

March 1th, 2024

Etoposide: Risk of infusion-related hypersensitivity reactions when administered with an in-line filter

Dear Healthcare Professional,

This letter is sent in agreement with the National Competent Authority to inform you of the implementation of a **risk of infusion-related hypersensitivity reactions when administered with an in-line filter.**

Summary

The following recommendations apply only to etoposide and not to etoposide phosphate.

- An increased risk of infusion-related hypersensitivity reactions has been observed with the use of in-line filters during administration of etoposide-containing medicinal products.
- It is currently unknown whether the risk increase occurs with all types of in-line filters or only with in-line filters made of certain materials.
- In-line filters should not be used.

Background on the safety concern

Etoposide-containing drugs are indicated for the treatment of various cancers in adults and children, including testicular cancer, small-cell lung cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute myeloid leukemia, gestational trophoblastic neoplasia and ovarian cancer.

Some cytostatics require the use of in-line filters during application, according to the technical information and usage information. These filter systems are made up of various components and their main function is to retain particles¹. Various guidelines have recommended the use of in-line filters during continuous or intermittent infusion of etoposide-containing medicinal products². The SmPC for medicines containing etoposide (except etoposide phosphate) does not mention the use of in-line filters. It is neither recommended nor prohibited. Therefore, it might be possible for in-line filters to be used according to local medical practice.

Studies have been published in the literature showing an increased risk of infusion-related hypersensitivity reactions when an in-line filter is used for administration^{3 4}. The exact mechanism behind this observation is not known, but it is suspected that the solubilizers used in etoposide-containing drugs interact with the filter or infusion system and that its components (e.g. plasticizers) dissolve.

Based on available literature data, European Medicine Agency (EMA)/ PRAC considers a causal relationship between the administration of drugs containing etoposide (not etoposide phosphate) with an in-line filter and the increased risk of hypersensitivity reactions to be at least possible.

The PRAC therefore concluded that the product information for medicinal products containing etoposide (not etoposide phosphate) for IV administration should be changed accordingly.

Based on available information, the safety information in section 4.4 "Special warnings and precautions for use" of the SmPC will be updated as appropriate to reflect the latest data and recommendations:

"An increased risk for infusion-related hypersensitivity reactions was observed when in-line filters were used during etoposide administration. In-line filters should not be used".

Call for reporting

Reporting suspected adverse reactions after approval is of great importance. It enables continuous monitoring of the benefit-risk ratio of the drug. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorization holder or to the relevant pharmaceutical commission in accordance with professional law.

Company contact point

{Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address}.

Note: Local country organizations should update their contact details with above mentioned information as applicable.

References

¹ **Kim** SH, Stollhof B, Krämer I. Selection and handling of in-line filters for parenteral administration of tumor therapeutics. Mainz, Germany: Hospital Pharmacy; 2018;39:11–18

² **BC** Cancer Agency. Provincial Pharmacy Directive III-50-04: Management of Particulate During Sterile Preparation. Vancouver, British Columbia: BC Cancer Agency; July 9, 2014.

³ **Tillman** EM, Suppes SL, Miles N, Duty AM, Kelley KL, Goldman JL. Risks and mitigation strategies to prevent etoposide infusion-related reactions in children. *Pharmacotherapy*. 2021 Aug;41(8):700-706. doi: 10.1002/phar.2603. Epub 2021 Jun 29. PMID: 34129705; PMCID: PMC8617599.

⁴ **Dodier** K, Laverdière I, Roy MJ. Etoposide hypersensitivity reactions associated with in-line filter use: A retrospective cohort study at CHU de Québec-Université Laval. *J Oncol Pharm Pract*. 2022 Dec 21:10781552221146801. doi: 10.1177/10781552221146801. Epub ahead of print. PMID: 36544381.