Summary Safety Review - Imbruvica (ibrutinib) - Assessing the Potential Risk of Hemophagocytic Lymphohistiocytosis

Product: Imbruvica (ibrutinib)

Potential Safety Issue: Hemophagocytic Lymphohistiocytosis (HLH), a condition where large numbers of immune cells destroy other blood cells.

Key Messages

- **Imbruvica (ibrutinib) is a drug authorized for sale in Canada to treat certain types of bone marrow and white blood cell cancers, alone or in combination with other therapies. It is also used for the treatment of patients who suffer from refractory chronic graft versus host disease after receiving transplanted tissue from a donor.**
- **Health Canada reviewed the potential risk of HLH, a rare life-threatening condition where a large number of immune cells attack and destroy other blood cells, with Imbruvica use. This review was triggered by 5 international cases published in scientific and medical literature and one case reported in Canada.[a]**
- **Health Canada's review of the available information did not establish a link between the use of Imbruvica and the risk of HLH. Health Canada will continue to monitor the safety of Imbruvica, as it does for all health products on the Canadian market, to identify and assess potential harms.**

Overview

Health Canada reviewed the potential risk of HLH in patients treated with Imbruvica (ibrutinib). The safety review was triggered by 5 published international cases and one Canadian case of HLH in patients taking Imbruvica.

HLH is a life-threatening overreaction of the immune system where a large number of immune cells attack and destroy other blood cells. HLH is characterized by a large release of certain proteins by immune cells in the blood (referred to as a "cytokine storm" or "cytokine release syndrome"), as well as the accumulation of activated immune cells (lymphocytes and macrophages) in organs and tissues.

Use in Canada

- Imbruvica (ibrutinib) is a prescription drug authorized for sale in Canada to treat:
    - Certain types of blood and bone marrow cancers, such as chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma, and Waldenström's macroglobulinemia.
    - Chronic graft versus host disease, a complication of organ transplantation, in patients who have failed first-line therapy and who need additional therapy.
- Imbruvica has been marketed in Canada since 2014. It is currently available as 140 mg, 280 mg, 420 mg, and 560 mg ibrutinib tablets, and 140 mg ibrutinib capsules.
- There were about 25,000 prescriptions filled for Imbruvica in Canada in 2019.

Safety Review Findings

- Health Canada reviewed information from searches of the Canada Vigilance database, international databases, published literature and clinical studies.
- Health Canada's review focused on 25 cases, including 5 cases published in the scientific and medical literature, in order to assess the link between the use of Imbruvica and HLH.
- The 25 cases include one Canadian and 24 international cases of HLH in patients taking Imbruvica. Of the 25 cases, 12 met the criteria for further assessment to determine if there was a link between Imbruvica and HLH. Among the 25 cases, 10 cases were found to be possibly linked to the use of Imbruvica; one case was not likely to be linked; and 14 cases did not have enough information to be assessed. Of the 10 cases possibly linked to the use of Imbruvica, 7 resulted in death (including the Canadian case). A possible link between the death and use of Imbruvica was established in all of these 7 cases. Assessing whether HLH was related to use of Imbruvica in these reports was challenging due to several contributing factors including other existing medical conditions (present in all 25 cases), such as cancer or infections that could have been possible causes of HLH, and patients taking other medications besides Imbruvica.
- Health Canada could not establish a link between the use of Imbruvica and HLH.
- A review of the literature did not identify a clear biological mechanism to explain how Imbruvica could lead to HLH.

Conclusions and actions

- Health Canada's review of the available information did not establish a link between the use of Imbruvica and the risk of HLH.
- Health Canada encourages consumers and healthcare professionals to report any side effects related to the use of this product.
- Health Canada will continue to monitor safety information involving Imbruvica, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action when any new health risks are identified.

Additional information

The analysis that contributed to this safety review included scientific and medical literature, Canadian and international information and what is known about the use of this drug both in Canada and internationally.

For additional information, contact the Marketed Health Products Directorate.

References

1. Ambinder AJ, Hambley B, Shanbhag S, Merrill SA. Ibrutinib-associated hemophagocytic lymphohistiocytosis: A case series from Johns Hopkins. Am J Hematol 2019;94(11):E296-E299.
2. Cavallari M, Ciccone M, Falzoni S et al. Hemophagocytic Lymphohistiocytosis after EBV reactivation and ibrutinib treatment in relapsed/refractory Chronic Lymphocytic Leukemia. Leuk Res Rep 2017;7:11-13.
3. Poole A, Girard N, Clayton F, Tantravahi SK. Rapid onset of hemophagocytic lymphohistiocytosis in a patient with refractory chronic lymphocytic leukemia treated with ibrutinib. Leuk Lymphoma 2017;58(5):1258-1261.
4. Kleynberg RL, Schiller GJ. Secondary hemophagocytic lymphohistiocytosis in adults: an update on diagnosis and therapy. Clin Adv Hematol Oncol 2012;10(11):726-732.
5. La RP, Horne A, Hines M et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133(23):2465-2477.

Footnotes

a. Canadian reports can be accessed through the Canada Vigilance Online Database.