Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Xaqua 5 mg Tablets

(metolazone)

PL 44696/0010

Renascience Pharma Limited

LAY SUMMARY

Xaqua 5 mg Tablets
(metolazone)

This is a summary of the Public Assessment Report (PAR) for Xaqua 5 mg Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Xaqua in this lay summary for ease of reading.

For practical information about using Xaqua, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Xaqua and what is it used for?
This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the UK for at least 10 years, with recognised efficacy and an acceptable level of safety.

Xaqua is used in the treatment of:
- fluid retention (oedema) related to the heart and kidneys by increasing the flow of urine.
- high blood pressure, taken alone or with other medication.

How does Xaqua work?
Xaqua contains the active substance metolazone, which is a diuretic.

How is Xaqua used?
The pharmaceutical form of this medicine is tablets and the route of administration is oral (taken by mouth).

The tablets have a score-line on one side and can be divided into equal halves. The patient should take the tablet with the same meal each day, e.g., breakfast.

Adults
Initially the dosage should be 2.5 mg per day (half a tablet). The patient's doctor may adjust the dosage to 5 mg per day (whole tablet) according to the patient's reaction, if necessary.

Oedema (fluid retention): 2.5-5 mg per day

Hypertension (high blood pressure): 2.5-5 mg per day.

Elderly
Xaqua should be used with caution in elderly patients.

Children
Xaqua in children aged under 18 years is not recommended.

The patient should not change the prescribed dosage on their own initiative. If the patient believes, they are not getting the adequate dosage, they should contact their doctor or pharmacist.

For further information on how Xaqua is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Xaqua have been shown in studies?
As the active substance metolazone has been in clinical use for over 10 years, data were provided in the form of literature references and two pharmacokinetic studies bridging to the literature to show that metolazone is a safe and efficacious treatment for fluid retention (oedema) related to the heart and kidneys and high blood pressure, taken alone or with other medication.

What are the possible side effects of Xaqua?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Xaqua approved?
It was concluded that the data provided from literature references and two supportive studies had shown that Xaqua is effective in the treatment of fluid retention (oedema) related to the heart and kidneys and in the treatment of high blood pressure, taken alone or with other medication. Furthermore, the well-established use of the active substance metolazone has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Xaqua?
A Risk Management Plan (RMP) has been developed to ensure that Xaqua is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Xaqua
A Marketing Authorisation for Xaqua was granted in the on 20 July 2021.

The full PAR for Xaqua follows this summary.

This summary was last updated in September 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Xaqua 5 mg Tablets (PL 44696/0010) could be approved.

The product is approved 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 5 mg tablets are also indicated for the treatment of mild and moderate hypertension, alone or in combination with other antihypertensive medicines of a different class.

The active substance, metolazone, is a diuretic. 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).

This application was approved under Regulation 54 of The Human Medicines Regulations 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application.

Metolazone was developed in the 1970s. Currently, it is available as tablets for oral administration in several countries. In the European Union, metolazone has been authorised for many decades and continuously marketed. The originator Metenix 5 mg tablets was also authorized in the UK until the product was withdrawn from the UK market in 2012.

No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references.

To support the application, the applicant submitted two pharmacokinetic studies (one comparative bioavailability study and one dose proportionality study) to bridge to the literature.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national Marketing Authorisation was granted in the United Kingdom (UK) on 20 July 2021.

II QUALITY ASPECTS

II.1 Introduction

This product contains 5 mg of metolazone in each tablet.

In addition to metolazone, this product also contain the excipients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and sodium stearyl fumarate.

The finished product is packaged in polyvinylchloride/polyvinylidene chloride/aluminium blisters, in pack sizes of 20, 60 and 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

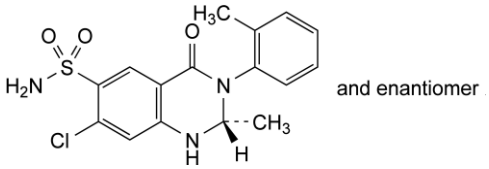
II.2 ACTIVE SUBSTANCE

rINN: Metolazone

Chemical Name: (2*RS*)-7-Chloro-2-methyl-3-(2-methylphenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide

Molecular Formula: $C_{16}H_{16}ClN_3O_3S$

Chemical Structure:



and enantiomer

Molecular Weight: 365.8 g/mol

Appearance: White or slightly yellowish, crystalline powder

Solubility: Very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethyl acetate, very slightly soluble in methylene chloride.

Metolazone is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a

suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final product.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the storage conditions 'This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
This application was submitted under Regulation 54 of The Human Medicines Regulations 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology
No new pharmacology data were submitted, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were submitted, and none were required for this application.

III.4 Toxicology
No new toxicology data were submitted, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of metolazone is well-known. With the exception of the data from two pharmacokinetic bridging studies (one comparative bioavailability study and one dose proportionality study), no new clinical studies were submitted and none were required, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

The studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics
The pharmacokinetic profile of metolazone is well known. The pharmacokinetic data presented are considered adequate to support this application. A summary of the pharmacokinetic data provided in the clinical overview is detailed below:

After oral administration, metolazone is almost completely absorbed from the gastrointestinal tract and reaches a peak in the plasma in about two hours. Food with high fat content has been reported to prolong the time needed for the drug to reach maximal plasma concentration (t_{max}). However, food does not seem to influence the parameters reflecting total exposure to the drug (C_{max}, AUC_{0-t} and $AUC0_{-\infty}$).

Metolazone is given as a single daily dose. In order to avoid possible variation in its bioavailability, intake should be at the same time in relation to food.

Despite extensive binding to plasma proteins and erythrocytes (95%), metolazone is highly distributed into the body (Vd/F=113 L). Metolazone also crosses the placenta and passes into breast milk**.**

Metolazone has a $t_{1/2}$ of 8-10 hours. About 70% of the absorbed dose is excreted into urine unchanged. It is estimated that less than 20% undergoes biotransformation to yield metabolites, deprived of any pharmacological or toxic action. A minimal proportion of the dose is also excreted with the faeces.

Pharmacokinetics in special patient groups

Patients with renal disease

Nephropathies hinder the absorption of metolazone, as well as the elimination of metolazone from the body. A study showed that absorption of metolazone was reduced to about 40% in some patients with renal disease, compared to 64% in healthy individuals. Also, in patients

with severe renal insufficiency, clearance was found to be only 20 ml/min, compared to 110 ml/min in normal subjects, despite the significant increase of the proportion of the removable free drug in the plasma (from 3% in normal subjects to 10% in severe renal disease).

The US National Kidney Foundation (NKF) has issued the following guidelines on metolazone treatment in chronic kidney disease: "Metolazone retains effectiveness at GFR (glomerular filtration rate) below 30 mL/min/1.73 m^2. Absorption should be taken into account when both a dose and frequency of dosing are being determined. Metolazone can be started at a dose of 2.5 to 5.0 mg daily and titrated to 10 mg to 20 mg daily, though these higher doses are seldom needed. Once metolazone has enhanced diuresis, it can typically be dosed as infrequently as two to three times a week because of its very long half-life. In terms of pharmacokinetics it should be pointed out that, at least partly metolazone is metabolised in the normal kidneys".

