SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Xaqua 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg metolazone.

Excipients with known effect: Each tablet contains 53 mg lactose monohydrate. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Round, biplanar, white to off-white tablets with bevelled edges and single score-line, diameter: 7.0 mm

The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Xaqua is indicated for the treatment of

- oedema related to kidney diseases, including the nephrotic syndrome and states of impaired renal function
- oedema related to congestive heart failure

Xaqua is also indicated for the treatment of mild and moderate hypertension, alone or in combination with other antihypertensive medicines of a different class.

4.2 Posology and method of administration

Important note: Xaqua tablets bioavailability may be different from other metolazone preparations (see section 5.2). Therefore, the recommended doses (expressed in mg) can differ from other metolazone products. A dose adjustment may be necessary and individualised titration based on patient's response and tolerability is advised if switching from Xaqua tablets to another metolazone product, or vice versa.

Posology

Adults

Treatment of Oedema

Metolazone should generally be administered once daily

The tablet should always be taken at the same time in relation to food.

The following dosages should serve as guidelines:

Oedema related to congestive heart failure and kidney disease: 2.5-5 mg/day.

The therapy should be initiated with a dose of 2.5 mg/day and the dose must be adjusted according to the individual reaction of the patient. Once the desired therapeutic effect has been achieved, it may be advisable to reduce the maintenance dose if possible

Hypertension

Mild and moderate hypertension: 2.5mg-5mg/day

The recommended initial dose in mild and moderate hypertension is 2.5 mg/day, and the dose must be adjusted according to the individual reaction of the patient. Once the desired therapeutic effect has been achieved, it may be advisable to reduce the maintenance dose.

Renal impairment

Metolazone should be used with caution in patients with severe impaired renal function. If azotemia and oliguria deteriorate during treatment of patients with severe renal disease, metolazone should be discontinued. (see section 4.3 and 4.4).

Hepatic impairment

Metolazone should be used with caution in patients with severe impaired hepatic function (see section 4.3 and 4.4).

Patient with electrolyte disturbances

Metolazone should be used with caution in patients with preexisting electrolyte disturbances. Careful monitoring of the fluid and electrolyte balance is required (see section 4.3 and 4.4).

Elderly

Metolazone should be used with caution in elderly patients.

Paediatric population

The safety and efficacy of Xaqua in children aged under 18 years has not yet been established.

No data are available.

4.3 Contraindications

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

Anuria.

Hepatic coma or precomatose conditions.

Severe disturbances of the electrolyte balance.

4.4 Special warnings and precautions for use

Renal impairment

Metolazone should be used with caution in patients with severe renal impairment. Renal function should be regularly monitored during thiazide therapy.

Hepatic impairment

In severe hepatic impairment, hypokalaemia caused by diuretics can precipitate encephalopathy.

Electrolyte imbalance

Fluid and electrolyte balance should be carefully monitored during treatment with Xaqua, especially if the drug is used concurrently with medicines also affecting electrolyte balance such as other diuretics (risk of hypokalaemia), corticosteroids, ACE-inhibitors, angiotensin-II-antagonists and aldosterone antagonists.

All patients receiving metolazone should have serum electrolytes measured at regular intervals and be observed for clinical signs of fluid and/or electrolyte imbalance; namely, hypokalaemia, hyponatraemia, hypochloraemic alkalosis. Serum and urine electrolyte measurements are particularly important when the patient is vomiting excessively, has severe diarrhoea, or is receiving parenteral fluids.

Warning signs of electrolyte imbalance irrespective of cause are: dryness of mouth; thirst; weakness; lethargy; drowsiness; restlessness; muscle pains or cramps; muscular fatigue; hypotension; oliguria; tachycardia; and gastrointestinal disturbances such as nausea and vomiting.

The risk of hypokalaemia is increased when larger metolazone doses are used, when diuresis is rapid, when severe liver disease is present, when corticosteroids are given concomitantly, when oral intake is inadequate or when excess potassium is being lost extrarenally such as with vomiting or diarrhoea. Hypokalaemia should be corrected by the addition of potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes to the regimen. Hyperkalaemia may also occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended.

Hyponatraemia may occur at any time during long term therapy and, on rare occasions, may be life threatening. Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Primary adrenal insufficiency

Diuretics should be avoided for the treatment of hypertension if the patient has primary adrenal insufficiency, known as Addison's disease.

Concurrent treatment with other drugs

Special care is advised, especially during initial therapy, when metolazone is used with other antihypertensive drugs of a different class to avoid hypotension (see section 4.5). Orthostatic hypotension associated with diuretics may be enhanced by alcohol, barbiturates and opioids.

