Direct Healthcare Professional Communication

Xaqua® (metolazone) 5mg tablets: differences with other metolazone preparations and safety considerations required when switching patients

November 2022

Dear Healthcare Professional,

Renascience Pharma Limited in agreement with Medicines and Healthcare products Regulatory Agency would like to inform you of the following:

Summary

- As a licensed medicine, Xaqua® should be considered in preference to unlicensed metolazone medicines, however, care is needed when switching patients to Xaqua® due to potential differences in bioavailability and posology compared with other metolazone products
- When initiating patients on metolazone you should prescribe and dispense the licensed Xaqua® preparation
- You should assess individual patient factors (listed in the "Considerations" sub-section) before switching patients from unlicensed imported metolazone products to Xaqua®.
- Dose adjustment and individualised titration should be considered at the time of switching from unlicensed imported metolazone products to Xaqua®, taking into account patient factors and differences in bioavailability between metolazone preparations where these data are available
- Patients should be monitored closely to assess the clinical impact of the switch, including regular measurement of serum electrolytes and other parameters and observation for clinical signs of fluid and/or electrolyte imbalance. Arrangements for monitoring should be done on an individual basis after an assessment of the individual clinical risk
- Advise patients being switched to be vigilant for warning signs of electrolyte imbalance and sub-therapeutic dosing (listed in the "Advice to give to patients" sub-section) and seek medical care if these occur

Background to the safety concern

Metolazone (Xaqua®) is indicated for oedema in congestive heart failure, oedema in renal disease and hypertension.

In recent years metolazone was only available in the UK as an unlicensed medicine, with several formulations prescribed to patients when clinically necessary. In February 2021, Renascience Pharma Ltd received marketing approval for a new metolazone product: Xaqua® 5mg Tablets.

The MHRA has received notifications of concerns from healthcare professionals with respect to switching patients between metolazone preparations due to potential differences in bioavailability and posology between Xaqua® and other unlicensed medicines.

This Direct Healthcare Professional Communication is intended to reinforce recent Specialist Pharmacy Services (SPS) guidance to healthcare professionals on the differences between metolazone preparations and safety considerations. Healthcare professionals should consult the SPS guidance at the following link: https://www.sps.nhs.uk/articles/differences-between-metolazone-preparations-and-safety-considerations/

Switching patients from unlicensed metolazone preparations to licensed Xaqua® 5mg Tablets

Considerations

Individual patient factors need to be considered before switching. These include:

- how stable the patient is currently;
- the risk of adverse effects from supra or sub-therapeutic dosing;
- what monitoring arrangements are in place;
- the patient's understanding of the implication of the switch and when to contact a healthcare professional; and
- the patient's ability to manage the handling of part tablets (halving tablets) or alternate day dosing regimens

Dose and Frequency

The initial recommended dose for Xaqua® is 2.5mg daily, increased if necessary to 5mg daily. Xaqua® 5mg Tablet is divisible and can offer 2.5mg (half-tablet) and 5mg (whole tablet) dosing.

Comparative bioavailability studies have shown that the bioavailability of Xaqua® may differ significantly (up to approximately 2-fold) from the originator product Metenix. The bioavailability of Xaqua® has not been compared to any other unlicensed metolazone so any switch should consider that differences in bioavailability may or may not be apparent.

Switching from the unlicensed (imported) product to Xaqua® may or may not require dose adjustments and individualised titration based on patient's response and tolerability.

Monitoring

When switching between products, the patient should be closely monitored to assess the clinical impact of the switch. The following monitoring parameters may be used to assess the clinical effect of the switch.

- Urea and electrolytes (U&Es)
- Creatinine
- Blood pressure
- Weight

Advice to give to patients

Where possible involve the patient and/or carer:

- ensure they are aware of the intended brand, dose, frequency of dosing and arrangements for monitoring;
- give advice and compliance aids to support the handling of part tablets or alternate day dosing. Where Xaqua® tablets require splitting, this should be only into halves using the tablet score-line;
- give advice on the symptoms of electrolyte imbalance or sub-therapeutic dosing and when to contact a healthcare professional

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.

Patients should also be made aware of relevant signs and symptoms related to a sub-therapeutic metolazone dose. These signs and symptoms will relate to exacerbation of their underlying illness. Relevant features include increasing breathlessness, weight gain and worsening peripheral oedema.

Patients should be advised to speak to a healthcare professional if these occur.

Call for reporting

Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme.

You can report via:

- the Yellow Card website https://yellowcard.mhra.gov.uk/
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, timing onset, treatment dates, and product brand name.

Company contact details

If you have any questions please contact Renascience Pharma Limited by phone on 01582 227470 or via email at info@renasciencepharma.com

Kind regards,

Digitally signed by Peter Mollison
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Qualified Person

Qualified Person for Pharmacovigilance