Important Safety Information on
PLAQUENIL in the context of COVID-19 for risk of QT prolongation and drug-drug interactions

May 14, 2020

Audience
General practitioners, hospitals, pharmacists, infectious disease specialists, internists, emergency physicians

Key messages

- **Hydroxychloroquine has no Marketing Authorization for the management of COVID-19 anywhere in the world. Therefore, any prescription of hydroxychloroquine for this medical purpose is off-label.**
- **Hydroxychloroquine is known to cause QT prolongation and subsequent arrhythmias, including torsade de pointe, in patients with specific risk factors. The magnitude of QT prolongation may also increase with increasing concentration of hydroxychloroquine. This cardiac risk could be potentiated by the association of hydroxychloroquine with other drugs known to prolong the QT interval, such as azithromycin.**
- **A significant number of serious and life-threatening cases of QT prolongation, torsade de pointe, syncope, cardiac arrest, and sudden death temporally associated with the concomitant use of hydroxychloroquine with other drugs known to prolong the QT interval (such as azithromycin), have recently been reported.**
- **Healthcare professionals are advised to show caution in using hydroxychloroquine off-label in the management of COVID-19. In particular, cardiac ECG monitoring at hospital is advised in patients with specific risk factors (e.g. co-administration of hydroxychloroquine with other drugs known to prolong the QT interval, including but not limited to some anti-infectives, such as azithromycin).**

What is the issue?
A significant number of serious and life-threatening cases of QT prolongation, torsade de pointe, syncope, cardiac arrest, and sudden death have been reported to Sanofi Global Pharmacovigilance over the last couple of weeks in the context of COVID-19 management. In most of these cases, hydroxychloroquine was co-administered with a drug known to induce QT prolongation (e.g. azithromycin). The majority of patients recovered after hydroxychloroquine discontinuation.

In view of the seriousness of these cases, the off-label use of hydroxychloroquine in COVID-19 management should carefully be evaluated by the prescribers, and its use in combination with any drug that prolongs the QT should be supervised by a physician at hospital. Close monitoring of patients should be carried out, which includes at least the following:

- Use the lowest dose of hydroxychloroquine possible
- Conduct cardiac monitoring at the outset and during treatment
- Monitor serum potassium and magnesium regularly
- Consider discontinuation of hydroxychloroquine, if QTc increases by >60 milliseconds or absolute QTc >500 milliseconds

Products affected
PLAQUENIL (hydroxychloroquine sulfate tablets)

Background information
To date, there is insufficient clinical evidence to draw any conclusion over the clinical efficacy and safety of hydroxychloroquine in the management of COVID-19, whether it is used as a single agent or in combination with any other medicines such as azithromycin.

Hydroxychloroquine has a long terminal elimination half-life ranging from 30 to 60 days.

Hydroxychloroquine is known to prolong QT interval in some patients in a dose-dependent way. This cardiac risk is multifactorial and is potentiated by the association of hydroxychloroquine with other drugs known to prolong the QT interval, e.g., class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives (such as azithromycin), as well by patient's underlying conditions:

- cardiac disease, heart failure, myocardial infarction
- bradycardia (< 50 bpm)
- history of ventricular dysrhythmias
- uncorrected hypocalcemia, hypokalemia and/or hypomagnesemia

Caution is advised in patients with hepatic or renal disease, in whom a reduction in hydroxychloroquine dosage may be necessary.

Information for health care professionals
Healthcare professionals should report any off-label use with or without adverse reactions associated with the use of hydroxychloroquine.

Report health or safety concerns
Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any case of off-label **PLAQUENIL** use, with or without serious or unexpected side effects, should be reported to sanofi-aventis Canada Inc. or Health Canada.

sanofi-aventis Canada Inc.
2905 Place Louis-R.-Renaud, Laval, Quebec, H7V 0A3
www.sanofi.ca 1-800-265-7927

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate
E-mail: hc.mhpd-dpsc.sc@canada.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Sincerely,

Original signed by

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