Patients with heart disease
According to the study mentioned above, patients with heart insufficiency had a markedly reduced absorption of metolazone, but elimination was found to be normal.

Patients with liver disease
In patients with ascites due to liver disease, metolazone has been used as a potent diuretic, with an initial daily dose of 5 mg, which may be escalated. In theory, several pharmacokinetic parameters might be different, mainly due to significant hemodynamic changes and also due to the fall of plasma albumins. There are no scientific reports on these issues.

Elderly patients
In old age, possible pathophysiological conditions of the kidneys, the liver and the heart, as well as a decrease of the albumin fraction of the plasma proteins, may influence pharmacokinetic and pharmacodynamic parameters related to metolazone. To date, these parameters have not been specifically addressed, despite the frequent use of metolazone in diseases of the elderly.

Paediatric patients
Metolazone has been used in paediatric patients, but there is no data concerning the pharmacokinetics of metolazone in children.

Bridging studies
In a well-established use application, a bridge needs to be established between the literature and the proposed product, In support of the application, the applicant submitted the following two (a comparative bioavailability study and a dose proportionality study) pharmacokinetic studies to bridge to the literature:

Study 1 Comparative bioavailability study (under fasting conditions)
This study was an open-label, randomised, two-period, two-treatment, two-sequence, single-dose, cross-over, bioequivalence study comparing the test product Metolazone 5 mg tablets versus the originator product Metenix 5 mg tablets in healthy adult, human, subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 5 mg tablet; 5 mg) of either treatment with approximately 200 ml of water. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 10 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Bioequivalence Results Summary			
Parameter	**Point Estimate**	**Lower limit**	**Upper limit**
$AUC_{0\text{-}inf}$	1.8134	1.6664	1.9735
$AUC_{0\text{-}last}$	1.9267	1.7739	2.0926
C_{max}	2.5417	2.3309	2.7716

Discussion and conclusion

The study initially aimed at assessing bioequivalence between the two products. However, the results demonstrated that C_{max} and $AUC_{0\text{-}inf}$ values for the test product were on average 2.54 times and 1.93 times higher, respectively, than those for the originator product. Hence the study findings suggest suprabioavailability of the test product compared to the originator product by a factor of approximately x 2.

On this basis, the applicant conducted a second study (a dose proportionality study) to determine the relative bioavailability and dose proportionality between 5 mg and 2.5 mg metolazone administered as one tablet (5 mg) and one-half of a tablet (2.5 mg), respectively, of the proposed product. The purpose of this second study, was to inform a modified posology, compared to the originator product, Metenix. Details of the dose proportionality study is provided below.

Study 2 - A dose proportionality study (under fasting conditions)

This study was an open-label, randomised, two-period, two-treatment, two-sequence, single-dose, cross-over, dose proportionality study comparing the test product Metolazone 5 mg tablets (x 1 tablet) versus the reference product Metolazone 2.5 mg (x 0.5 mg Metolazone 5 mg tablets) in healthy adult, male, human, subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose of either treatment dose (5 mg metolazone (1 tablet) or 2.5 mg metolazone (half a tablet)) with approximately 200 ml of water. Blood samples were taken pre-dose and up to 12 hours post dose, with a washout period of 7 days between the treatment periods.

Results and conclusion

The $AUC_{0\text{-}tlast}$ geometric mean values were 201.2 ng/ml·h and 102.8 ng/ml·h for one and one-half metolazone tablet, respectively. The geometric mean peak concentrations C_{max} were 33.72 ng/ml (5 mg metolazone) and 18.57 ng/ml (2.5 mg metolazone), respectively.

For test/reference (T/R) ratio the estimate (90% confidence interval) of the primary parameter $AUC_{0\text{-}tlast}$ was 1.9573 (1.7604, 2.1761). The estimate (90% confidence interval) of C_{max} was 1.8159 (1.5511, 2.1258). For T/(2 x R)-ratio of the parametric point estimate for $AUC_{0\text{-}tlast}$ was 97.9% and for C_{max} 90.8%. The 90% confidence limits of treatment effect are included within the 80%-125%-range for $AUC_{0\text{-}tlast}$ (88.0%-108.8%), whereas the lower confidence limit for C_{max} (77.6%-106.3%) was smaller than 80%.

Therefore, dose proportionality between one Metolazone 5 mg tablets and one-half

Metolazone 5 mg tablets was shown with respect to $AUC_{0\text{-}tlast}$ with respect to the criteria set for dose proportionality. Indirectly, the findings suggest that a 2.5 mg dose (half tablet) of the proposed preparation should result in a similar exposure as the originator 5 mg tablet.

However dose proportionality was not entirely demonstrated for C_{max} as the administration of 5 mg metolazone resulted in a slightly lower mean C_{max} value of 35.29 mg/ml, instead of calculated doubled value of 38.65 mg/ml based on the data obtained with 2.5 mg metolazone. As the upper limit of the bioequivalence range of 80-125% was not exceeded, a safety issue can be excluded. The potentially reduced efficacy has no implication as each patient is titrated individually starting with a 2.5 mg dose.

Conclusion of the bridging pharmacokinetic studies
Suprabioavailability of the applicant's product, Metolazone 5 mg tablets was observed, when the product was compared to Metenix 5 mg tablets (Aventis UK). Dose proportionality of one Metolazone 5 mg tablets and one-half Metolazone 5 mg tablets was shown with respect to $AUC_{0\text{-}tlast}$ but not for C_{max}.

The results of the pharmacokinetic studies can support the bridge to literature data.

IV.3 Pharmacodynamics

A summary of the main conclusions from the pharmacodynamic literature review is provided below.

Metolazone is a sulfonamide diuretic with a mechanism of action similar to the thiazides. Metolazone decreases sodium reabsorption along the renal tubules, however it acts mostly in the distal convoluted tubule. The enhancement of sodium excretion also results in an increased loss of chloride and water. During sustained maximal water diuresis, metolazone has been shown to produce a mean increment in sodium excretion of 3.5% of filtered load.

The shift in water and electrolytes results in hypovolaemia, keeping the peripheral vascular resistance low and normalising the cardiac output. The increased water excretion resolves oedema and lowers blood pressure. While metolazone is similar to thiazide diuretics in its mechanism of action, it does differ in its use in patients with impaired renal function.

Thiazide diuretics decrease glomerular flow rate (GFR) and are therefore less effective in patients with renal impairment. Because metolazone works primarily in the distal convoluted tubule, rather than the proximal convoluted tubule, it has little effect on GFR and can be used in patients with a reduced GFR. Metolazone stimulates diuresis in patients with a very low glomerular filtration rate (less than 30-40 mL/min/1.73 m^2).

