

30-Apr-2020

## **Use of Hydroxychloroquine [Plaquenil®] in the context of COVID 19 – Risk of QT prolongation and drug/drug interactions**

Dear Healthcare professional,

Sanofi in agreement with the Directorate General of Drug Administration 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 via [adrmcell.dgda@gmail.com](mailto:adrmcell.dgda@gmail.com) and [Bangladesh.pharmacovigilance@sanofi.com](mailto:Bangladesh.pharmacovigilance@sanofi.com).

### ***Company contact point***

[www.sanofi.com.bd](http://www.sanofi.com.bd)

Please refer to [www.dgda.gov.bd](http://www.dgda.gov.bd) and /or [www.sanofi.com.bd](http://www.sanofi.com.bd) for the current approved Summary of Product Characteristics and Patient Information Leaflet or PIL.

### ***Annexes***

For information, see below the labelling variation text being submitted by Sanofi to concerned local Health Authorities for their review and approval.

*Annex 1: List of contraindicated medications and latest information on drug interactions and corresponding precautions for use*

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### *Pharmacodynamic interactions*

#### Drugs known to prolong QT interval / with potential to induce cardiac arrhythmia

Hydroxychloroquine should be used with caution in patients receiving drugs known to prolong the QT interval, e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives due to increased risk of ventricular arrhythmia (see sections Warnings and Overdose). Halofantrine should not be administered with hydroxychloroquine.

#### Antidiabetic drug

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

#### Antimalarials

Administration of hydroxychloroquine with antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.

#### Antiepileptic drugs

The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

#### Others

There is a theoretical risk of inhibition of intra-cellular  $\alpha$ -galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

### *Effects of other medicinal products on hydroxychloroquine:*

#### Antacids

Concomitant administration with magnesium-containing antacids or kaolin may result in reduced absorption of chloroquine. Per extrapolation, hydroxychloroquine should therefore be administered at least two hours apart from antacids or kaolin.

#### Ciclosporin

An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered

### *Effects of hydroxychloroquine on other medicinal products:*

#### Digoxin

Hydroxychloroquine sulphate has been reported to increase plasma digoxin in levels. Serum digoxin levels should be closely monitored in patients receiving concomitant treatment.

#### Praziquantel

In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are

co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine.

**In addition, Sanofi updated its reference safety information with the following text to report potential interactions with CYP inhibitors and inducers and on p-gp substrates (that includes digoxin and ciclosporin):**

**This text was submitted in EU countries (e.g. Ireland, France) in early April 2020 for review and approval, hence the approved SPC provided with hydroxychloroquine supplies does not include it yet.**

#### CYP inhibitors or inducers

Concomitant use of cimetidine, a moderate CYP2C8 and CYP3A4 inhibitor, resulted in a 2-fold increase of chloroquine exposure. Per extrapolation, due to the similarities in structure and metabolic elimination pathways between hydroxychloroquine and chloroquine, a similar interaction could be observed for hydroxychloroquine. Caution is advised (e.g. monitoring for adverse reactions) when CYP2C8 and CYP3A4 strong or moderate inhibitors (such as gemfibrozil, clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice) are concomitantly administered.

Lack of efficacy of hydroxychloroquine was reported when rifampicin, a CYP2C8 and CYP3A4 strong inducer, was concomitantly administered. Caution is advised (e.g. monitoring for efficacy) when CYP2C8 and CYP3A4 strong inducers (such as rifampicin, St John's Wort, carbamazepine, phenobarbital) are concomitantly administered.

#### P-gp substrates

The inhibitory potential of hydroxychloroquine on P-gp substrates has not been evaluated. In vitro observations show that all other aminoquinolines tested inhibit P-gp. Therefore, there is a potential for increased concentrations of P-gp substrates when hydroxychloroquine is concomitantly administered. An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered. Increased digoxin serum levels were reported when digoxin and hydroxychloroquine were coadministered. Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when P-gp substrates with narrow therapeutic index (such as digoxin, ciclosporin, dabigatran) are concomitantly administered.