Particular caution is also required when metolazone is used in combination with ACE-inhibitors, angiotensin-II-antagonists, aldosterone-antagonists and/or NSAIDs since there have been cases of renal failure, mostly due to enhanced dehydration. Dose adjustments may be required

Concomitant use of metolazone and furosemide may lead to unusually large or prolonged losses of fluid and electrolytes.

Gout attacks

Azotemia and hyperuricemia may occur during the administration of thiazide therapy. Infrequently, attacks of gout have been reported in persons with a history of gout

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains

uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Lupus erythematosus

Sulfonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus.

Porphyria

Although not reported with Xaqua, thiazides have been associated with acute attacks of porphyria. Caution is required when Xaqua is used in porphyric patients.

Glucose metabolism

Xaqua has only a slight effect on the glucose metabolism. Xaqua may increase the blood sugar level, which in patients with diabetes mellitus or latent diabetes mellitus may lead to hyperglycaemia and glycosuria. Therefore, blood sugar levels should be checked on a regular basis. In diabetic patients the antidiabetic treatment may have to be adjusted.

Laboratory values

Although not reported with metolazone, thiazides and thiazide-like diuretics have been reported to adversely effect the plasma lipid profile by increasing VLDL or LDL-cholesterol and triglycerides. The clinical relevance of these observations is unclear.

Excipients

This product contains lactose. 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 tablet that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed with Xaqua.

Loop Diuretics (e.g. furosemide)

Concurrent use of furosemide and presumably also of other loop diuretics may potentiate the effect of metolazone considerably and lead to serious disturbances of the electrolyte balance (see section 4.4).

Curariform Drugs

Diuretic-induced hypokalemia may enhance neuromuscular blocking effects of curariform drugs (such as tubocurarine). The most serious effect would be respiratory depression which could proceed to apnea. Accordingly, it is advisable to discontinue metolazone tablets three days before elective surgery.

Cyclosporine

Concurrent administration of metolazone and cyclosporine may lead to an increase in serum creatinine.

Alcohol, barbiturates and narcotics

Alcohol, barbiturates and narcotics may potentiate orthostatic hypotension which may occur during treatment with metolazone.

Antidiabetic medicinal products (oral agents and insulins)

Dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4).

Corticosteroids and ACTH

Corticosteroids and ACTH may increase the risk of hypokalaemia and increase salt and water retention.

Cardiac Glycosides

Hypokalaemia may increase the risk of digitalis toxicity with higher risk of severe arrhythmias. In case of concurrent administration with digitalis drugs the dosage may need to be adjusted (see section 4.4.).

Antiarrhythmic Drugs (e.g. Sotalol*)*

Hypokalaemia associated with thiazide therapy may increase the risk of sotalol-induced arrhythmia (syncope, prolonged QT interval).

Non-steroidal anti-inflammatory drugs (NSAIDs)

The administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics. As with other diuretics, metolazone may

increase the risk of nephrotoxicity of NSAIDs and lead to deterioration of renal function.

Sympathomimetics

May decrease the antihypertensive effect of metolazone. Metolazone may decrease arterial responsiveness to

norepinephrine, but this effect is not sufficient to preclude effectiveness of the pressor agent for therapeutic use

Antigout medicinal products

Dosage adjustments of antigout medicinal products may be necessary as thiazide diuretics may raise the level of serum uric acid (see section 4.4). Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

Calcium salts

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Lithium

Concurrent use of lithium and thiazides may reduce lithium clearance leading to intoxication.

Other antihypertensive drugs

Concomitant administration of Xaqua and other antihypertensive drugs may result in hypotension. Particular caution is required in the initial phase. Dosage adjustments of other antihypertensives may be necessary.

Cross-reactivity with other drugs

Cross reactions may occur in patients who are allergic to sulfonamides or thiazides.

Anticoagulants

Metolazone, as well as other thiazide-like diuretics, may affect the hypoprothrombinemic response to anticoagulants; dosage adjustments may be necessary.

Methenamine

Efficacy may be decreased due to urinary alkalizing effect of metolazone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Thiazide diuretics and related diuretics may pass over to the foetus and cause electrolyte imbalance. Cases of neonatal thrombocytopenia have been reported. Therefore, metolazone must not be administered during the last trimester of pregnancy unless absolutely necessary, and then with the lowest recommended dose.

Breast-feeding

Metolazone passes over to the breast milk in such an amount that there is a risk for the baby child even at therapeutic doses. Inhibition of lactation has been observed in treatment with diuretics.

4.7 Effects on ability to drive and use machines

Metolazone may cause adverse reactions affecting the ability to drive a vehicle and/or to operate machines, such as dizziness and fatigue.