Metolazone shares with thiazides, furosemide and acetazolamide, the presence of an unsubstituted sulfamoyl group ($-SO_2NH_2$), which is known to exert an inhibitory action on the enzyme human alpha-carbonic anhydrase (hCA). However, metolazone's action does not seem to lead to any overt alteration in urinary pH or bicarbonate excretion. On the other hand, metolazone induces a slight phosphaturia which is believed to be due to the inhibition of a sodium transport mechanism linked to that of phosphate in the proximal tubule. So, metolazone exerts its major effect in the cortical diluting segment, where it inhibits sodium re-absorption in the distal tubule, but also in the proximal tubule and the ascending branch of the loop of Henle. Potassium excretion is affected by metolazone to a lesser extent.

At the optimal therapeutic dosage metolazone leads to approximately the same diuretic activity as the thiazides. Diuresis starts within the first hour after administration, reaches a

maximum effect at two hours, and continues for 12 to 24 hours depending on the dose, and the formulation.

Metolazone qualifies as a strong diuretic which has been shown to be clinically effective in oedematous patients with renal disease, uncompensated heart failure and also in hypertensive patients, as monotherapy, or in combination with loop diuretics and spironolactone.

Drug interactions
Thiazide diuretics may interact with other medicinal products through various mechanisms related with pharmacodynamic as well as with pharmacokinetic factors. Considering the fact that metolazone and other diuretics are often used in patients with renal impairment, pharmacokinetic interactions become more complicated when the involved drugs are known to be excreted mainly into the urine.

Drugs affecting metolazone
Anticholinergics
These may increase metolazone absorption, by decreasing the motility of the gastrointestinal system.

Cholestyramine and colestipol
These bind metolazone and may reduce its gastrointestinal absorption.

Ethanol
Potentiation of the hypotensive effect due to vasodilation. Moreover, it may enhance diuresis, by inhibiting the secretion of antidiuretic hormone (ADH).

Opioids
Therapeutic doses of morphine-like opioids can produce peripheral vasodilation and reduced peripheral resistance. This may lead to a potentiation of the hypotensive effect of diuretics in general.

Nonsteroidal anti-inflammatory drugs
Salicylates and related anti-inflammatory drugs decrease sodium excretion and reduce the natriuretic and antihypertensive effects of thiazides.

Drugs affected by metolazone
Pharmacodynamic interactions
Metolazone influences the action of several other drugs, through various mechanisms of physiological antagonism or through synergy.

Anticoagulants (thrombin inhibitors)
Metolazone enhances the anti-thrombin action of the newer anticoagulants, because it also inhibits thrombin. It has been found to exert inhibitory activity almost similar to that of a well-known thrombin inhibitor argatroban.

Anticoagulants (coumarin derivatives)
It has been reported that metolazone may potentiate the effect of warfarin, however the mechanism of this interaction could not be clarified. However, the ability of metolazone to inhibit thrombin was reported in another study.

Antidiabetic agents
Metolazone may increase blood-glucose concentration, especially in prediabetic and diabetic patients. Thiazide diuretics impair glucose tolerance and deteriorate insulin resistance, but these effects are largely and possibly wholly reversible.

Antigout agents
Due to its similarities to thiazides, metolazone may increase blood uric acid levels.

Calcium salts
Metolazone increases distal Ca^{++} reabsorption, so concomitant administration of preparations of calcium salts may lead to extreme hypercalcaemia, as is the case with the thiazide diuretics in general.

Cyclosporine
Thiazides combined with cyclosporine have been reported to increase the risk of renal toxicity. In a patient with a renal transplant, the addition of a low dose of metolazone (2.5 mg/day) for two weeks caused an increase of serum creatinine concentrations from 193 to 449 mcmol/L. The discontinuation of metolazone resulted in a return of serum creatinine concentration to the previous value. The bioavailability of cyclosporine was not changed. The underlying mechanism of this interaction is not fully understood. It is not known whether it is related with an enhancement of cyclosporine metabolism due to the induction of CYP3A4 by metolazone. Monitoring of serum creatinine levels is recommended when metolazone is given to patients under cyclosporine treatment.

Carbonic anhydrase inhibitors
Metolazone was shown to inhibit alpha-carbonic anhydrase (hCA) isoforms from the kidneys and other organs, which should be attributed to the primary sulfamoyl moiety of its molecule. This fact may lead to two different types of interaction. A pharmacodynamic interaction, expressed as synergy with the diuretic acetazolamide (the prototype inhibitor of hCA), and also a theoretical pharmacokinetic interaction, due to the inhibition of carbonic anhydrase which might render more alkaline the pH of the pre-urine. In alkaline pH, the passive diffusion of weak bases is facilitated. Thus, all pharmaceuticals with a high Km value would be expected to have a prolonged action, because they can be easily reabsorbed back into the blood.

Digitalis glycosides
Metolazone-induced hypokalaemia increases sensitivity of the myocardium to digitalis. Serious arrhythmias may occur.

Methenamine
Efficacy may be decreased, presumably due to the urinary alkalising effect of metolazone.

Norepinephrine and other pressor amines
The effect of pressor amines may be decreased by metolazone, as has already been documented for other antihypertensives. Hydrochlorothiazide (50 mg daily for a week) attenuated the pressor responses to infusions of norepinephrine (2 to 10 mcg/min). Also, it has been reported that the pressor response to norepinephrine was significantly reduced after prolonged treatment with lisinopril and hydrochlorothiazide. It is recommended to adjust the dosage of metolazone in patients who are to undergo surgery.

Tubocourarine
The effect of non-depolarizing skeletal muscle relaxants may be potentiated by diuretics due to electrolyte imbalance and especially hypokalaemia. This concerns mainly patients with renal impairment treated with the loop diuretics. Hypokalaemia affects neuromuscular function and may be manifested as a minimal weakness but also as a frank paralysis. No report of such an interaction exists for metolazone.

Pharmacokinetic interactions
Metolazone can induce the expression of CYP3A4, a cytochrome involved in the microsomal oxidation of many medicinal products of common use. At least in theory, acceleration of hepatic metabolism might necessitate dosage readjustment of the following drugs: alprazolam, astemizole, buspirone, calcium channel blockers (felodipine, nidedipine), carbamazepine, cisapride, cyclosporine, doxorubicin, erythromycin, etoposide, fentanyl, HIV protease inhibitors, ifosfamide, lovastatin, midazolam, pimozide, quinidine, quinine, simvastatin, tacrolimus, terfenadine, and triazolam.

Lithium salts.
Thiazide diuretics and metolazone may lead to a relative increase of lithium blood levels, with possibly toxic consequences. Metolazone decreases tubular excretion of lithium on one hand and on the other hand by increasing diuresis it leads to a restricted volume for its distribution.

Drugs mutually affected with metolazone
Diuretics
Combination of loop diuretics with thiazides produces synergy, leading to large and prolonged losses of fluid and electrolytes. With furosemide, complications occurring may include severe natriuresis and hypokalaemia. Dosage titration may be necessary, according to urine volume and changes in body weight. It is important to supplement potassium in diuretic-induced hypokalaemia (serum potassium less than 3.5 mmol/L). Despite this possible pharmacodynamic interaction, it has been reported that metolazone does not affect the pharmacokinetics of furosemide.

