28 April 2020

# Use of Hydroxychloroquine (Plaquenil®) in the context of COVID 19 – Risk of QT prolongation and drug/drug interactions

Dear Healthcare professional,

Sanofi would like to inform you of the following important information about hydroxychloroquine:

## *Summary*

- **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 reports 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 has recently increased.**

- **Healthcare professionals are advised to show caution in using hydroxychloroquine off label in the management of COVID-19. In particular, in patients with specific risk factors (e.g. co-administration of hydroxychloroquine with other drugs known to prolong the QT interval, such as some anti-infectives, including azithromycin), cardiac ECG monitoring at hospital is advised.**

## *Background on the safety concern*

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.

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 use of hydroxychloroquine off-label 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, and 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

## *Call for reporting*

Healthcare professionals should report any off-label use with or without adverse reactions associated with the use of hydroxychloroquine, in accordance with the national spontaneous reporting system.

- Health Product Vigilance Center, Food and Drug Administration, Ministry of Public Health, Thailand

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