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Human Medicines Evaluation

EU Risk Management Plan for Metolazone 5mg Tablets

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[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Metolazone
Pharmacotherapeutic group(s) (ATC Code)	Cardiovascular system, diuretic. C03BA08
Marketing Authorisation <Holder> <Applicant>	Renascience Pharma Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Metolazone 5mg tablets (Metolazone 5mg tablets)
Marketing authorisation procedure	National procedure
Brief description of the product	Metolazone is a diuretic antihypertensive preparation.
	Metolazone is a quinazoline diuretic, with properties generally similar to the thiazide diuretics. The actions of Metolazone results from interference with the renal tubular mechanism of electrolyte reabsorption. Metolazone acts primarily to inhibit sodium reabsorption at the cortical diluting site and to a lesser extent in the proximal convoluted tubule. Sodium and chloride ions are excreted in approximately equivalent amounts. The increased delivery of sodium to the distal-tubular exchange site results in increased potassium excretion. The antihypertensive mechanism of action of Metolazone is not fully understood, although it has been related to its saluretic and diuretic properties.
	Metolazone is a well-established active pharmaceutical ingredient; it is manufactured using a synthetic process.

Hyperlink to the Product Information	On approval, the current approved product information can be found here: https://products.mhra.gov.uk/
Indication(s) in the EEA	Current: 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.
	Proposed (if applicable): 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.

Dosage in the EEA	Current: *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* 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.

	Proposed (if applicable): *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* 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.
Pharmaceutical form(s) and strengths	Current (if applicable): 5mg tablet Round, biplanar, white to off-white tablets with bevelled edges and single score-line, diameter: 7.0 mm

	Proposed (if applicable): 5mg tablet Round, biplanar, white to off-white tablets with bevelled edges and single score-line, diameter: 7.0 mm
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

N/a

Part II: Module SII - Non-clinical part of the safety specification

N/a

Part II: Module SIII - Clinical trial exposure

N/a

Part II: Module SIV - Populations not studied in clinical trials

N/a

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

N/a

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

N/a

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

N/a

Part II: Module SV - Post-authorisation experience

N/a

SV.1 Post-authorisation exposure

N/a

Part II: Module SVI - Additional EU requirements for the safety specification

N/a

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Medication/Prescribing error is an important potential risk.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

N/a

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Potential Risk: Medication/prescribing error

Risk-benefit impact:

Metolazone tablets bioavailability may be different from other metolazone preparations. Therefore, the recommended doses (expressed in mg) can differ from other metolazone products. UK Clinicians/Healthcare Professionals have continuously and extensively utilized Metolazone formulations of differing bioavailability since the 1970s in the form of licensed, unlicensed and specials/extemporaneous formulations.

Higher dosing may lead to dehydration and electrolyte disturbance, leading to undesired effects such as thirst, nausea, vomiting, disorientation, somnolence, headache, muscle cramps, arterial hypotension, and in severe cases dysrhythmia (hypokalaemia). Lowering dosing may effect efficacy of treatment. However, all patients prescribed the product are individually dosed and extensively monitored, and dose adjustment are made if necessary. Once the appropriate dose has been identified for a patient with a certain product, this product should not be readily exchanged with another product.

However, the applicants Metolazone is currently the only licensed formulation of metolazone in the UK. The availability of a licensed, consistent product for patients will significantly reduce risk of medication errors over the present alternative of sourcing any type/dosage form of Metolazone (including unlicensed, foreign language packs and special formulations) Therefore, once patients have been initiated in the clinical practice, potential risk of medication error will be negligible/diminished.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

N/a

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

<Important Identified/Potential Risk>: Medication/prescribing error

Potential mechanisms:

Metolazone tablets bioavailability may be different from other metolazone preparations. UK patients at present are provided with any available dosage form be it unlicensed product or

special formulations. Therefore, switching between different metolazone products can lead to potential dosing error.

Evidence source(s) and strength of evidence:

Metolazone preparations are utilized widely by UK healthcare professionals to meet the clinical need of patients. The UK BNF states that there can be variation in the licensing of different medicines containing the same drug. Accordingly, Metolazone tablets bioavailability may be different from other metolazone preparations currently utilized by patients.

Characterisation of the risk:

The frequency of medicating/prescribing error is very low, with very few recorded medicating/prescribing error in the UK with the use of Metolazone in the last 40 years.

As Metolazone is currently utilized and initiated via clinical specialists. Healthcare professionals are aware that bioavailability from one product to another product may vary.

Risk factors and risk groups:

Metolazone tablets bioavailability may be different from other metolazone preparations. Therefore, the recommended doses can differ from other metolazone products.