Antihypertensives
There is a mutual potentiation in reducing the systolic and diastolic blood pressure between thiazides and other antihypertensives. Symptomatic hypotension may be expected to occur in patients who are volume and/or sodium depleted.

Deterioration of renal function has been reported in patients treated with thiazides and inhibitors of angiotensin converting enzyme (ACE). It has been suggested that natriuresis and a fall in blood pressure caused by the diuretic might have compromised an already low renal perfusion pressure when auto-regulatory mechanisms were blocked by captopril or other ACE inhibitors. Restoration of normal synthesis of angiotensin represents a necessary compensatory mechanism.

Analysis of data from 74 patients showed that acute renal failure was diagnosed only in 2.4% of individuals treated with ACE inhibitors alone, while this percentage was 33% in patients with combined treatment of an ACE inhibitor and a diuretic. Nearly all patients who developed acute renal failure in the context of ACE inhibition were consuming salt-restricted diets or receiving diuretic therapy. In clinical practice, older individuals should be monitored carefully for intercurrent volume depletion when they are taking ACE inhibition. The preservation of a positive sodium balance promotes the recovery of renal function after the combined administration of ACE inhibitors and diuretics, which is a rather common fixed

combination for treating hypertension. It should be noted that, to date, such interaction with ACE inhibitors has not been reported for metolazone.

Corticosteroids or ACTH
These drugs may lead to severe hypokalaemia, with symptoms of weakness and muscle cramps, and with the serious risk of cardiac arrhythmias (especially when metolazone is combined with furosemide, a rather common practice). On the other hand, retention of sodium and water antagonises the action of metolazone.

Summary comments
The available data suggest that metolazone acts by inhibiting sodium transport across the epithelium of the renal tubules (mostly in the distal tubules), resulting in a decrease in sodium reabsorption and an increase in sodium, chloride, and water excretion. This diuretic effect leads to relief of oedema (and can have an antihypertensive effect). While metolazone is similar to thiazide diuretics in its mechanism of action, it does differ in its use in patients with impaired renal function. Thiazide diuretics may decrease GFR and are therefore less effective in patients with renal impairment.

Metabolism of metolazone is minimal, therefore the potential of significant effects of enzyme inhibitors/inducers on its concentrations is expected to be low. On the other hand, the effect of metolazone on drug-metabolising enzymes is uncertain.

IV.4 Clinical efficacy

The efficacy of metolazone is well-established and supported in various clinical trials as well as in case studies. Metolazone can potentiate the effect of other diuretics and is effective in oedema resistant to other therapy.

Oedema related to kidney disease
Several early clinical trials have demonstrated the beneficial effect of oral thiazide therapy in oedematous patients with nephropathy, even with severe nephrotic syndrome, either complicated with hypertension or not. Despite their important findings, these early studies cannot be easily evaluated, as they were open-label, uncontrolled trials, and usually the patients were not randomised.

In one study, metolazone was used to treat 52 oedematous patients (gender not specified) in hospital. The first group (35 patients) received metolazone, while the second group (17 patients) received a combined treatment of metolazone with spironolactone or furosemide. Dosages differed from patient to patient, depending on the response and the diagnosed cause of the oedema. Despite serious methodological drawbacks, this paper clearly demonstrated the synergistic effect of thiazides and loop diuretics.

The metolazone-furosemide combination has been reported as efficacious in cases where removal of volume overload becomes necessary, as in chronic renal insufficiency, nephrotic syndrome, congestive heart failure, or cirrhosis. The efficacy of this combination is reported as independent of patient age.

Nephrotic Syndrome
There have been several reports on the efficacy of metolazone monotherapy in the control of oedema in the nephrotic syndrome, with or without renal failure. In patients with nephrotic syndrome and resistant to loop diuretics, the addition of metolazone treatment frequently produces an impressive diuretic response.

In a crossover, randomised study in nephrotic patients with oedema (n=9), patients were treated with furosemide (2 mg/kg per dose) and either metolazone (dose varied according to weight: 14-28 kg, 1.0 mg; 28-40 kg, 2.0 mg 40-55 kg, 3.0 mg; and 55-68 kg, 4:0 mg) or chlorothiazide (10 mg/kg per dose). The metolazone-furosemide combination was shown equally effective as the chlorothiazide-furosemide combination. An additive natriuretic and diuretic effect was observed after either metolazone or chlorothiazide were combined with furosemide. Both diuretic combinations were associated with marked kaliuresis.

Chronic Renal Failure
Although it is not the case with the classic thiazides, metolazone monotherapy is able to elicit a diuretic response in advanced renal failure As previously stated, a diuretic response has been demonstrable even with a very low GFR; this has also been reported in patients undergoing maintenance hemodialysis.

The doses of metolazone needed for a satisfactory diuretic response in renal failure, may be surprisingly variable, and typically do not have a defined relationship to the GFR. For instance, doses as high as 100 mg-200 mg have been reported. Several parameters, such as the rate and extent of metolazone absorption, metolazone's prolonged elimination half-life, and the rather modest tubular delivery rate necessary for a threshold diuretic response, have been proposed as an explanation for the reported variability in the dose required for a satisfactory diuretic response.

A case is reported of a hypertensive patient with oedema, nephrocalcinosis, and cardiac decompensation, who did not respond during 11 months of metolazone therapy at 40 mg/day. The addition of furosemide 160 mg/day to metolazone resulted in a dramatic diuresis. A subsequent trial of furosemide 360 mg/day alone failed to prevent recurrent fluid retention and heart failure; combined treatment with metolazone again reproduced the earlier dramatic response. The patient was subsequently stabilised without oedema, receiving 10 mg/day of metolazone and 160 mg/day of furosemide.

In a meta-analysis of clinical trials concerning thiazides and thiazide-like diuretics in nephropathies, the authors concluded that thiazides are effective drugs in controlling oedema and hypertension, even in patients with stage 4 chronic kidney disease.

Chronic Heart Failure
Combination diuretic therapy seems to have been most frequently employed in the management of chronic heart failure (CHF) with volume overload. Metolazone potentiates the effect of loop diuretics and is effective in treating oedema associated with heart insufficiency resistant to other therapies. It has been shown that combining metolazone with furosemide does not change the metabolism or urinary excretion of the latter. The combination of loop diuretics with metolazone exerts concomitant actions at three segments of the nephron: the proximal tubule, the thick ascending limb of the loop of Henle, and the distal tubule. This multi-segmental blockade diminishes the physiological renal countereffects observed when using metolazone or a loop diuretic as monotherapy. It is postulated, that thiazide-type diuretics counteract the enhanced sodium reabsorption seen in the distal tubules due to treatment with a loop diuretic.

The efficacy of co-administered metolazone together with other diuretics and especially loop diuretics is well-established and supported by many clinical trials and case studies in patients with chronic heart failure.

In chronic heart failure, an aggressive dosage regimen with metolazone is usually applied, so

that diuresis is elicited and maintained. For example, in one study combination therapy was initiated with metolazone 1.25 mg/day and 200 mg - 500 mg/day of furosemide in a group of patients with severe chronic heart failure (n=17). Metolazone was titrated to a maximum dose of 10 mg/day according to the desired response; 12 of the 17 patients responded with diuresis within 72 hours of starting therapy. Failure to respond to combination therapy was an ominous prognostic finding. This is a well-designed pivotal clinical trial showing the clinical efficacy of diuresis in patients with chronic heart failure after the combined administration of metolazone and furosemide.

A randomised, blind, controlled trial compared the sodium excreting efficacy of a "furosemide plus indapamide" combination versus "furosemide plus metolazone" in patients with class III and IV refractory heart failure. The patients (n=150) included had not responded to intravenous furosemide doses of 120 mg (40 mg Q8hr). The subjects were randomised to two groups (75 in each group). Both groups received intravenous furosemide (40 mg Q12hr), while additionally, group 1 received metolazone (5 mg Q24hr) and group 2 received indapamide (2.5 mg Q24hr). Analysis of the results revealed that both combinations had comparable efficacy and safety profiles. Moreover, indapamide and metolazone were effective even in patients with severe renal dysfunction (GFR<30 mL/min). Hypokalaemia was the most common adverse event. Due to the large number of patients included in this clinical trial, the results give further support to earlier observations on the beneficial effects of metolazone and indapamide, even in cases of refractory cardiac insufficiency with a severe decrease of GFR.

A retrospective study of hospitalised acute heart failure patients (n=242) compared the diuretic effect of three different regimens: (a) continuous infusion furosemide (n=160), (b) furosemide plus metolazone (n=42), (c) continuous infusion bumetanide (n=40). Primary end points were the change of mean hourly urine output and evaluation of renal function. Compared to baseline, all regimens increased mean hourly urinary output ($p < 0.0001$ for all). Most effective was the treatment "furosemide plus metolazone" (109+171 mL), followed by "bumetanide" (90+90 mL) and "furosemide" (48+103 mL; $p = 0.009$). No difference in the incidence of worsening renal function was found; however, electrolyte abnormalities may be more prevalent when furosemide is combined with metolazone or when bumetanide is used. This investigation would have been more informative by adding a group of patients treated with bumetanide plus metolazone.

Several retrospective cohort studies have compared chlorothiazide versus metolazone as adjunct treatments for patients with loop diuretic resistance.

One study evaluated the efficacy and safety of oral metolazone versus intravenous chlorothiazide as add-on therapy to loop diuretics in patients hospitalised with acute decompensated heart failure and renal dysfunction. The primary endpoint was net urine output at 72 hours after initiation of thiazide-like diuretics. Safety endpoints were also included, with regard to renal function, blood pressure and electrolyte balance. Of the 55 patients enrolled, 33 patients received metolazone and 22 patient received chlorothiazide. When diuretic dosing was examined by each individual day of the 72-hours study period, the median daily dose of metolazone was 2.5 mg (Interquartile range (IQR) 2.5-2.5 mg). The median daily dose of chlorothiazide was 500 mg (IQR 500-875 mg) on day 1, 750 mg (IQR 500-1000 mg) on day 2, and 1000 mg (625-1000 mg) on day 3. Analysis of the data revealed that sequential nephron blockade with either metolazone or chlorothiazide appears to be efficacious and safe in acute decompensated heart failure, renal dysfunction, and loop diuretic resistance. There was no significant difference in the defined safety endpoints (hypotension, worsening renal function, hyponatraemia, or hypokalaemia). Hospital length of

stay was shorter in the metolazone cohort (median 7 days) compared to chlorothiazide (median 15 days).

In a similar retrospective cohort study, the efficacy and safety of intravenous chlorothiazide versus oral metolazone were assessed in patients with acute decompensated heart failure and loop diuretic resistance. Adults with a diagnosis of acute decompensated heart failure who were treated in hospital between 2005 and 2015 and had not responded to intravenous furosemide (160 mg/day or higher) or to an equivalent dose of intravenous bumetanide, during hospitalisation, and who then received at least one dose of intravenous chlorothiazide (88 patients) or oral metolazone (89 patients) to augment diuresis, were evaluated. Mean doses were 491±282 mg for chlorothiazide and 5.8±3.5 mg for metolazone. Analysis of the data showed that oral metolazone was equally effective to intravenous chlorothiazide for enhancing net urine output in patients with acute decompensated heart failure and loop diuretic resistance. No major adverse events were noted in either group.

A third study, with the same methodology and endpoints as the two previous studies, was reported. Patients (n=168) with heart failure and reduced ejection fraction, received either chlorothiazide (at least one dose ≥500 mg) or metolazone (at least one dose ≥5 mg). Both metolazone and chlorothiazide increased in a similar way the 24-hour total urine output.

These data support the use of oral preparations of metolazone instead of intravenous formulations of thiazides. However, it is considered that a prospective, randomised, controlled trial would be ideal to determine whether an efficacy difference exists between chlorothiazide and metolazone.

Mild and moderate hypertension
Diuretics, as monotherapy, still remain useful drugs for the treatment of hypertension. However, diuretics in combination with drugs of other categories are more frequently useful for the treatment of hypertension, depending on the underlying pathophysiological mechanism for the increased blood pressure.

In an early double-blind clinical trial, metolazone (1.0, 2.5 or 5 mg orally (p.o.), daily) was compared with chlorthalidone (100 mg p.o., daily) for the treatment of non-oedematous hypertensive patients (n=57). Both drugs significantly reduced blood pressure, to the same extent. They also equally produced frequent hypokalaemia.

A single-blind , cross-over, clinical trial compared metolazone (5 mg p.o. daily) with hydrochlorothiazide (25 mg p.o., twice daily) in hypertensive patients (n=22). Each patient received a separate 6-week treatment with metolazone or hydrochlorothiazide in random order. Each treatment was separated from the other by a washout period of 2 weeks. Metolazone was shown to be more potent than hydrochlorothiazide, in that it caused a greater reduction in both systolic and diastolic blood pressure. Significant decreases in plasma potassium were observed with both treatments.

In a database of systematic reviews, thiazides and thiazide-like diuretics are reported to exert similar maximal blood pressure-lowering effects, when applied as antihypertensive monotherapy in primary hypertension. Overall, thiazides have been found to reduce average blood pressure by 9 mmHg/4 mmHg (systolic/diastolic), compared to placebo. In a placebo-controlled trial, metolazone was given orally at daily doses 0.5 to 2.0 mg to 105 patients, 46 males and 59 females, with a baseline blood pressure 150/98 mmHg (systolic/diastolic). Metolazone was administered as monotherapy for six weeks. The placebo-corrected systolic/diastolic blood pressure-lowering with metolazone was

11.6/5.8 mmHg. Direct comparison of doses did not show any significant differences in systolic or diastolic blood pressure-lowering between the different doses used.

