From: [redacted]
To: [redacted]
Subject: FW: Sanofi - Plaquenil Dear HCP letter [SEC=OFFICIAL]
Date: Thursday, 30 April 2020 2:27:31 PM
Attachments: image001.jpg
image002.jpg
01-plaquenil-dhcp-final-28apr20.pdf
03-plaquenil-minpi-v4-28apr20.pdf

From: [redacted]
Sent: Thursday, 30 April 2020 2:27:29 PM (UTC+10:00) Canberra, Melbourne, Sydney
To: [redacted],
Grant
Subject: FW: Sanofi - Plaquenil Dear HCP letter [SEC=OFFICIAL]

Hi All,

Sanofi have sent through the final DHCP letter for plaquenil which has included our changes (attached). Sanofi have indicated they are happy for us to publish the letter (though presumably once they've distributed it) or a web statement. In addition, they advised that Medsafe are intending to publish the letter on their website (though this hasn't happened yet).

Please let me know if there's anything further on this you'd like me to do.

Kind regards,
[redacted]

From: [redacted]@sanofi.com>
Sent: Thursday, 30 April 2020 1:04 PM
To: [redacted]@health.gov.au>
Cc: [redacted]@sanofi.com>; [redacted]
[redacted]@sanofi.com>
Subject: RE: Sanofi - Plaquenil Dear HCP letter [SEC=OFFICIAL]

Dear [redacted]

Thanks for your time today on the call. Please find attached the final signed DCHP letter for Plaquenil. We are making plan to distribute to the HCP groups you have advised. Also the mini PI will be dispatched together with the letter.

Please feel free to let me know if you have any further question regarding this.

Regards,

[redacted]

SANOFI | Research and Development
Global Regulatory Affairs – Regulatory Affairs Manager Australia and New Zealand
[redacted]

From: [redacted]@health.gov.au>

Sent: Friday, 24 April 2020 4:13 PM
To: [redacted]@sanofi.com>
Cc: [redacted]@sanofi.com>; [redacted]@sanofi.com>
Subject: [EXTERNAL] RE: Sanofi - Plaquenil Dear HCP letter [SEC=OFFICIAL]

EXTERNAL : Real sender is [redacted]@health.gov.au

Dear [redacted],

Please accept my apologies for the delays in providing feedback on the DHCP letter. Attached are our comments on the letter (note: we have not reviewed the Annex). I have discussed the SRR with PMAB and they have confirmed it is being evaluated as a matter of priority. PMAB may contact you or [redacted] in regards to this as well – at this stage it appears likely to be completed next week. If you wish to send the letter prior to the PI amendments being evaluated, then it would be acceptable for you to foreshadow these changes, and represent them as being under evaluation in the DHCP letter.

With regards to the distribution strategy, we support it going to GPs, Pharmacists and specialists. Please confirm that you intend to include the relevant representative groups for these practitioners. In addition, please confirm you will send it to hospital pharmacists, and the specialty areas identified in the recent scheduling change (dermatology; intensive care medicine; paediatrics and child health; physician; emergency medicine). Lastly, as discussed with [redacted], it is important that this letter also be sent to clinical trial investigators. Please sent to ACTA, and also any groups that requested supply for clinical trials, and any other investigators that you are aware of.

Please let me know if you have any further questions.
Kind regards,
[redacted]

From: [redacted]@sanofi.com>
Sent: Tuesday, 21 April 2020 2:10 PM
To: [redacted]@health.gov.au>
Cc: [redacted]@sanofi.com>; [redacted]@sanofi.com>
Subject: Sanofi - Plaquenil Dear HCP letter [SEC=No Protective Marking]

Hi [redacted],

I hope this email finds you well.

I have attached for your review the Plaquenil Dear HCP letter.

The information included in Annex 1 with a "*" is currently under TGA evaluation however, we are hoping to be able to speed up the SRR approval so that all content in the letter is approved by the time the letter is sent out to HCPs.

We would also appreciate your feedback with regards to the target audience for this letter - we are proposing to distribute to GPs, Pharmacists and specialists.

I look forward to hearing from you.

Kind regards

[redacted]

[redacted]
Sanofi Australia & New Zealand
Talavera Corporate Centre - Building D,
12-24 Talavera Road
Macquarie Park NSW 2113
[redacted] sanofi.com

cid:image002.jpg@01D61EEE.5A14F160

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 the Therapeutic Goods Administration (TGA) 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 Australia. 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 hypomagnesaemia.

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 pointes, 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 Australia Product Information (PI) 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 www.tga.gov.au/reporting-problems. 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: 1800 818 806

Email: medinfo.australia@sanofi.com

Yours sincerely,

[redacted]

ANNEX 1 - PLAQUENIL PI 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 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.

