroxylation of fampridine to 3-hydroxy-4-aminopyridine by human liver microsomes appeared to be catalysed by Cytochrome P450 2E1 (CYP2E1).

There was evidence of direct inhibition of CYP2E1 by fampridine at 30 µM (approximately 12 % inhibition) which is approximately 100 times the average plasma fampridine concentration measured for the 10 mg tablet.

Treatment of cultured human hepatocytes with fampridine had little or no effect on induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities.

Elimination:

The major route of elimination for fampridine is renal excretion, with approximately 90 % of the dose recovered in urine as parent medicine within 24 hours. Renal clearance (CLR 370 ml/min)

is substantially greater than glomerular filtration rate due to combined glomerular filtration and active excretion by the renal OCT2 transporter. Faecal excretion accounts for less than 1 % of the administered dose.

Fampridine is characterized by linear (dose-proportional) pharmacokinetics with a terminal elimination half-life of approximately 6 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase proportionately with dose. There is no evidence of clinically relevant accumulation of fampridine taken at the recommended dose in patients with full renal function. In patients with renal impairment, accumulation occurs relative to the degree of impairment.

Special populations

Elderly

Clinical studies of fampridine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Fampridine is primarily excreted unchanged by the kidneys, and with creatinine clearance known to decrease with age, monitoring of renal function in older patients should be considered (see section 4.2).

Paediatric population

No data are available.

Patients with renal impairment

Fampridine is eliminated primarily by the kidneys as unchanged medicine and therefore renal function should be checked in patients where renal function might be compromised. Patients with mild renal impairment can be expected to have approximately 1,7 to 1,9 times the fampridine concentrations achieved by patients with normal renal function. Fampridine must not be administered to patients with mild, moderate, and severe renal impairment (see section 4.3).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Hydroxypropyl methylcellulose (Hypromellose)

Magnesium stearate

Microcrystalline cellulose

Film coating (Opadry Y-1-7000H White):

Hypromellose (E464)
Macrogol (E1521)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.
Keep bottle tightly closed.
Keep blisters in cartons until required for use.

6.5 Nature and contents of container

Fampridine 10 mg Ascend is packed in white, high-density polyethylene (HDPE) bottles with child resistant cap containing 60 tablets, as well as in Aluminium-aluminium blister strips of 10 tablets each.
The strips are packed in pack sizes of 10 (1x 10's), 30 (3 x 10's) and 60 (6 x 10's) tablets in a printed cardboard carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Ascend Laboratories (Pty) Ltd.
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Corner Rivonia Road and 5th Street
Sandton, Gauteng, 2196

8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT