28th May 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 Malta Medicines Authority 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. Use of Hydroxychloroquine in COVID-19 pandemic in Malta should only be carried out in line with nationally agreed clinical protocols and with clinical supervision. In Malta, the use of Hydroxychloroquine in COVID-19 pandemic is defined and granted under art. 20 of the Malta Medicines ACT of 2003 for a specific product.**

- **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 closely follow nationally agreed clinical protocols and recommendations on the use of hydroxychloroquine in the management of COVID-19. Healthcare professionals are advised to show caution 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 in COVID-19 management should only be used as part of clinical trials or in line with nationally agreed clinical protocols 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:

- Follow the nationally approved dosing recommendations for hydroxychloroquine in the management of COVID-19
- 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 adverse reactions associated with the use of hydroxychloroquine to the Malta Medicines Authority using the ADR reporting form available at www.medicinesauthority.gov.mt/adrportal and sending it to Post-licensing Directorate, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 Malta, MALTA, or via e-mail to postlicensing.medicinesauthority@gov.mt

Company contact point

If you have any questions or require additional information, please write to

Sanofi Medical Information at Informazioni.medicoscientifiche@sanofi.com OR to Sanofi Pharmacovigilance at PharmacovigilanceMalta@sanofi.com

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: **Latest information on drug interactions and corresponding precautions for use**

Please refer to Medicines Authority website for the current approved Summary of Product Characteristics and Patient Information Leaflet.
In addition, the following drug-drug interactions were submitted within the worksharing procedure IE/H/xxxx/WS/120 in 04/2020. Hence the approved Summary of Product Characteristics and Patient Information Leaflet do not include them yet.

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 Section Warnings and Section Overdose).
Halofantrine should not be administered with hydroxychloroquine.

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.

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.

Effects of hydroxychloroquine on other medicinal products:
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 coadministered. 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.