SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Eytazox 250 mg Prolonged-Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg acetazolamide.

Excipients with known effect:
Also contains sunset yellow FCF.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

Hard gelatin capsule with a clear body and orange cap, printed with 'AM250' in black ink', containing round orange pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glaucoma

4.2 Posology and method of administration

Posology
Adults: One or two 250mg capsules a day.

Children: This product is not intended for administration to children.

Use in Elderly Patients: Eytazox should be used with particular caution in elderly patients or those with potential obstruction in the urinary tract or with disorders rendering their electrolyte balance precarious or with liver dysfunction.

Use in Patients with Renal Impairment: In patients with moderate to severe renal impairment, the dose should not exceed 250mg per day or the dosage interval should be increased to every 12 hours.

Method of administration

For oral administration.

Capsules should be swallowed whole. Do not chew or crush.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Eytazox is contra-indicated in situations in which sodium and/or potassium blood levels are depressed, in cases of marked renal impairment and liver disease or dysfunction, suprarenal gland failure, and hyperchloraemic acidosis. Eytazox should not be used in patients with liver disease or impairment of liver function including cirrhosis as this may increase the risk of hepatic encephalopathy. Eytazox is contra-indicated in patients with hypokalemia and hyponatraemia.

Long-term administration of Eytazox is contra-indicated in patients with chronic non-congestive angle-closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intra-ocular pressure.

Eytazox should not be used in patients hypersensitive to sulfonamides or other sulfonamide derivatives including acetazolamide or any excipients in the formulation.

4.4 Special warnings and precautions for use

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomized placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for acetazolamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

When Eytazox Prolonged-Release Capsules is prescribed for long-term therapy, special precautions are advisable. The patient should be cautioned to report any unusual skin rash. Prior to initiating therapy and at regular intervals during therapy, monitoring of blood cell counts and electrolyte levels are recommended. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including

acetazolamide, such as Steven-Johnson syndrome and toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias and anaphylaxis. A precipitous drop in formed blood cell elements or the appearance of toxic skin manifestations should call for immediate cessation of Eytazox therapy.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, acetazolamide should be discontinued and any subsequent administration of acetazolamide contraindicated.

Hypersensitivity reactions may recur if a sulfonamide or sulfonamide derivative is re-administered, irrespective of the route of administration. If signs of hypersensitivity reactions or other serious reactions occur, acetazolamide must be discontinued.

Acetazolamide treatment may cause electrolyte imbalances, including hyponatraemia and transient hypokalaemia, as well as metabolic acidosis. Therefore, periodic monitoring of serum electrolytes is recommended. Particular caution is recommended in patients with conditions that are associated with, or predispose to, electrolyte and acid/base imbalances, such as patients with impaired renal function (including elderly patients), pulmonary obstruction, emphysema, patients with diabetes mellitus and patients with impaired alveolar ventilation. Severe metabolic acidosis has been reported in patients with normal renal function during treatment with acetazolamide and salicylates.

Both increases and decreases in blood glucose levels have been described in patients treated with acetazolamide. This should be taken into consideration in patients with impaired glucose tolerance or diabetes mellitus.

In patients with a past history of renal calculi, benefit should be balanced against the risks of precipitating further calculi.

Acetazolomide Prolonged-Release Capsules contains sunset yellow FCF (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Eytazox is a sulfonamide derivative. Sulfonamides may potentiate the effects of folic acid antagonists. Possible potentiation of the effects of folic acid antagonists, hypoglycaemics and oral anti-coagulants may occur. Concurrent administration of acetazolamide and acetylsalicylic acid may result in severe toxicity and increase central nervous system toxicity. Severe metabolic acidosis has been reported in patients with normal renal function during treatment with acetazolamide and salicylates. Adjustment of dose may be required when Eytazox is given with cardiac glycosides or hypertensive agents.

When given concomitantly, Eytazox Prolonged-Release Capsules modifies the metabolism of phenytoin leading to increased serum levels of phenytoin. Severe osteomalacia has been noted in a few patients taking acetazolamide in combination

with other anticonvulsants. There have been isolated reports of reduced primidone and increased carbamazepine serum levels with concurrent administration of acetazolamide.

Concomitant use with other carbonic anhydrase inhibitors is not advisable because of possible additive effects.

Both increases and decreases in blood glucose levels have been described in patients with acetazolamide. This should be taken into consideration in patients treated with anti-diabetic agents.

By increasing the pH of renal tubular urine, acetazolamide reduces the urinary excretion of amphetamine and quinidine and so may enhance the magnitude and duration of the effect of amphetamines and enhance the effect of quinidine.

By increasing the pH of urine, acetazolamide may prevent the urinary excretion of methenamine compounds.

Acetazolamide increases lithium excretion due to impaired re-absorption of lithium in the proximal tubule. The effect of lithium carbonate may be decreased.

The use of concurrent sodium bicarbonate therapy enhances the risk of renal calculus formation in patients taking acetazolamide.

When given concomitantly, acetazolamide may elevate cyclosporine blood levels. Caution is advised when administrating acetazolamide in patients receiving cyclosporine.

Interference with Laboratory and other Diagnostic Tests:

Acetazolamide may produce an increased level of crystals in the urine.

