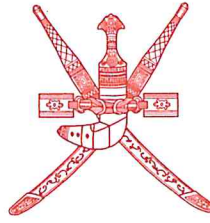


# Sultanate of Oman

## Ministry of Health

Directorate General of Pharmaceutical Affairs  
and Drug Control

MUSCAT



سلطنة عمان  
وزارة الصحة  
المديرية العامة للأدوية  
والرقابة الدوائية  
مسقط

To:

THE DIRECTOR GENERAL OF HEALTH SERVICES IN ALL GOVERNORATES  
Commanding Officer, Armed Forces Hospital (Al Khoudh & Salalah)  
Director General of Engineering Affairs, MOH  
Director General of Royal Hospital  
Director General of Khoula Hospital  
Director General of Medical Supplies (MOH)  
Director General of Pvt. Health Est. Affairs (to kindly arrange distribution to all Pvt. Hospitals)  
Director General of Surveillance & Disease Control  
Directorate General of Quality Assurance Centre  
Hospital Director (Al Nahda Hospital)  
Hospital Director (Al Massara Hospital)  
The Head of Medical Services in SQU Hospital  
The Head of Medical Services in Royal Oman Police  
The Head of Medical Services in Ministry of Defence  
The Head of Medical Services in The Diwan  
The Head of Medical Services in The Sultan's Special Force  
The Head of Medical Services in Internal Security Services  
The Head of Medical Services in Petroleum Development of Oman  
The Head of Medical Services in LNG Oman  
ALL PRIVATE PHARMACIES & DRUG STORES

After Compliments,

Please find attached our Circular No. ....88..... dated 28/04/2020 regarding the use of Hydroxychloroquine Plaquenil® in the context of COVID 19 – Risk of QT prolongation and drug/drug interactions.

Copy to:

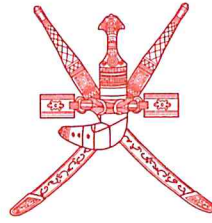
- Director, Office of H.E. The Undersecretary for Health Affairs
- Director of Pharmacovigilance & Drug Information Dept, DGPA&DC
- Director of Drug Control Department, DGPA&DC
- Director of Pharmaceutical Licensing Department, DGPA&DC
- Director of Central Quality Control Lab., DGPA&DC
- Director of Medical Device Control, DGPA&DC
- Supdt. of Central Drug Information

# Sultanate of Oman

Ministry of Health

Directorate General of Pharmaceutical Affairs  
and Drug Control

MUSCAT



سلطنة عمان  
وزارة الصحة  
المديرية العامة للصيد  
والرقابة الدوائية  
مسقط

Circular No. 88 / 2020

014 -09-1441 H

28 -04-2020

---

**Dear Health Professional Communication (DHPC): Use of Hydroxychloroquine  
Plaquenil® in the context of COVID 19 – Risk of QT prolongation and drug/drug  
interactions:**

---

Please be informed that a DHPC is approved for communication to all health care providers in the context of off- label use of Hydroxychloroquine in the treatment algorithm for COVID-19 pandemic.

The communication is aimed to (DHPC letter enclosed with this communication) inform HCPs about the safety concerns of Hydroxychloroquine and concomitant use of hydroxychloroquine with other drugs known to prolong the QT interval.

Healthcare professionals are encouraged to report any adverse events suspected to be associated with the above product or any other medicinal product to the Department of Pharmacovigilance & Drug Information in DGPA&DC.

  
**Dr. Mohammed Hamdan Al Rubaie**  
**Director General**



## **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 Ministry of Health Authority in Oman 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. coadministration 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 are requested to 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 the national reporting system:

**Department of Pharmacovigilance & Drug Information**

Phone No. +968 22357686,7687,

Fax: +968 22358489,

[www.moh.gov.om](http://www.moh.gov.om)

**And to Sanofi Gulf Pharmacovigilance department:**

24/7 contact number: 00971 561747001

Email: [Gulf.pharmacovigilance@sanofi.com](mailto:Gulf.pharmacovigilance@sanofi.com)

***Company contact point***

SANOFI, Level 3, One JLT, Jumeirah Lake Towers (JLT), DMCC

PO Box 53899, Dubai, UAE, Tel: +971 4 550 3600, Fax: +971 4 552 1050

For medical information, please call +971 565776791, or email: [medical-information.gulf@sanofi.com](mailto:medical-information.gulf@sanofi.com)

## ***Annex 1: Latest information on drug interactions and corresponding precautions for use***

### ***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 coadministered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine.



### **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.