Preventability:

Metolazone is initiated via clinical specialists. Patient dose adjustment may be necessary and individualised adjusted based on patient's response and tolerability. Healthcare professionals in the UK are familiar with the clinical role of metolazone.

Impact on the risk-benefit balance of the product:

Metolazone preparations are utilized widely by UK healthcare professionals to meet the clinical need of patients. Metolazone continues to offer important clinical benefit to patients initiated and guided under the direction of healthcare professionals. Medication errors monitoring continues to be part of routine pharmacovigilance activities. Risk-benefit balance of the product continues to remain favourable.

Public health impact:

The UK BNF for Metolazone states that there can be variation in the licensing of different medicines containing the same drug. Availability of a licensed metolazone preparation will offer healthcare professionals clinical choice and bring significant benefit to UK patients. The core safety profile of metolazone is well-established at the population level and not expected to have any significant change.

SVII.3.2. Presentation of the missing information

N/a

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	N/a
Important potential risks	Medication/Prescribing error
Missing information	N/a

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

III.2 Additional pharmacovigilance activities

N/a

III.3 Summary Table of additional Pharmacovigilance activities

N/a

Part IV: Plans for post-authorisation efficacy studies

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

N/a

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety profile of the proposed product information is well characterized and well-established. Summary of product characteristics will include important note informing Healthcare Professionals that the tablets bioavailability may be different from other metolazone preparations. Medication errors monitoring will continue to be part of routine pharmacovigilance activities. Monthly signal detection will be undertaken to ensure this risk can be monitored effectively and the MHRA will be notified immediately of any signal of disproportionate reporting. The MAH will continue this activity until experience with the medicinal product suggests that it is no longer necessary for the safe and effective use.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Medication/Prescribing error	**Routine risk communication:** The SmPC will contain an appropriate Posology and method of administration in section 4.2 and pharmacokinetics properties section 5.2. Equivalent wording will be included in the relevant product information. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** "**Important note:** Metolazone 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 Metolazone tablets to another metolazone product, or vice versa." **Other routine risk minimisation measures beyond the Product Information:** BNF will be informed of new product information including the "important note" and availability of licensed product on successful approval of the MAA. MHRA INS department will be contacted on successful approval of the MAA. This will ensure that unlicensed preparations are not utilized over licensed preparations.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation

Objectives:

N/A

Rationale for the additional risk minimisation activity:

Target audience and planned distribution path:

N/A

Plans to evaluate the effectiveness of the interventions and criteria for success:

N/A

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication/Prescribing error	Proposed text in SmPC: 4.2 Posology and method of administration "***Important note:*** Metolazone 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 Metolazone tablets to another metolazone product, or vice versa." 5.2 Pharmacokinetics properties "Comparative bioavailability studies have shown that the bioavailability (AUC) of Metolazone may differ significantly (up to approximately 2-fold from 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."	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	The medicinal products safety profile is well-established and well characterized.	

Part VI: Summary of the risk management plan

Summary of risk management plan for Metolazone 5mg Tablets

This is a summary of the risk management plan (RMP) for Metolazone 5mg Tablets. The RMP details important risks of Metolazone 5mg Tablets, how these risks can be minimised, and how more information will be obtained about Metolazone Tablets risks and uncertainties (missing information).

Metolazone 5mg Tablets's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Metolazone 5mg Tablets should be used.

I. The medicine and what it is used for

Metolazone 5mg Tablets is authorised for the treatment of oedema of kidney diseases, including the nephrotic syndrome and states of impaired renal function as well as for oedema of congestive heart failure insufficiency, and mild and moderate hypertension. (see SmPC for the full indication). It contains Metolazone as the active substance and it is given by Oral administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Metolazone 5mg Tablets, together with measures to minimise such risks and the proposed studies for learning more about Metolazone 5mg Tablets risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Metolazone 5mg Tablets is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Metolazone 5mg Tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Metolazone 5mg Tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association

has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risks	N/a
Important potential risks	Medication/Prescribing error
Missing information	N/a

II.B Summary of important risks

The safety profile of the proposed product information is well characterized and well-established. Summary of product characteristics will include important note informing Healthcare Professionals that the tablets bioavailability may be different from other metolazone preparations. Medication errors monitoring will continue to be part of routine pharmacovigilance activities.

II.C Post-authorisation development plan

N/a

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Metolazone 5mg Tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Metolazone 5mg Tablets.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

N/a

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

N/a

Annex 4 - Specific adverse drug reaction follow-up forms

N/a

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

N/a

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

N/a

Annex 7 - Other supporting data (including referenced material)

N/a

Annex 8 – Summary of changes to the risk management plan over time

N/a