Special groups of patients

Elderly

The therapeutic indications of metolazone refer to diseases and pathological conditions occurring mostly in the elderly. The side effects of metolazone reported in clinical trials concern, as a rule, elderly people who are statistically more prone to suffer from cardiovascular and renal diseases co-existing with hypertension or oedema. The situation becomes more complicated when kidney disease progresses to complete renal insufficiency, necessitating dialysis. Equally problematic are patients with ascites due to liver cirrhosis (see 'Hepatopathy' section below). In one study, elderly patients (n=3) with renal failure and refractory fluid overload resistant to oral furosemide were successfully treated with short-term (2-5 days) metolazone administration (2.5 to 5 mg). Oedema was clinically improved and the drug was well tolerated, without any significant blood pressure fluctuations or electrolyte disturbances.

Severe renal insufficiency

It has been reported that the thiazide-like diuretics indapamide and metolazone may retain their natriuretic effect in patients with very low GFR. However, when hypovolaemia has been established after chronic treatment, lowering of blood pressure may lead to a further decrease of glomerular filtration rate and possibly to histological renal damage.

In patients with very low GFR, the thiazide-like diuretics indapamide and metolazone may retain their natriuretic effect.

A review evaluated the antihypertensive effect of thiazides in patients with renal insufficiency. The objective was to determine whether thiazides have a chronic antihypertensive effect, in the absence of diuresis, in patients with severe renal disease (creatinine clearance <30 mL/min) or in those receiving dialysis. Thiazide diuretics are associated with a chronic reduction in peripheral vascular resistance secondary to a purported vasodilatory effect. However, their antihypertensive effect is mediated though diuresis secondary to natriuresis. Hydrochlorothiazide, chlorothiazide, and indapamide provided long-term blood pressure reduction in patients with severe renal disease who were not on dialysis. In studies involving patients on dialysis, hydrochlorothiazide 50 mg daily and metolazone 5 mg daily did not affect blood pressure, with the exception of one study suggesting that indapamide 2.5 mg daily may confer an antihypertensive effect. All studies were small (<12 subjects) and had methodological limitations. The authors concluded that thiazide diuretics cannot be routinely recommended for chronic antihypertensive treatment in patients with severe renal disease or in those on dialysis.

In patients with chronic renal failure and hypertension (n=35), the efficacy of increasing doses of metolazone (5, 10, 20 mg) were compared with those of furosemide (40 mg, 80 mg and 160 mg). Both diuretics were given as a monotherapy. Antihypertensive potency was comparable during a treatment period of up to 12 weeks. Maximal response was achieved with 10 mg of metolazone or 160 mg of furosemide. However, blood pressure could be normalised with the monotherapy of metolazone or furosemide (diastolic blood pressure <95 mm Hg) in only 25% of the cases.

Hepatopathy
In patients with ascites due to liver disease, metolazone has been used as a potent diuretic, with an initial daily dose of 5 mg which may be escalated. When metolazone is used alone the high incidence of hypokalaemia (80%), hypochloraemia (35%), and encephalopathy (35%) compared with the results of other series is a major disadvantage and indicates that this drug should be used with caution in patients with liver disease. Hypokalaemia can usually be prevented by the simultaneous administration of amiloride or spironolactone.

Paediatric use
Possible changes in the pharmacokinetic parameters of metolazone in paediatric patients have not been studied. Furosemide and metolazone have been employed regularly in the management of the full spectrum of oedematous conditions found in childhood .

One study evaluated the response in infants with bronchopulmonary dysplasia (n=24) to furosemide, metolazone, or their combination. Although the initial doses of either furosemide (1 mg/kg. i.v. daily) or metolazone (0.2 mg/kg p.o. daily) alone elicited a diuretic response, this quickly disappeared with succeeding doses. The physiologic tolerance to repetitive administration of either furosemide or metolazone was overcome when both drugs were administered together .

Combination diuretic therapy should be undertaken cautiously in the paediatric population. Administration of metolazone to paediatric patients usually occurs on a milligram per kilogram basis, extrapolated arbitrarily from doses given to adults, since formal dose-ranging studies have not been conducted in children.

A descriptive, retrospective study carried out in patients less than a year old (n=97, age: 0.32±0.25 years), that had received metolazone over a 2-year period in a paediatric cardiac intensive care unit is reported. The study categorised a total of 66 patients (68.0%) as responders. Changes in urine output were not associated with the dose of metolazone.

In conclusion, the use of metolazone in paediatric patients is not recommended due to lack of sufficient clinical data.

Posology
The applicant has discussed in detail and provided evidence for the recommended posology in all indications (presented as starting, range, and maximum dose).

Considering the results of the bridging pharmacokinetic studies, the proposed SmPC recommends a modified posology (half) compared to that provided in the originator SmPC (and assumed used in literature). This is accepted.

Metolazone is given orally and it is available in tablets of 5 mg. The therapy should be initiated with a dose of 2.5 mg/day and the dose must be individualised according to the severity of the condition of the patient and their reaction to the treatment. Once the desired therapeutic effect has been achieved, it may be advisable to reduce the maintenance dose if possible.

It is important to note that different metolazone products have different bioavailability and it should be noted that a paragraph has been included in the proposed SmPC (Section 4.2) as follows:
“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."

Special populations
Metolazone should be used with caution in elderly patients, in patients with impaired renal or hepatic function and in patients with electrolyte disturbances. There is no conclusive data on the use and dosage of metolazone in paediatric patients (the drug is not recommended for use in patients under 18 years of age).

IV.5 Clinical safety
Overall the provided information is sufficient to characterise the key aspects of metolazone safety, which to a large extent reflect the safety of the thiazide class. A summary of the data provided in the clinical overview is provided below.

Adverse effects
Electrolyte imbalance
Administration of metolazone can be followed by serious electrolyte abnormalities, especially when it is combined with a loop diuretic. In order to avoid serious electrolyte disturbances when metolazone is introduced in patients taking loop diuretics, metolazone should be given in low doses to start with in hospital, and at the same time the dosage of the loop diuretic should be reduced under careful biochemical monitoring.

It has been reported that weight loss of more than 2–3 pounds daily in an oedematous patient marks those patients predisposed to the development of more severe electrolyte abnormalities. In this regard, careful selection of starting doses of a loop diuretic and metolazone and monitoring of the rate of body weight loss are important safety considerations.

The most common electrolyte abnormalities with combination diuretic therapy include hypokalaemia, hypomagnesemia, contraction alkalosis and, occasionally, hyponatraemia. Supplemental potassium may be necessary. Patients with a persistent need for large amounts of supplemental potassium are not uncommonly hypomagnesemic, in that hypomagnesemia hinders renal potassium-conserving ability.

In a retrospective cohort study, patients with acute decompensated heart failure and loop diuretic resistance were treated with chlorothiazide (n=88) or metolazone (n=89) at a mean dosage of 491±282 mg (chlorothiazide, i.v.) and 5.8±3.5 mg (metolazone, p.o.). Safety outcomes were similar between the two groups. No significant differences in renal function were observed (serum creatinine concentration, blood urea nitrogen concentration, and glomerular filtration rate). The incidence of acute kidney injury was also similar (17.1% and 23.6% in the chlorothiazide and metolazone groups, respectively). Rates of severe hypokalaemia did not significantly differ between the two groups, nor did the rates of severe hyponatraemia, or severe hypomagnesemia.

