Uramox®

1. Name of the medicinal product

URAMOX®

2. Qualitative and quantitative composition

Each tablet contains 250 mg acetazolamide.

Excipients with known effect:

This medicine contains lactose and sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

White, round tablet, one side engraved with "T53". Other side cross scored.

4. Clinical particulars

4.1. Therapeutic indications

Uramox tablets are for oral administration.

Uramox is an enzyme inhibitor which acts specifically on carbonic anhydrase. It is indicated for:

1. Adjunctive treatment of drug induced edema and edema due to congestive heart failure.
2. Chronic simple (open angle) glaucoma, secondary glaucoma and pre operatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.
3. Acute mountain sickness.

4.2. Posology and method of administration

Congestive Heart Failure: For diuresis in congestive heart failure, the starting dose is usually 250 to 375 mg once daily in the morning. If, after an initial response, the patient fails to continue to lose edema fluid, do not increase the dose but allow for kidney recovery by skipping medication for a day. Acetazolamide tablets yield best diuretic results when given on alternate days, or for two days alternating with a day of rest.

Failures in therapy may be due to overdosage or too frequent dosage. The use of acetazolamide does not eliminate the need for other therapy such as digitalis, bed rest and salt restriction.

Drug Induced Edema: Recommended dosage is 250 to 375 mg of acetazolamide once a day for one or two days, alternating with a day of rest.

Glaucoma: Acetazolamide should be used as an adjunct to the usual therapy. The dosage employed in the treatment of chronic simple (open-angle) glaucoma ranges from 250 mg to 1 g of acetazolamide per 24 hours,

usually in divided doses for amounts over 250 mg. It has usually been found that a dosage in excess of 1 g per 24 hours does not produce an increased effect. In all cases the dosage should be adjusted with careful individual attention both to symptomatology and ocular tension. Continuous supervision by a physician is advisable.
In treatment of secondary glaucoma and in the postoperative treatment of some cases of acute congestive (close-angle) glaucoma, the preferred dosage is 250 mg every four hours, although some cases have responded to 250 mg twice daily on short-term therapy. In some acute cases, it may be more satisfactory to administer an initial dose of 500 mg followed by 125 or 250 mg every four hours depending on the individual case.

A complementary effect has been noted when acetazolamide has been used in conjunction with miotics or mydriatics as the case demanded.

Acute Mountain Sickness: Dosage is 500 mg to 1,000 mg daily, in divided doses. In circumstances of rapid ascent such as in rescue or military operations, the higher dose level of 1,000 mg is recommended. It is preferable to initiate dosing 24 to 48 hours before ascent and to continue for 48 hours while at high altitude, or longer as necessary to control symptoms.

The change from other medication to Uramox should be gradual.

Elderly: Uramox should only 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.

4.3. Contraindications

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

Acetazolamide is contra-indicated in situations in which sodium and/or potassium blood levels are depressed, in cases of marked kidney and liver disease or dysfunction, suprarenal gland failure, and hyperchloremic acidosis. Uramox should not be used in patients with hepatic cirrhosis as this may increase the risk of hepatic encephalopathy.

Long-term administration of Uramox 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 intraocular pressure.

Uramox should not be used in patients hypersensitive to sulphonamides.
Uramox should not be used in pregnancy.

4.4. Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised 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.
Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia.

Increasing the dose often results in a decrease in diuresis. Under certain circumstances, however, very large doses have been given in conjunction with other diuretics in order to secure diuresis in complete refractory failure.

When Uramox is prescribed for long-term therapy, special precautions are advisable. The patient should be cautioned to report any unusual skin rash. Periodic blood cell counts and electrolyte levels are recommended. Fatalities have occurred, although rarely, due to severe reactions to sulphonamides. A precipitous drop in formed blood cell elements or the appearance of toxic skin manifestations should call for immediate cessation of Uramox therapy.

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, Uramox may aggravate acidosis and should be used with caution.

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

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

Cases of choroidal effusion/detachment have been reported after the use of acetazolamide. Symptoms include acute onset of decreased visual acuity or ocular pain and can occur within hours after initiation of acetazolamide treatment. If choroidal effusion/detachment is suspected, acetazolamide should be discontinued as rapidly as possible.

This medicine contains lactose and sodium.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dose,

that is to say essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

Uramox is a sulphonamide derivative. Sulphonamides 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 aspirin may result in severe acidosis and increase central nervous system toxicity. Adjustment of dose may be required when Uramox is given with cardiac glycosides or hypertensive agents.

When given concomitantly, acetazolamide 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.

Because of possible additive effects, concomitant use with other carbonic anhydrase inhibitors is not advisable.

