Direct Healthcare Professional Communication

24th August 2021

Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion - Potential for crystallisation

Dear Healthcare professional,

In agreement with the Medicines and Healthcare products Regulatory Agency (MHRA), the UK Marketing Authorisation Holders of products containing amiodarone hydrochloride 50 mg/ml concentrate, namely hameln pharma gmbh, Bowmed Ibisqus Limited/ Ibigen S.r.l. and Aventis Pharma Limited trading as Sanofi, would like to inform you of the following:

- **Reports have been received of visible crystals of amiodarone hydrochloride within the solution of a small number of ampoules of marketed product**

Healthcare professionals are advised to:

- **Visually inspect ampoules of amiodarone for clarity, particulate matter, discolouration and the integrity of the container**
- **Only use the solution if it is clear and the container is undamaged and intact**

Background information

Amiodarone hydrochloride is an antiarrhythmic used for the management of life-threatening ventricular arrhythmias (tachycardia or fibrillation) and supraventricular arrhythmias (fibrillation or flutter) and Wolff-Parkinson-White Syndrome.

The potential for amiodarone solutions to crystallise and the associated potential for amiodarone-induced phlebitis are known and have been previously discussed in the scientific literature [1, 2].

Amiodarone in aqueous solution is associated with crystallisation due to poor solubility. To overcome this, the molecule is typically solubilised as part of a *micellar system* using an excipient, such as polysorbate 80, which acts as a surfactant. Any breakdown of this micellar system can lead to crystallisation of amiodarone in solution, which has been observed both at high concentrations of amiodarone (e.g. in ampoules of concentrate) and at low concentrations (e.g. in infusion bags during administration).

While the potential for amiodarone solutions to crystallise is known, following receipt of a small number of reports of crystallisation in ampoules from separate batches of product, and the subsequent investigations undertaken, the Marketing Authorisation Holders would like to highlight this potential for crystallisation to healthcare professionals.

Adverse reactions

As noted in the prescribing information for the products, infusion phlebitis is listed as one of the most common adverse drug effects reported with intravenous amiodarone hydrochloride.

There has been no identified increase in the reporting of adverse reactions that would be considered related to the crystallisation of amiodarone during infusion (e.g. phlebitis, thrombophlebitis). While this

doesn't exclude the possibility of adverse health consequences, it further supports the overall probability that the occurrence of such reactions is low.

Recommendations for use

To inform healthcare professionals of the potential for crystallisation, the Marketing Authorisation Holders, in agreement with the MHRA, have issued this Direct Healthcare Professional Communication to provide additional information for healthcare professionals.

Healthcare professionals should continue to follow the advice below:

Before use, the sterile concentrate should be visually inspected for clarity, particulate matter, discolouration and the integrity of the container. The solution should only be used if it is clear and the container is undamaged and intact.

Although the use of in-line filters is not considered to be standard practice in the UK for all infusions of medicinal products, healthcare professionals may wish to consider the use of in-line filters for infusions of solutions that are known to crystallise, including solutions of amiodarone [1,2].

Call for reporting

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

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason;
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼.

It is easiest and quickest to report ADRs online via the Yellow Card website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store.

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.

Suspected side effect can also be reported by calling 0800 731 6789 for free.

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

Company contacts

This letter concerns all amiodarone hydrochloride 50 mg/ml concentrate medicinal products that are licensed in the UK and has been agreed by the below listed companies.

Marketing Authorisation Holder	**Registered Product Name**	**Contact details**
hameln pharma gmbh	Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion	hameln pharma ltd Nexus, Gloucester Business Park Gloucester, GL3 4AG Tel: 01452 621 661 drug.safety@hameln-pharma.co.uk
Bowmed Ibisqus Limited/ Ibigen S.r.l.	Amiodarone 150 mg/3 ml Concentrate for Solution for Injection/Infusion	Bowmed Ibisqus Limited The Old Dairy, Brynkinalt Business Centre Brynkinalt, Chirk, Tel: 01483 212 151 medinfo@bowmed.com
Aventis Pharma Limited Trading as Sanofi	Cordarone X 150 mg/3 ml Solution for Injection	Sanofi 410 Thames Valley Park Drive Reading, Berkshire, RG6 1PT Tel: 0800 035 2525 uk-medicalinformation@sanofi.com

Signed on behalf of the above MA Holders

Richard Wysocki MRPharmS
Medical Affairs Director, hameln pharma ltd

References

1) Phlebitis in Intravenous Amiodarone Administration: Incidence and Contributing Factors. *Crit Care Nurse* (2019) 39 (1): e1–e12 https://aacnjournals.org/ccnonline/article/39/1/e1/20866/Phlebitis-in-Intravenous-Amiodarone-Administration

2) Phlebitis in Amiodarone Administration. Incidence, Contributing Factors, and Clinical Implications. *Am J Crit Care* (2013) 22 (6): 498-505 https://medest118.files.wordpress.com/2013/12/phlebitis-in-amiodarone-administration.pdf