PLEASE READ

Important Patient Safety Information

Approved by HPRA

May 2020

Use of Hydroxychloroquine [Plaquenil 200mg Film-Coated Tablets PA 540/155/1] in the context of COVID 19 – Risk of QT prolongation

Dear Healthcare professional,

Sanofi in agreement with the HPRA (Health Products Regulatory Authority) would like to inform you of the following important information about hydroxychloroquine:

Summary

- **Hydroxychloroquine is authorised in Ireland for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, dermatological conditions caused or aggravated by sunlight and, in combination with other therapies, juvenile idiopathic arthritis. The licensed dose in authorised indications in adults is 200mg or 400mg per day.**

- **Hydroxychloroquine is being used globally in the context of the ongoing pandemic in the management of patients with COVID-19 and is being investigated in clinical trials. However, hydroxychloroquine has no marketing authorisation for the management of COVID-19 anywhere in the world and therefore, prescription of hydroxychloroquine for this purpose, outside the context of a clinical trial, 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.**

- **The number of reports received globally by Sanofi 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 exercise caution in using hydroxychloroquine in the management of COVID-19. In particular, in patients who are at increased risk for QT prolongation (e.g. co-administration of hydroxychloroquine with other drugs known to prolong the QT interval, such as some anti-infectives, including azithromycin), close cardiac monitoring for QT prolongation and subsequent arrhythmias is advised. At present, national clinical guidance advises that prescribing of hydroxychloroquine for the management of patients with confirmed COVID-19 disease should be restricted to hospitals only. Prescribers should refer to the HSE 'Interim Guidance for the Use of Antiviral Therapy in the Clinical Management of Acute Respiratory Infection with SARS-CoV-2 (COVID-19)', which is updated as new evidence emerges.**

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 which is approximately 50 days in whole blood and 32 days in plasma.

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 concomitant administration 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:

- congenital or documented acquired QT prolongation
- 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 occurring globally have been reported to Sanofi Global Pharmacovigilance over the last number 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 (including, but not limited to, 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 carefully be evaluated by the prescribers and, in line with national clinical guidance, its use should be appropriately supervised by a physician in a hospital setting. Monitoring of patients should be carried out according to national protocols. The latest national clinical advice and recommendations provided by the HSE relating to the prescription of

hydroxychloroquine and monitoring of patients in the context of use for the management of COVID-19 should be followed.

For your information, updates to product information relating to supplemental information on the potential for interactions with strong and moderate CYP3A4 and CYP2C8 inhibitors and strong CYP2C8 and CYP3A4 inducers and on potential effect on p-gp substrates when administered concomitantly, are currently under review. Please regularly refer to www.medicines.ie or www.hpra.ie for the latest approved Summary of Product Characteristics and Patient Information Leaflet.

Call for reporting

Healthcare professionals should report any adverse reactions associated with the use of hydroxychloroquine, via HPRA Pharmacovigilance Website: www.hpra.ie

Adverse events arising from the use of medicines manufactured by Sanofi may also be reported to the Sanofi IE Pharmacovigilance department at: Sanofi, 18 Riverwalk, Citywest Business Campus, Dublin 24. Tel: +353 1 403 5600, Email: IEPharmacovigilance@sanofi.com

Company contact point

If you have any questions, please contact IEMedInfo@sanofi.com or call 01 4035600.

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