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

Ciclosporin: acetazolamide may elevate ciclosporin levels.

Methenamine: acetazolamide may prevent the urinary antiseptic effect of methenamine.

Lithium: acetazolamide increases lithium excretion and the blood lithium levels may be decreased.

Sodium bicarbonate: acetazolamide and sodium bicarbonate used concurrently increases the risk of renal calculus formation.

4.6. Pregnancy, lactation and fertility

Pregnancy

Acetazolamide has been reported to be teratogenic 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, Uramox should not be used in pregnancy, especially during the first trimester.

Breast-feeding

Uramox has been detected in low levels in the milk of lactating women who have taken Uramox. Although it is unlikely that this will lead to any harmful

effects in the infant, extreme caution should be exercised when Uramox is administered to lactating women.

Fertility

Not available

4.7. Effects on ability to drive and use machines

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia. Less commonly, fatigue, dizziness and ataxia have been reported. Disorientation has been observed in a few patients with oedema due to hepatic cirrhosis. Such cases should be under close supervision. Transient myopia has been reported.

These conditions invariably subside upon diminution or discontinuance of the medication.

4.8. Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention:

Not known: frequency cannot be estimated from the available data

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Not known	Thrombocytopenia, leukopenia, aplastic anaemia, bone marrow depression, pancytopenia, agranulocytosis****
Metabolism and nutrition disorder	Not known	Metabolic acidosis, electrolyte imbalance* and thirst**
Psychiatric disorders	Not known	Depression, irritability, reduced libido, occasional instances of confusion
Nervous system disorders	Not known	Paraesthesia, particularly a “tingling” feeling in the extremities, dizziness, headache, occasional instances of drowsiness, convulsions, flaccid paralysis
Eye disorders	Not known	Transient myopia*** choroidal effusion,

		choroidal detachment
Ear and labyrinth disorders	Not known	Impaired hearing and tinnitus
Gastrointestinal disorders	Not known	Melaena, taste disturbance, nausea, vomiting, diarrhoea
Hepatobiliary disorders	Not known	Fulminant hepatic necrosis****, hepatitis or cholestatic jaundice
Skin and subcutaneous tissue disorders	Not known	Urticaria, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)****, thrombocytic purpura, photosensitivity, acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Not known	Haematuria, crystalluria****, renal and ureteral colic****, renal lesions, renal failure, calculus formation****, glycosuria, polyuria
General disorders and administration site conditions	Not known	Fever****, fatigue, anaphylaxis****, flushing
Investigations	Not known	Abnormal liver function

* During long-term therapy, metabolic acidosis and electrolyte imbalance may occasionally occur. This can usually be corrected by the administration of bicarbonate.

**Adverse reactions during short-term therapy are usually non-serious.

***This condition invariably subsides upon diminution or withdrawal of the medication.

****Acetazolamide is a sulphonamide derivative and therefore some side-effects similar to those caused by sulphonamides have occasionally been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk

balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9. Overdose

No specific antidote. Supportive measures with correction of electrolyte and fluid balance. Force fluids.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Carbonic anhydrase inhibitors.
ATC Code: S01EC01

Acetazolamide is an inhibitor of carbonic anhydrase. By inhibiting the reaction catalysed by this enzyme in the renal tubules, acetazolamide increases the excretion of bicarbonate and of cations, chiefly sodium and potassium, and so promotes alkaline diuresis.

Continuous administration of acetazolamide is associated with metabolic acidosis and resultant loss of diuretic activity. Therefore, the effectiveness of Uramox in diuresis diminishes with continuous use.

By inhibiting carbonic anhydrase in the eye, acetazolamide decreases intra-ocular pressure and is therefore useful in the treatment of glaucoma.

5.2 Pharmacokinetic properties

Absorption
Acetazolamide is fairly rapidly absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 2 hours after administration by mouth.

Distribution
It has been estimated to have a plasma half-life of about 4 hours. It is tightly bound to carbonic anhydrase and accumulates in tissues containing this enzyme, particularly red blood cells and the renal cortex. It is also bound to plasma proteins.

Elimination
It is excreted unchanged in the urine; renal clearance being enhanced in alkaline urine.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate, corn starch, talc, gelatin, glycerin, sodium starch glycolate, magnesium stearate

6.2 Incompatibilities

None.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after opening: 8 months.

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

HDPE plastic bottle, with a child-proof PP cap.
Each package contains 30 tablets.

6.6 Special precautions for disposal and other handling

None.

7. Marketing authorisation holder and manufacturer

Taro Pharmaceutical Industries Ltd.,
14 Hakitor St., Haifa Bay 2624761

8. Marketing authorisation number

01694.21225

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