FRESENIUS MEDICAL CARE
Global Medical Office

MEMO

TO: **Health Care Professionals and Providers, Patients, Employees, Affiliates and Partners**

FROM: **Global Medical Office**

DATE: **August 05, 2020**

SUBJECT: **Statement Regarding Root Cause Investigations of Dialyzer-Associated Adverse Events Appearing Clinically as Hypersensitivity (Like) Reactions**

In 2011, Fresenius Medical Care (FME) introduced a new family of dialyzers called FX CorDiax. This high-performance dialyzer was designed with a profile specifically aimed at enhancing cardioprotection and reducing the risks associated with cardiovascular disease in dialysis dependent patients. With growing market penetration of the CorDiax dialyzer family in various countries, a low yet increased and higher than expected rate of hypersensitivity or hypersensitivity-like reactions [HS(L)Rs] were observed with FX CorDiax dialyzers compared to the FX class of dialyzers. Thus, on March 2nd, 2015, FME issued a field safety notice regarding this observation.

As a company committed to providing best-in-class products and therapies for our patients and customers, we proactively established a project team including various experts with the mandate to scrutinize this issue from different perspectives and investigate the root cause of the observed HS(L)Rs. All activities of the project team were conducted with the utmost diligence and highest sense of responsibility. Even though the rate of HS(L)Rs graded with severity levels 3-5 according to the CTCAE (Common Terminology Criteria of Adverse Events) classification declined in the following years, the project group continued to explore the root cause with almost 40 distinct in-vitro as well as in-vivo studies.

The investigations that FME performed, now completed, can be segmented into three main areas:

- Understanding the potential pathophysiological pathways involved: complement activation, lectin pathway, bradykinin release/activation, gene expression, cytokine levels, chemokine stimulation, basophil activation, white blood cell, and platelet activation,

- Evaluating the clinical profiles of the affected patients, their treatment characteristics, as well as, characteristics of the dialysis facilities where the events took place,

- Identifying causal and non-causal factors with a focus on analyzing the potential role of each component of the dialysis procedure as well as all materials involved in the production of the dialyzers and supplies used during therapy: membrane extracts, membrane surface, protein adsorption on the membrane, biocompatibility profiles of polysulfone membranes, machine hydraulics, priming procedure.

The investigations initiated in the scope of this root cause project did not culminate in identifying a single, distinguishable root cause for the increased frequency of HS(L)Rs with FX CorDiax dialyzers. Analyses focusing on particular clinical applications provided trends pointing to increased occurrence in incident versus prevalent patients, occurrence predominantly within the first 30 minutes of treatment, clustering and higher frequency of events mainly in regions within four countries. A reduced rate of occurrence was noted when patients were introduced gently to their initial dialysis treatment with adjustment such as low blood flows during HD initiation as modality. One summative vigilance report of a cluster of 18 HS(L)Rs in four patients in one country made the project team also consider climatic influences, such as low relative humidity, as potential contributing factors. Individual practice patterns and the storage conditions of some clinics also seemed to have an impact on the occurrence rates of HS(L)Rs. The project team also investigated standard

operating procedures with regard to disinfection protocols. Yet, as mentioned before, a single, uniquely identifiable causative was not found.

In light of these investigations performed in the course of this root cause investigation of the CorDiax dialyzer family, our current conclusions are:

- The rate of adverse events CTCAE grades 3-5 has declined since the release of the field safety notice and is now lower than 3 cases per million dialyzers sold. We believe that the recommendations communicated in the field safety notice might have played a role in this reduction.

- HS(L)Rs occur mostly in incident patients and frequently resolve with a gentle initiation of dialysis. This was addressed in the field safety notice previously mentioned. Additional root-cause investigations confirmed this observation and recommendation.

- A single, specific root cause for the HS(L)Rs could not be found; the root cause is felt to be multi-factorial.

- HS(L)Rs appear in clusters. Clustering of the events not only emphasizes the importance of standardized processes but also application, monitoring and adherence to these procedures and in particular strict compliance with the instructions for use.

Fresenius Medical Care is committed to the well-being of all patients and providing dialysis products of the highest quality. FME also continues to uphold the commitment to understanding the causes of HS(L)Rs and informing the community of health professionals of what we learn from such investigations.

After reviewing all the results of the extensive investigations performed over several years with the support and endeavor from multiple competent experts, we have chosen to close the active project. The company will continue to closely follow up cases of HS(L)Rs according to our stringent corporate safety guidelines and standard operating procedures with any additional root cause investigations as appropriate.

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