Acetazolamide interferes with the HPLC method of assay for theophylline. Interference with the theophylline assay by acetazolamide depends on the solvent used in the extraction; acetazolamide may not interfere with other assay methods for theophylline.

4.6 Fertility, pregnancy and lactation

Pregnancy: Acetazolamide has been reported to be teratogenic (defects of the limbs) and embryotoxic in rats, mice, hamsters and rabbits at oral or parenteral doses in excess of ten times those recommended in human beings. Although there is no evidence of these effects in human beings, there are no adequate and well-controlled

studies in pregnant women. Therefore, Eytazox Prolonged-Release Capsules should not be used in pregnancy, especially during the first trimester.

Breastfeeding: Acetazolamide has been detected in low levels in the milk of lactating women who have taken acetazolamide. Although it is unlikely that this will lead to any harmful effects in the infant, extreme caution should be exercised when Eytazox Prolonged-Release Capsules is administered to lactating women.

4.7 Effects on ability to drive and use machines

Some adverse reactions to acetazolamide, such as drowsiness, fatigue and myopia, may impair the ability to drive and operate machinery.

4.8 Undesirable effects

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).

Blood and lymphatic system disorders
Not known: thrombocytopenic purpura, leucopenia, pancytopenia, agranulocytosis, bone marrow depression, aplastic anaemia

Immune system disorders
Not known: anaphylactic reaction

Metabolism and nutrition disorders
Not known: decreased appetite, metabolic acidosis, electrolyte imbalance including hypokalaemia and hyponatraemia, hyperglycaemia, hypoglycaemia

Psychiatric disorders
Not known: confusion, depression, agitation

Nervous system disorders
Not known: hypoaesthesia, somnolence, dysgeusia, convulsion, paraesthesia (particularly tingling of the extremities), headache, dizziness, ataxia, flaccid paralysis

Eye disorders
Not known: myopia transient

Ear and labyrinth disorders
Not known: hearing impaired, tinnitus

Vascular disorders
Not known: flushing

Gastrointestinal disorders

Not known: nausea, vomiting, diarrhoea, melaena

Hepatobiliary disorders
Not known: hepatic impairment, fulminant hepatic necrosis, jaundice cholestatic, hepatitis

Skin and subcutaneous tissue disorders
Not known: urticaria, photosensitivity, rash (including erythema multiforme), Stevens Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP)

Musculoskeletal and connective tissue disorders
Not known: osteomalacia (especially with long-term phenytoin therapy)

Renal and urinary disorders
Not known: polyuria, haematuria, glycosuria, crystalluria, nephrolithiasis (especially during long-term therapy), renal failure

General disorders and administration site conditions
Not known: fever, fatigue

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 the Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

No specific antidote.

Treatment should be symptomatic and supportive.

Electrolyte imbalance, development of an acidotic state and central nervous effects might be expected to occur. Serum electrolyte levels, (particularly potassium) and blood pH should be monitored.

Supportive measures are required to restore electrolyte and pH balance. The acidotic state can usually be corrected by the administration of bicarbonate.

Despite its high intra-erythrocytic distribution and plasma protein binding properties, acetazolamide is dialyzable. This may be particularly important in the management of acetazolamide overdosage when complicated by the presence of renal failure.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Carbonic Anhydrase Inhibitors, ATC code S01E C01.

Acetazolamide is a potent inhibitor of the enzyme carbonic anhydrase; the enzyme that catalyses the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In the eye, this inhibitory action of acetazolamide decreases the secretion of the aqueous humor and results in a drop of intraocular pressure and is thus used to treat glaucoma.

5.2 Pharmacokinetic properties

Eytazox 250 mg Prolonged-Release Capsules is a sustained release formulation designed to obtain a smooth and continuous clinical response. Acetazolamide is readily absorbed after oral administration and binds tightly to plasma proteins as well as to the enzyme carbonic anhydrase. The drug begins to accumulate in tissues in which this enzyme is present notably red blood cells and the renal cortex. It is also bound to plasma proteins.

Peak plasma levels of the drug are reached 1-3 hours after oral administration with whole blood levels reaching peak concentrations approximately one hour later. Plasma levels decay more rapidly than red blood cell or whole blood levels with the elimination frequently being biphasic. The first phase having a half-life in 2 hours and the second phase in 13 hours. This terminal phase half-life corresponds to the leakage from red blood cells.

Acetazolamide is completely cleared by the renal route with the measured unbound renal clearance being some 5-6 times greater than creatinine clearance. Overall, clearance is dependent also on plasma protein binding.

5.3 Preclinical safety data

Nothing of note to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Coated Pellets:

Hypromellose

Microcrystalline cellulose

Purified talc

Colloidal anhydrous silica

Ethylcellulose

Light liquid paraffin

Opaspray orange [hydroxypropylcellulose, titanium dioxide (E171), talc & sunset yellow FCF (E110)]

Capsule Shell:

Gelatin

Titanium dioxide (E171)

Iron oxide yellow (E172)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC foiled aluminium blister.

Pack of 30 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Auden Mckenzie (Pharma Division) Ltd
Whiddon Valley
Barnstaple
North Devon
EX32 8NS
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 17507/0139

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/06/2013

10 DATE OF REVISION OF THE TEXT

04/01/2018