sanofi

פברואר, 2024

Plaquenil Film Coated Tablets

חומר פעיל:

Hydroxychloroquine sulfate 200mg

ההתוויה המאושרת:

Plaquenil is indicated for the suppresive treatment and treatment of acute attacks of malaria due to Plasmodium vivax, p. malaria. p. ovale and susceptible strains of p. falciparum.
It is also indicated for the treatment of discoid and systemic lupus erythomatosus and rehumatoid arthritis.

חברת סאנופי מבקשת להודיע על עדכון העלון לרופא והעלון לצרכן.

העדכונים העיקריים הינם:

בעלון לרופא:

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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Pharmacokinetic Interactions

In vivo, in humans, hydroxychloroquine is metabolised and eliminated unchanged in urine (20-25% of dose). In vitro, hydroxychloroquine is metabolised by CYP2C8, CYP3A4 and CYP2D6, as well as by FMO-1 and MAO-A, with no major involvement of a single CYP or enzyme (see Section 5.2 Pharmacokinetic properties). Therefore, inhibitors and inducers of CYP2C8 and CYP3A4 have the potential to interact on hydroxychloroquine. In the absence of in vivo drug interaction studies, caution is advised (e.g. monitoring for adverse reactions) when cimetidine or CYP2C8 and/or CYP3A4, or CYP2D6 strong inhibitors (such as gemfibrozil, clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice, fluoxetine, paroxetine, quinidine) are concomitantly administered.

P-glycoprotein substrates

Hydroxychloroquine inhibits P-gp in vitro at high concentrations. Therefore, there is a potential for increased concentrations of P-gp substrates when hydroxychloroquine is concomitantly administered. Increased digoxin serum levels were reported when digoxin and hydroxychloroquine were administered. 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, dabigatran) are concomitantly administered.

CYP2D6 substrates

Hydroxychloroquine inhibits CYP2D6 in vitro. In patients receiving hydroxychloroquine and a single dose of metoprolol, a CYP2D6 probe, the Cmax and AUC of metoprolol were increased by 1.7-fold, which suggests that hydroxychloroquine is a mild inhibitor of CYP2D6.

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Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when CYP2D6 substrates with narrow therapeutic index (such as flecainide, propafenone) are concomitantly administered.

CYP3A4 substrates

Hydroxychloroquine inhibits CYP3A4 in vitro. In the absence of in vivo interaction studies with sensitive CYP3A4 substrates, caution is advised (e.g. monitoring for adverse reactions) when CYP3A4 substrates (such as ciclosporin, statins) are concomitantly administered with hydroxychloroquine.

Hydroxychloroquine has no significant potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and the main transporters BCRP, OATP1B1, OATP1B3, OAT1, and OAT3. However, hydroxychloroquine has the potential to inhibit OCT1, OCT2, MATE1 and MATE2-K transporters. Hydroxychloroquine has no significant potential to induce CYP1A2, CYP2B6 and CYP3A4.

Effects of other medicinal products on hydroxychloroquine:

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CYP inhibitors or inducers

Physiologically Based PK (PBPK) predictions show that strong~~Concomitant use of cimetidine, a moderate~~ CYP2C8 or~~and~~ CYP3A4 inhibitors would~~inhibitor, resulted in a 2-fold~~ increase ~~of chloroquine exposure. Per extrapolation, due to the similarities in structure and metabolic elimination pathways between~~ hydroxychloroquine exposure by less than 1.5-fold. In the absence of in vivo drug~~and chloroquine, a similar~~ interaction studies, caution~~could be observed for hydroxychloroquine. Caution~~ is advised (e.g. monitoring for adverse reactions) when CYP2C8 and/or CYP3A4 strong ~~or moderate~~ inhibitors (such as gemfibrozil, clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice) are concomitantly administered.

PBPK predictions show that strong CYP2C8 and/or CYP3A4 inducers would decrease by 2-fold hydroxychloroquine exposure. Lack of efficacy of hydroxychloroquine was reported when rifampicin, a CYP2C8 and/or 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:

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P-glycoprotein substrates

Hydroxychloroquine inhibits P-gp in vitro at high concentrations. Therefore, there is a~~The inhibitory~~ potential for increased concentrations of P-gp substrates when 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-~~ is concomitantly 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.

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5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, peak plasma or blood concentrations is achieved in approximately 3 to 4 hours. Mean absolute oral bioavailability is 79% (SD: 12%) in fasting conditions. Food does not modify the oral bioavailability of hydroxychloroquine.

Distribution

Hydroxychloroquine has a large volume of distribution (5500 L when assessed from blood concentrations, 44 000 L when assessed from plasma concentrations), due to extensive tissue accumulation (such as eyes, kidney, liver and lungs) and has been shown to accumulate in blood cells, with a blood to plasma ratio of 7.2. Approximately 50% of hydroxychloroquine is bound to plasma proteins.

Metabolism

Hydroxychloroquine is mainly metabolised to N-desethylhydroxychloroquine, and two other metabolites in common with chloroquine, desethylchloroquine and bidesethylchloroquine. In vitro, hydroxychloroquine is metabolised mainly by CYP2C8, CYP3A4 and CYP2D6 as well as by FMO-1 and MAO-A, with no major involvement of a single CYP or enzyme.

Excretion

Hydroxychloroquine presents a multi-phasic elimination profile with a long terminal half-life ranging from 30 to 50 days. PBPK predictions indicate that the effective accumulation half-life of hydroxychloroquine is about 5.5 days and that 90% of steady state is achieved within 5 weeks in blood after repeated oral administration of 400 mg hydroxychloroquine sulfate once a day in patients with rheumatoid arthritis. Approximately 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine. After chronic repeated oral administration of 200 mg and 400 mg hydroxychloroquine sulfate once a day in adult patients with lupus or rheumatoid arthritis, the average steady-state concentrations were around 450-490 ng/mL and 870-970 ng/mL in blood, respectively.

The pharmacokinetics of hydroxychloroquine appears to be linear in the therapeutic dose range of 200 to 500 mg/day.

Renal impairment

Renal impairment is not expected to significantly modify the pharmacokinetics of hydroxychloroquine in patients with renal impairment because hydroxychloroquine is mainly metabolised and only 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine. PBPK predictions show that hydroxychloroquine exposure would increase by 17-30% in patients with severe renal impairment (see Section **Error! Reference source not found.** Special warnings and precautions for use – Use in renal impairment).

Hepatic impairment

The effect of hepatic impairment on hydroxychloroquine pharmacokinetics has not been evaluated in a specific PK study. PBPK predictions show that hydroxychloroquine exposure would increase by 41%-57% in patients with moderate and severe hepatic impairment (see Section **Error! Reference source not found.** Special warnings and precautions for use – Use in hepatic impairment).

Paediatric use

The pharmacokinetics of hydroxychloroquine in children aged below 18 years of age have not been established.

~~No data available.~~

בעלון לצרכן:

2. לפני השימוש בתרופה

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אינטראקציות/תגובות בין תרופתיות

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- תרופות לטיפול בדיכאון כולל פלואוקסטין, פארוקסטין והתכשיר הצמחי היפריקום (St. John's wort).
- דיגוקסין, פלקאיניד, פרופאפנון, קווינידין - לטיפול במחלות לב.
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העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום - סאנופי ישראל בע"מ, Greenwork Park, מתחם העסקים בקיבוץ יקום, בניין E (קומה 1), 6097600, יקום או בטלפון: 09-8633081.

להלן הקישור לאתר משרד הבריאות: https://www.gov.il/he/service/israeli-drug-index

בברכה,
חברת סאנופי ישראל בע"מ