



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 in agreement with Medsafe would like to inform you of the following important information about hydroxychloroquine:

Summary

- **Hydroxychloroquine is not approved for the management of COVID-19 anywhere in the world, including in New Zealand. 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. Therefore, any prescription of hydroxychloroquine for this medical purpose is considered off-label.**
- **Hydroxychloroquine is known to cause QT prolongation and subsequent arrhythmias, including torsade de pointes, 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.**
- **Recently there has been a significant increase in the number of reports of serious and life-threatening cases of QT prolongation, torsade de pointes, 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.**
- **Healthcare professionals are advised to use 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

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 hypocalcaemia, hypokalaemia and/or hypomagnesemia.

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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 off-label use of hydroxychloroquine in COVID-19 management should be carefully evaluated by prescribers and its use in combination with any drug that prolongs the QT interval should be supervised by a physician in a hospital setting. Close monitoring of patients should include the following:

- Use of the lowest dose of hydroxychloroquine as possible
- 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

In addition, several updates to **Section 4.5 Interactions with other medicines and other forms of interactions** of the New Zealand Data Sheet (DS) have been implemented and information on the changes is provided in Annex 1.

Call for reporting

Healthcare professionals should report any adverse reactions associated with the use of hydroxychloroquine, including those associated with off-label use, at <https://nzphvc.otago.ac.nz/reporting/>. In addition, off-label use outside of a clinical trial may also be reported, even when there is no adverse event.

Company contact point

If you would like any further information regarding Plaquenil please contact:

Sanofi Medical Information:

Tel: 0800 283 684 Option 2

Email: medinfo.australia@sanofi.com

Yours sincerely,



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ANNEX 1 - PLAQUENIL DATA SHEET UPDATES

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

(*new information on drug interactions)

Pharmacodynamic Interactions

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

Hydroxychloroquine should not be used 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 Special precautions and warnings for use and Section Overdose). Halofantrine should not be administered with hydroxychloroquine.

Antidiabetic drugs

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

Antimalarials

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other 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 α -galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

Concurrent use with drugs with oculotoxic or haemotoxic potential should be avoided if possible.

It has been suggested that 4-aminoquinolines are pharmacologically incompatible with monoamine oxidase inhibitors. Hydroxychloroquine sulphate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

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

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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.

Increased plasma cyclosporin levels have been reported when cyclosporin and hydroxychloroquine are 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.

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.