Cardiovascular system
In one study, patients hospitalised with acute decompensated heart failure were evaluated post hoc in data from ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure). Analysis of the data showed that among factors associated with hypotension was chronic metolazone therapy (odds ratio, 1.74; 95% CI, 1.17–2.60; P<0.001).

Endocrine system
Thiazide diuretics can precipitate hyperosmolar non-ketotic diabetes mellitus in susceptible individuals, and this has been reported also for metolazone. In a literature search (from 1966 to 2004), investigators identified 59 clinical trials constituting 83 thiazide diuretic study arms. Trial size, length, type of thiazide diuretic, and dose varied substantially among the studies. There was an association between average changes in potassium and glucose in the study arms, supported by a sensitivity analysis, by subset analyses of the effect of covariates, as well as by an inverse-variance weighting. The authors suggested that treatment of thiazide-induced hypokalaemia may reverse glucose intolerance and possibly prevent the future development of diabetes.

Idiosyncratic reactions
Some case reports imply that metolazone, similarly to the thiazides in general, may elicit idiosyncratic reactions, of unknown aetiology, although in some reports they are characterised as "autoimmune" without any further elaboration on their mechanism. Such reports refer to aplastic normochromic anaemia, neutropenia, vasculitis, hypercalcemia and acute pancreatitis, cholestatic liver disease, and Stevens-Johnson Syndrome (toxic epidermal necrolysis).

Special warnings and precautions for use
Electrolyte imbalance
Fluid and electrolyte balance should be carefully monitored during treatment with metolazone in all patients, especially if the drug is used at high doses or if is administered concurrently with loop diuretics and corticosteroids (risk of hypokalaemia). Hyponatraemia or hypochloraemia may occur. Hyponatraemia is accompanied by neurological symptoms (nausea, debility, progressive disorientation, apathy). Cases of hypomagnesemia have also been observed. In some patients (as it may happen also with other diuretics) serious hyponatraemia and hypokalaemia may occur immediately after the beginning of treatment. An individually adjusted dosage of a concurrently administered oral potassium salt (e.g. potassium chloride) may be considered for patients receiving digitalis or showing signs of coronary heart disease. Potassium supplements should be avoided in patients concurrently treated with an ACE inhibitor or with an angiotensin-II-antagonist, because these drugs produce hyperkalaemia. An individually adjusted dosage may also be considered for patients who are being treated with a high dose beta-adrenergic agonist, and in all cases when the potassium concentration in the serum is below 3.0 mmol/L.

In all cases of combined treatment, the maintenance or normalisation of the potassium balance should be monitored closely. If hypokalaemia is accompanied by clinical signs of potassium shortage (for instance muscular weakness, paresis or ECG-alterations) the administration of metolazone should be discontinued**.**

Patients with kidney and liver disease
Monitoring of serum electrolytes is particularly advisable in the elderly. Also, in patients with ascites due to liver cirrhosis, or in patients with oedema as a consequence of a nephrotic syndrome. For the latter condition, metolazone should be used only under control in normokalaemic patients who show no signs of volume depletion or hypoalbuminaemia. In case the condition of a patient with kidney insufficiency, oliguria or azotaemia deteriorates, the treatment should be discontinued.

There have been cases with renal failure mostly in the context of dehydration, aggravated by concomitant medication such as ACE-inhibitors, angiotensin-II-antagonists, aldosterone-antagonists and/or NSAIDs. Concurrent treatment with lithium should be avoided.

Cross-reactivity with sulfonamides
Cross reactivity may occur in patients who are allergic to sulfonamides or thiazides.

Gouty attacks
Like other diuretics, metolazone may raise the serum uric acid level, which in rare instances may lead to acute attacks 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 metolazone 5 mg tablets, thiazides have been associated with acute attacks of porphyria. Caution is required when metolazone 5 mg tablets are used in porphyric patients.

Glucose metabolism
Metolazone has only a slight effect on the glucose metabolism. In patients suffering from diabetes, treatment with antidiabetic drugs may have to be readjusted. In cases with latent diabetes, glycosuria and hyperglycaemia may occur. The blood sugar level should therefore be checked on a regular basis.

Laboratory values
Insignificant and partly reversible increases in the plasma concentration of total cholesterol, triglycerides, or LDL-cholesterol were observed during long term treatment with thiazide or thiazide-like diuretics. The clinical relevance of these observations is unclear.

Overdose
Symptoms and Findings
Overdosing may lead to dehydration and electrolyte disturbances (primarily hyponatraemia, but also loss of potassium and magnesium). The symptoms include thirst, nausea, vomiting, disorientation, somnolence, headache, muscle cramps, arterial hypotension, and arrhythmias (in severe cases of hypokalaemia).

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.

Bridging studies
No new or unexpected safety concerns were raised from the safety data submitted with the bridging clinical pharmacokinetic studies.

IV.6 Risk Management Plan (RMP)
The Applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The Applicant has submitted a bibliography of published material to support its claims on the clinical pharmacology, efficacy and safety of metolazone in the stated indications.

In order to support the bridge between the literature and the proposed product the Applicant submitted the results of two pharmacokinetic studies. Suprabioavailability of the applicant's product, Metolazone 5 mg tablets was observed, when the product was compared to Metenix 5 mg tablets. Dose proportionality of one Metolazone 5 mg tablets and one-half a Metolazone 5 mg tablets was shown with respect to $AUC_{0\text{-}tlast}$ but not for C_{max}. As the upper limit of the bioequivalence range of 80.00% -125.00% was not exceeded, a safety issue can be excluded. The potentially reduced efficacy has no implication as each patient is titrated individually starting with a 2.5 mg dose.

Overall, taking into account the findings of the submitted PK studies, it can be concluded that with the currently recommended posology (half of that previously advised of the originator product, Metenix 5 mg tablets), the proposed metolazone product can reasonably be expected to perform in a similar manner as the products used in the literature; on this basis the results of the studies can support the bridge to literature data.

From a clinical perspective, it is of importance that dosing is expected to be individualised and titrated based on patient response and tolerance and recommended doses are presented mainly as guidance.

The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to:

1. Metolazon Abcur 5 mg film-coated tablets (SE/H/890/01/DC), with respect to clinical information (content and key message).
2. Golden Eye 0.1% w/v Eye Drops Solution (PL 00551/0003; Typharm Limited) with respect to font style size, format and layout.

The bridging report submitted by the applicant is acceptable.

