WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

A World Federation of Hemophilia (WFH) Advisory on Particulate Matter in Emicizumab (HEMLIBRA) and Other Biologic Agents

8 October 2019

Background

Since the development of intravenous therapies, the presence of particulate matter in injectable drugs has been a concern for clinicians. While some particles can come from outside sources (e.g. when the product is prepared for use), others are "intrinsic" to the manufacturing process specific to the drug. In the latter case, sources for these particles may be the solution itself and its ingredients, contact with components used in manufacturing (e.g. tubing) or the product's package (e.g. rubber stopper). In some cases, intravenous infusion of injectables which contain particulate matter has been associated with harm. Accordingly, the United States Pharmacopeia (USP) has established fixed limits for the amount particulate matter in preparations intended for intravenous use and states that, prior to dispensing, all containers of intravenous preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter in their contents and not distributed if the amount exceeds the set limit. Test procedures for determination of the presence of particulate matter are set by the USP and manufacturers are required to follow these industry standards.

Particulate matter in injectables that are intended for intramuscular and subcutaneous administration would not carry the same risk as for intravenous administration, but industry standards still apply and limits are determined under review by the regulators (e.g. FDA).

Context for this Medical Communication

On October 5, 2019, the WFH received the following information from representatives of Roche/Genentech/Chugai, manufacturers of emicizumab (HEMLIBRA):

During a routine examination of drug product batches, as part of our quality assurance systems and processes, hardly visible, translucent particles were identified in Hemlibra® (emicizumab), outside our particle specification.

These particles are inherent to the drug product and based on toxicology and safety assessments and review of available data, the benefit/risk profile of Hemlibra remains unchanged as a result. They consist of protein (Hemlibra drug substance) and silicone oil (PDMS, polydimethylsiloxane). Silicone oil is a non-toxic, organic polymer that is included in all parenteral medicines. Translucent particles are commonly observed and present in other approved biologics.

We have informed health authorities in March 2019. The European Medicines Agency (EMA), US Food and Drug Administration (FDA), Swissmedic, Health Canada, and the Ministry for Health, Labour and Welfare (MHLW) in Japan all agreed with our assessment that the benefit/risk profile of Hemlibra remains unchanged, and have supported the continued distribution of Hemlibra to patients to avoid therapy interruption. We have submitted the results of our final analysis to the health authorities and continue to engage with these health authorities.

We are committed to producing high quality products for our patients, which is why we have rigorous manufacturing monitoring, controls and testing in place for all our medicines, including Hemlibra.

WFH Advisory

After the WFH was informed of this issue on October 5, 2019, representatives from Roche/Genentech/Chugai were available to answer questions.

The following points were presented to the WFH:

- The appearance of particulate matter includes vials of emicizumab that were used both during the clinical trial program and commercially available product. The particulate matter exceeded the manufacturers pre-established threshold.
    a. In a look-back at all previous lots of emicizumab, this problem has been present since the initial clinical trials but was only recently identified.
- This is a manufacturing issue that is well-described in scientific literature and subject to monitoring by regulatory health authorities, who have provided their assessment and most have deemed that there is no change to the risk-benefit evaluation for use of emicizumab.
    a. The finding of particulate matter in a limited number of vials of emicizumab has been reviewed by regulatory health authorities in the United States, Switzerland, Canada, Japan and the European Union who have all determined that there is no change to the risk-benefit evaluation of emicizumab as it is currently manufactured and available for patient use.
    b. Greece regulatory authorities have agreed that patients on the Roche expanded access program may remain on emicizumab, but have put a hold on switching additional patients to emicizumab until this matter is fully resolved.
- Risk from particulate matter in injectables intended for subcutaneous administration is likely reduced compared to intravenous injectables.
- No adverse events linked to the particulate matter have been reported. No reports from end-users of product have been received by Roche/Genentech/Chugai up to this point.

Based on the information that the WFH has available at this time, including information on the assessments of regulatory health authorities, the WFH does not recommend a change in prescribing practice nor interruption in the use of emicizumab for patients already using the product.

Further, the WFH has the following recommendations:

- WFH expects that Roche/Genentech/Chugai will conduct a full review of their manufacturing and quality control processes to determine how they may better ensure that all product meets their industry standard on the limits to particulate matter in emicizumab
- WFH has requested notification of any regulatory feedback of this manufacturing issue that changes the risk-benefit assessment and has requested any follow up on this matter after Roche/Genentech/Chugai have completed their manufacturing process and quality control review, including final resolution with the Greek authorities
- The current recommendation regarding no change in prescribing practice and no interruption in the use of emicizumab is an interim recommendation pending our assessment of the full review by Roche/Genentech/Chugai of their manufacturing and quality control
- WFH urges Roche/Genentech/Chugai to inform the health care providers and patient communities in a more timely and structured manner in the future. Once this issue began circulating among multiple regulatory agencies, the communication of this incident was inadequate: the communication to the national member hemophilia organizations (NMOs) was delayed overall; organizations received information at various points in time, if at all; and the facts provided were inconsistent between organizations. This is not an acceptable practice and not in keeping with the trust from the community Roche/Genentech/Chugai has indicated is important to them.

Any patient or caregiver who has questions or concerns about this matter should contact their Hemophilia Treatment Center. The WFH will continue to closely monitor this matter and provide additional updates as warranted.

References

United States Pharmacopeia. https://www.usp.org/biologics. Accessed October 6, 2019.

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Tran T, Kupiec TC, Trissel LA. Particulate Matter in Injections: What is It and What are the Concerns? International Journal of Pharmaceutical Compounding (2006) 10(3):202-204.