SAFETY ALERT

DRAP SAFTEY ALERT NO. 57

Potential Risk of Tumour Lysis Syndrome with Sorafenib.

Date: 23rd of April, 2025.

Target Audience.

- Provincial Health Departments/Provincial PV Centres/Healthcare Commissions;
- Manufacturers and importers of Sorafenib; and
- Healthcare Professionals.

Background.

Health Canada, in its safety review reports issued through the Infowatch Newsletter (June 2024 issue), informed about the potential risk of Tumor lysis syndrome (TLS) with the use of Nexavar. The safety review was triggered by a labelling update made by the EMA and international case reports published in the medical literature. Health Canada reviewed information provided by the manufacturer, and from searches of the Canada Vigilance database, international databases and the scientific literature. Health Canada reviewed 9 international cases of TLS in patients taking sorafenib, including 8 from the published literature. All 9 cases were found to be possibly linked to the use of sorafenib, although a potential contribution from spontaneous TLS (cancer cell breakdown in the absence of treatment) could not be ruled out. The reported time to the onset of TLS ranged from 3 to 34 days after starting treatment with sorafenib. Five deaths were reported among the 9 cases assessed. All 5 deaths were found to be possibly linked to TLS from sorafenib treatment. However, other causes of death, such as cancer progression, could not be ruled out. Health Canada reviewed 1 additional article published in the scientific literature. A link between sorafenib and TLS could not be established due to study limitations. Health Canada concluded the review and found a possible link between the use of Nexavar and the risk of TLS. Health Canada is working with the manufacturer to update the CPM for Nexavar to include the risk of TLS.

Previously, the PRAC committee of the European Medicines Agency (EMA) in its February 2022 meeting considered the available evidence, including the data submitted by the MAH (Bayer AG), and recommended including the following information in the warning and precaution sections of Sorafenib.- "*Cases of TLS, some fatal, have been reported in postmarketing surveillance in patients treated with sorafenib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.* Likewise, the PRAC also recommended listing tumour lysis syndrome in the ADRs section with the frequency 'not known'.

Tumour lysis syndrome is a potentially life-threatening condition that can occur during cancer treatment. When cancer cells are killed by the cancer treatment, they release their contents (salts and proteins) into the blood. When cancer cells break down faster than the kidneys can remove these substances from the blood, it can cause changes to the chemical balance in the blood, which may result in damage to organs, most commonly the kidneys, heart and brain.

Action in Pakistan.

The case was discussed in the 5th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) held on 2nd of Janauary, 2025 which decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 that registration holders should update the product information of Sorafenib by including information about the risk of tumour lysis syndrome (TLS) in the warning and precaution section and also to list TLS in the adverse drug reaction section with "unknown" frequency.

Therapeutic Good Affected.

Name: Nexavar (Sorafenib) is a prescription drug for the treatment of liver cancer (hepatocellular carcinoma) that cannot be treated by surgery, late-stage kidney cancer (renal cell carcinoma) and late-stage thyroid cancer (thyroid carcinoma).

Advice for Healthcare Professionals.

Healthcare Professionals are informed that cases of TLS, some fatal, have been reported in postmarketing surveillance in patients treated with sorafenib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.

Advice for patients.

If you are on the treatment with sorafenib and experience the following symptoms, contact your doctor immediately as this can be a life-threatening condition: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness. These may be caused by a group of metabolic complications that can occur during the treatment of cancer, which are caused by the breakdown products of dying cancer cells (Tumour lysis syndrome (TLS)) and can lead to changes in kidney function and acute renal failure.

Guidelines for reporting Adverse Drug Reactions (ADRs).

Healthcare professionals and patients are requested to report any adverse drug reaction with Sorafenib and/or any other medicine to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) through the Med Vigilance E-Reporting System (E-forms) available on the DRAP website. Similarly, adverse events and adverse drug reactions can also be reported through the VigiMobile App, which can be downloaded by scanning the barcode available on the DRAP website.

References.

- Minutes of the 5th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC), DRAP.
- Health Canada: Health Product InfoWatch: June 2024
- PRAC recommendations on signals adopted at the 7-10 February 2022 PRAC meeting.