European Haemophilia Consortium (EHC) Communication
on Particulate Matter in Emicizumab (Hemlibra®) and Other Biologic Agents

Background information: Since the development of intravenous therapies, the presence of particulate matter in injectable drugs has been a concern for clinicians and patients. 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, regulators have established fixed limits for the amount of 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 these are not distributed if the amount exceeds the set limit. Test procedures for determination of the presence of particulate matter are set by regulators 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. European Medicines Agency).

Context for this Communication
On October 5, 2019, the EHC received the following statement from representatives of Roche, 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.*

EHC Statement
The EHC was informed of this issue on October 5, 2019. Representatives from Roche were available to answer questions on October 6. The EHC verified the information presented by Roche with representatives from the European Medicines Agency (EMA) on October 7.

The EHC herewith communicates the following:

- 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 manufacturer's pre-established threshold.

- In a look-back at all previous lots of emicizumab, this problem has been present since the initial clinical trials but was not identified at that time.
- This is a manufacturing issue that is described in scientific literature and subject to oversight by regulatory health authorities who have provided their assessment and deemed that there is no change to the risk-benefit evaluation for use of emicizumab.
- The finding of particulate matter in vials of emicizumab has been reviewed by regulatory health authorities in the European Union, Switzerland, the United States, Canada and Japan 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.
- Greek regulatory authorities have agreed that patients on the Roche expanded access program may remain on emicizumab, but no new patients may be started 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 the product have been received by Roche up to this point.

Based on the information available, the EMA has not recommended a change in prescribing practice nor interruption in the use of emicizumab for patients already using the product.

The EHC has the following recommendations:

- The EHC expects that Roche 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;
- The EHC expects that Roche conduct a retrospective review of all adverse events in patients exposed to emicizumab;
- The EHC has requested access to the EMA assessment report relating to this investigation;
- The EHC has requested notification by Roche 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 have completed their manufacturing process and quality control review, including final resolution with the Greek authorities;
- Any patient or caregiver who has questions or concerns about this matter should contact their Haemophilia Treatment Centre or National Patient Organisation;
- **The EHC calls on Roche to inform patient communities and healthcare providers when there are potential safety issues in a transparent and timely manner.**

The EHC will continue to closely monitor this matter and provide additional updates as needed.