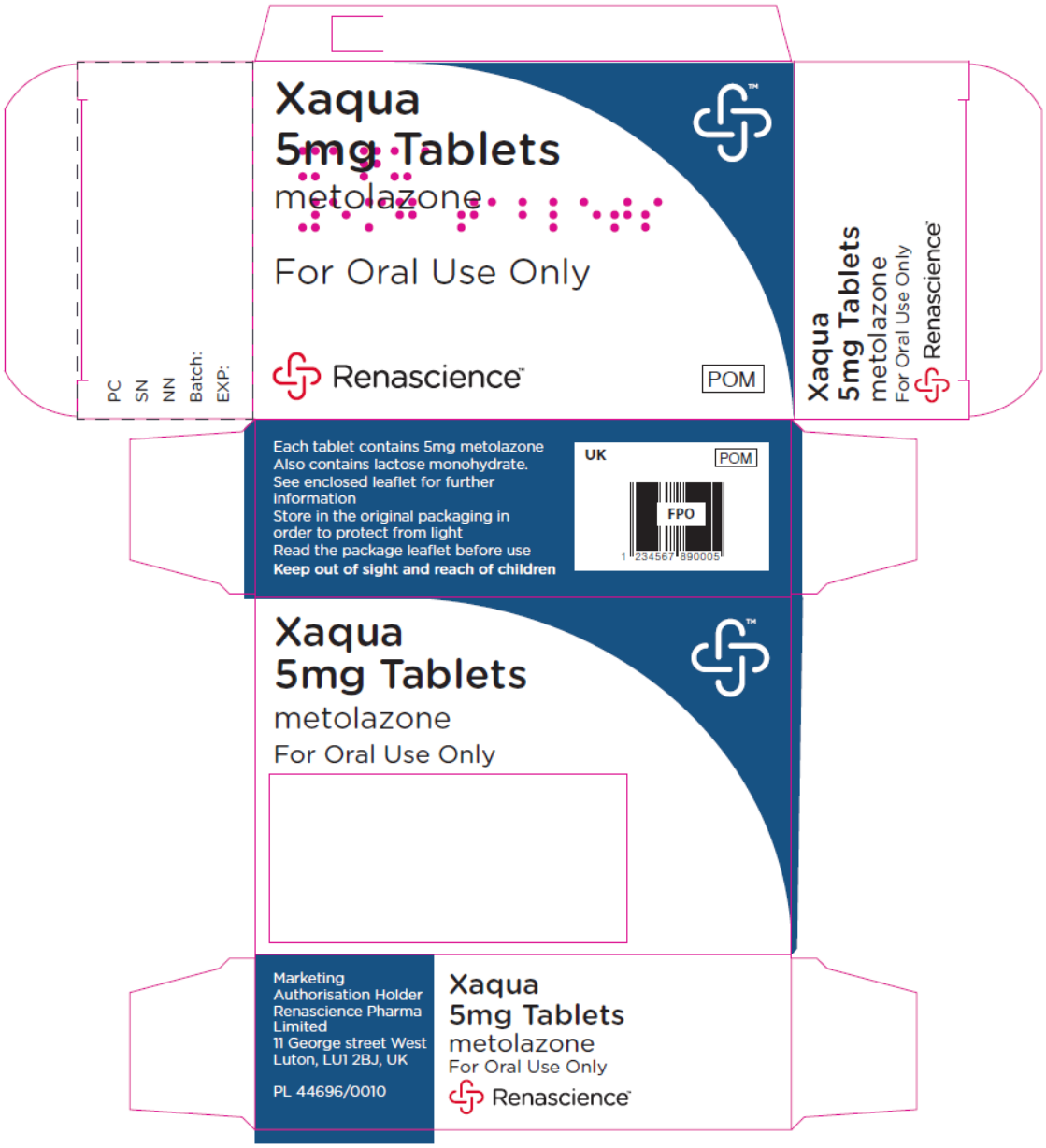
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with metolazone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


Xaqua
5mg Tablets
metolazone
For Oral Use Only
Renascience
POM
PC
SN
NN
Batch:
EXP:
Xaqua
5mg Tablets
metolazone
For Oral Use Only
Renascience
Each tablet contains 5mg metolazone
Also contains lactose monohydrate.
See enclosed leaflet for further information
Store in the original packaging in order to protect from light
Read the package leaflet before use
Keep out of sight and reach of children
UK
POM
FPO
1 234567 890005
Xaqua
5mg Tablets
metolazone
For Oral Use Only
Marketing Authorisation Holder
Renascience Pharma Limited
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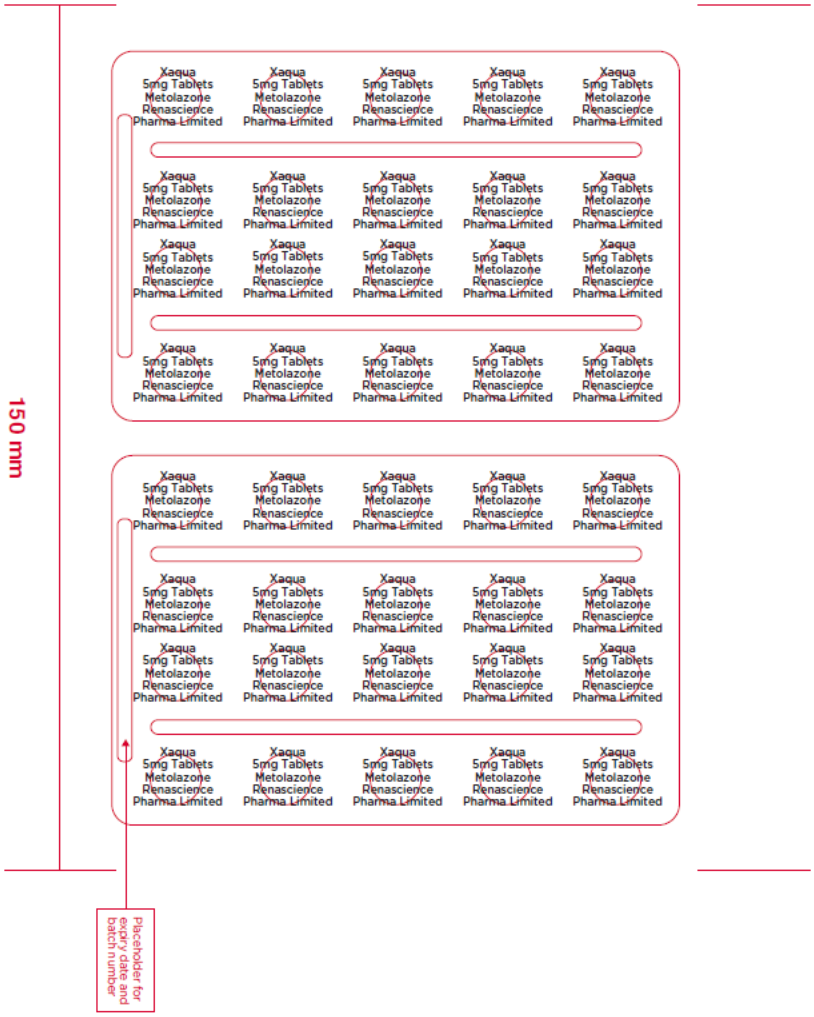
Luton, LU1 2BJ, UK
PL 44696/0010
Xaqua
5mg Tablets
metolazone
For Oral Use Only
Renascience


150 mm
Xaqua 5mg Tablets Metolazone Renascience Pharma Limited
Placeholder for expiry date and batch number

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**