MINIMUM PRODUCT INFORMATION

PLAQUENIL (hydroxychloroquine sulfate) 200mg Tablets

INDICATIONS: Rheumatoid arthritis; mild systemic and discoid lupus erythematosus; the suppression and treatment of malaria.

CONTRAINDICATIONS: patients with pre-existing maculopathy of the eye, known hypersensitivity to 4-aminoquinoline compounds, long-term therapy in children, and use in children <6 yrs.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Not effective against chloroquine-resistant strains of P.falciparum. Patients with severe gastrointestinal, neurological or blood disorders. Periodic blood counts are advised. Porphyria or psoriasis may be exacerbated. Irreversible retinal damage. Ophthalmological examinations initially and 6-monthly (refer to the full PI). Corneal changes subside on reducing the dose or on interrupting therapy, but any suggestion of retinal change or restriction in the visual field is an indication for complete withdrawal of the drug. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Plaquenil should be discontinued if it develops. Has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without anti-diabetic medications. Hydroxychloroquine should be used with caution in patients with congenital or documented acquired QT prolongation and/or known risk factors for prolongation of the QT interval. Patients with hepatic or renal disease. Caution in patents with sensitivity to quinine, and in glucose-6-phosphate dehydrogenase deficiency. Pleomorphic skin eruptions, itching, dryness and increased pigmentation. Periodic full blood counts for patients on long-term therapy. If evidence of agranulocytosis, aplastic anaemia, thrombocytopenia or leucopenia becomes apparent, Plaquenil should be discontinued. Periodic examinations to detect muscular weakness. Rheumatoid arthritis: discontinue if improvement does not occur within 6 months. Caution when driving and operating machinery. Pregnancy Category D. Not recommended for nursing mothers. (refer to the full PI).

INTERACTIONS: MAO's, concomitant hydroxychloroquine and digoxin or hypoglycaemic treatments, drugs known to prolong QT interval, increased plasma ciclosporin levels, other anti-malarial that also lower convulsion threshold, antiepileptic drugs, magnesium-containing antacids or kaolin, CYP inhibitors or inducers, P-gp substrates (such as digoxin, ciclosporin, dabigatran)**,** praziquantel (refer to the full PI).

ADVERSE EFFECTS: Corneal and retinal changes, maculopathies and macular degeneration (see full PI). Allergic Reactions. Bone marrow depression, anaemia, aplastic anaemia, leucopenia, thrombocytopenia. Vertigo, tinnitus, headache, nerve deafness, convulsions, neuromyopathy. Absent or hypoactive deep tendon reflexes, muscle weakness or neuromyopathy. Nausea, diarrhoea, abdominal pain, anorexia, vomiting. Abnormal liver function tests. Cardiomyopathy, QT interval prolongation, skin rashes including DRESS syndrome, alopecia, pigmentary changes. Exacerbation or precipitation of porphyria and attacks of psoriasis. Suicidal behaviour. (refer to the full PI).

DOSAGE AND ADMINISTRATION:

Rheumatoid Arthritis: Initially, adults: 400 to 600mg daily. The dose may be gradually increased. Maintenance dose: when a good response is obtained the dose can be reduced to 200 to 400mg daily. Combination Therapy: May be used in combination with corticosteroids, salicylates, NSAIDS, and methotrexate and other second line therapeutic agents.

Lupus Erythematosus: Adults: Initial dose of 400-800mg daily, maintained for several weeks and then reduced to a maintenance dose of 200-400mg daily.

Malaria - Suppression: Begin 2 weeks prior to exposure. Adults: 400mg on exactly the same day of each week. Children: The weekly suppressive dose is 5 mg (base) per kg bodyweight but should not exceed the adult dose regardless of weight. Continue for 8 weeks after leaving endemic area.

Malaria - Acute Attack: Adults: 800mg followed by 400mg in 6 to 8 hours and 400 mg on each of 2 consecutive days. A single dose of 800 mg has also proved effective. Children: dosage is calculated on the basis of bodyweight [total dose of 25 mg base per kg]. (refer to the full PI).
PRESENTATION: Plaquenil 200mg Tablets are available in packs of 100 Tablets.

NAME OF SPONSOR

sanofi-aventis australia pty ltd, 12-24 Talavera Road, Macquarie Park, NSW 2113. ABN 31 008 558 807.

Please review full Product Information before prescribing.

Full Product Information is available from sanofi australia pty ltd at www.sanofi.com.au or 1800 818 806.

Date of Preparation: 29 April 2020. Based on Full PI with TGA date of approval of 19 August 1994 with most recent amendment on 28 April 2020.