4.8 Undesirable effects

Within each System Organ Class, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: 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); not known (cannot be estimated from the available data).

System organ class	
Blood and lymphatic system disorders	
Uncommon:	Leukopenia
Rare:	Aplastic or hypoplastic anemia, agranulocytosis, thrombocytopenia
Immune system disorders	
Rare:	Allergic reactions, including anaphylactic reactions
Metabolism and nutrition disorders	
Common:	Hypokalemia, hyponatremia, hypomagnesemia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, azotemia, glycosuria, increased serum urea (BUN) and serum creatinine
Rare:	Hypercalcemia, hypophosphatemia
Psychiatric disorders	
Rare:	Psychotic depression, confusion
Nervous system disorders	
Common:	Headache, dizziness, fatigue
Rare:	Neuropathy, vertigo, paresthesia, lethargy, drowsiness, weakness, restlessness (sometimes resulting in insomnia), apathy, seizures, hepatic encephalopathy
Eye disorders	
Rare	Transient blurred vision

Cardiac disorders	
Rare	Tachycardia, chest pain, palpitation
Vascular disorders	
Common:	Hypotension, orthostatic hypotension
Rare:	Syncope, dehydration, hemoconcentration, venous thrombosis
Gastrointestinal disorders	
Common:	Nausea, vomiting, constipation, diarrhoea
Rare:	Abdominal pain, anorexia, abdominal bloating
Hepatobiliary disorders	
Rare:	Hepatitis, intrahepatic cholestasis, pancreatitis
Skin and subcutaneous tissue disorders	
Uncommon:	Exanthema incl. urticaria, vasculitis
Rare:	Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), purpura, dermatitis (photosensitivity)
Musculoskeletal and connective tissue disorders	
Common:	Muscle pain, muscle cramps
Uncommon:	Joint pain, gout
Renal and urinary disorders	
Rare:	Renal insufficiency , oliguria
Reproductive system and breast disorders	
Rare	Erectile disfunction
General disorders and administration site conditions	
Rare:	Chills
Investigations	
Rare:	Increased LDL cholesterol, increased trigylcerides

Description of selected adverse reactions:

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

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

4.9 Overdose

Symptoms: Overdosing may lead to dehydration and electrolyte disturbances (primarily hyponatremia, but also loss of potassium and magnesium), and as a consequence the patient may experience thirst, nausea, vomiting, disorientation, somnolence, headache, muscle cramps, arterial hypotension, and in severe cases dysrhythmia (hypokalemia).

Treatment: Within the first hour of ingestion the absorption may be reduced by administration of medicinal charcoal (1 g/kg body weight). Thereafter priority should be given to establish adequate hydration and re- establishment of the electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain, ATC code: C03BA08

Mechanism of action

Metolazone obstructs the re-absorption of sodium in the ascending branch of the loop of Henle and in the proximal tubules, which leads to excretion of approximately equivalent amounts of sodium and chloride.

At the optimal therapeutic dosage metolazone leads to approximately the same diuretic activity as diuretic of the thiazide-type. However, it may also stimulate the diuresis in patients with a very low glomerular filtration rate (less than 20 ml/min).

The diuresis starts within the first hour after administration and will continue for 12-24 hours depending on the dose. The maximum effect will be achieved after approximately 2 hours.

5.2 Pharmacokinetic properties

Comparative bioavailability studies have shown that the bioavailability of Xaqua may differ significantly (up to approximately 2-fold) from Metenix. Bioavailability has not been compared to any other metolazone products (see section 4.2). Therefore, once the appropriate dose has been identified for a patient with a certain product, this product cannot readily be exchanged with another product.

Absorption

Metolazone is rapidly absorbed in the digestive tract. The maximal plasma concentration is on average reached after 2 hours. The rate and extent of absorption are formulation dependent. The effect of concomitant food on the bioavailability of Xaqua has not been evaluated. In order, to minimise variability for the individual patient, the tablet should always be taken at the same time in relation to food (see section 4.2)

Distribution

The apparent volume of distribution is estimated approximately 113 litres; 95 % of the substance is bound to red blood cells and to plasma proteins. Metolazone crosses the placenta and passes into breast milk.

Metabolism and Elimination

Metabolism of metolazone appears to be minimal. Most of the absorbed drug is excreted in urine, mainly unchanged. The elimination half-life of metolazone is reported to be 8-10 hours. In case of impaired kidney function the excretion is delayed, as the clearance of metolazone is directly related to renal function (creatinine clearance).

5.3 Preclinical safety data

No data is available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters containing 20, 60 or 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Slough, Berkshire,

SL1 2BE,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 44696/0010

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10 DATE OF REVISION OF THE TEXT

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