Safety considerations for use of Metolazone preparations in adults

Situation

The Xaqua® brand, manufactured by Renascience Pharma Limited, is currently the only licensed metolazone preparation in the UK. The MHRA therefore state it should be used preferentially over previously unlicensed or special formulations. The summary of product characteristics [1] indicates Xaqua® has greater bioavailability than other metolazone products which has raised concern over the safety of switching between formulations.

Background

The manufacturer states comparison or bioavailability data in healthy adults with previously licensed brand, Metenix®[2] shows up to a two-fold increase in bioavailability. However, Metenix®, was discontinued over a decade ago and replaced in clinical practice by several unlicensed or special formulations.
It is widely recognised that all metolazone preparations have differing bioavailability to one another; this includes existing unlicensed and special formulations. We do not know how newly licensed Xaqua® compares to those products most recently used in clinical practice particularly use in oedematous patients.

Assessment

Absorption from the GI tract is known to vary in oedematous states such as chronic kidney disease and heart failure. This inherently affects bioavailability between diuretics, as well as between different formulations of the same diuretic. As with all diuretics, there is wide interpatient variability and doses are titrated according to need and effect.
Xaqua® is a 5mg divisible tablet and offers dosing variability. The manufacturers recommended *starting* dose is 2.5mg (half a tablet) but there is no direct equivalence when *switching* products.

Recommendation

Metolazone preparations should be prescribed and dispensed by brand.

For short term use:
Metolazone is a potent diuretic typically used short term and under close supervision. In clinical practice, potential greater efficacy of Xaqua® is not anticipated to impact clinical outcome. Patients using metolazone are acknowledged to be diuretic resistant and therefore a small change in bioavailability is unlikely to translate to a change in clinical effect.

For longer term use:
For patients established on a stable dose of metolazone, it is recommended that they are switched directly with close monitoring and the dose titrated as per usual practice; recognising that if patients are switched to Xaqua® there may be an increased efficacy and adverse effects. (In some cases it may be better to make a downward dose adjustment and risk a decrease in efficacy and then titrate up).
The switch should be clearly documented and communicated with all care providers and the patient.

Patient advice [3]:

- Patients should be aware that their brand of metolazone should not be switched unless recommended by a healthcare professional.
- Patients should be warned of the symptoms of under and over dosing.
- Patients should be advised that a tablet cutter can be given to support taking part tablets.

1. https://www.medicines.org.uk/emc/product/13419
2. https://mhraproducts4853.blob.core.windows.net/docs/947a25ae32f3cb439b77b68a83615718ab5bd6cc
3. https://www.sps.nhs.uk/articles/differences-between-metolazone-preparations-and-safety-considerations/