ZOGENIX

Zogenix, Inc. 5959 Horton Street, Suite 500 Emeryville, CA 94608 US
Zogenix.com Main: 1-866-ZOGENIX Fax: +1 510 658 3745

27 March 2020

Hydroxychloroquine use in ZX008 Clinical Trials

Dear ZX008 Investigators

We are closely monitoring the global situation with coronavirus (COVID-19) and the safety of study patients is one of our highest priorities.

There has been recent news around the use of hydroxychloroquine for the treatment of COVID-19 infection.

We would like to inform you that hydroxychloroquine, and the parent compound chloroquine, may both have serotonin antagonist properties, and as such have the potential to result in loss of efficacy and an increase in seizure frequency.

If there is an urgent need for short-term use to treat acute COVID-19 infection please contact the Medical Monitor to discuss, per the protocol.

Please contact your CRA, Medical Monitor, or Zogenix Study Lead should you have any additional questions.

Glenn Morrison, MSc, PhD
VP, Global Clinical Development

Updated to March 24, 2020

Clinically relevant Drug-Drug interaction between AEDs and medications used in the treatment of COVID-19 patients

The Liverpool Drug Interaction Group (based at the University of Liverpool, UK), in collaboration with the University Hospital of Basel (Switzerland) and Radboud UMC (Netherlands) (http://www.covid19-druginteractions.org/) is constantly updating a list of interactions for many comedication classes. This table is adapted from their valuable work and includes other drugs.
In light of pharmacological interaction, single cases management is mandatory.

Drugs reported (constantly updated): ATV, atazanavir; DRV/c, darunavir/cobicistat LPV/r, lopinavir/ritonavir; RDV, remdesivir/GS-5734; FAVI, favipiravir; CLQ, chloroquine; HCLQ, hydroxychloroquine; NITA, nitazoxanide; RBV, ribavirin; TCZ, tocilizumab; IFN-β-1a; interferon β-1a; OSV, oseltamivir.

	ATV	*DRV/c[1]	*LPV/r	RDV[2]	FAVI	CLQ	HCLQ	NITA	RBV	TCZ[3]	IFN-β-1a[4]	OSV
Brivaracetam	↔	↔	↓	↔	↔	↑	↑	↔	↑	↔	↔	↔
Carbamazepine	⇓↑	⇓↑	⇓↑	⇓	↔	⇓	⇓	↔	↔	↓	↔	↔
Cannabidiol	↔	↑	↑	↔	↔	↑	↑	↔	↔	↔	↔	↔
Cenobamate	⇓	⇓	⇓	↔	↔	⇓	⇓	↔	↔	↔	↔	↔
Clonazepam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Clobazam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Diazepam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Eslicarbazepine	⇓♥	⇓	⇓♥	⇓	↔	⇓	⇓	↔	↔	↔	↔	↔
Ethosuximide	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Felbamate	↓	⇓	↓	↔	↔	♥↓	♥↓	↔	↔	↔	↔	↔
Gabapentin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lacosamide	♥↔	⇑	♥↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lamotrigine	↔	↑	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
Levetiracetam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Oxcarbazepine	⇓	⇓↓	⇓	⇓	↔	⇓	⇓	↔	↔	↔	↔	↔
Perampanel	↑	⇓	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Phenytoin	⇓	⇓	⇓	⇓	↔	⇓	⇓	↑	↔	↓	↔	↔
Phenobarbital	⇓	⇓↓	⇓	⇓	↔	⇓	⇓	↔	↔	↓	↔	↔
Pregabalin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Primidone	⇓	⇓	⇓↓	⇓	↔	⇓	⇓	↔	↔	↓	↔	↔
Retigabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rufinamide	⇓	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↔	↔	↔
Sulthiame	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Tiagabine	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Topiramate	↔	⇓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Valproic acid	↔	⇓	⇑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Vigabatrin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zonisamide	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

**Should not be administered without booster drug (ritonavir or cobicistat).*

↑ *Potential increased exposure of the co-medication;*
↓ *Potential decreased exposure of the co-medication;*
⇑ *Potential increased exposure of COVID drug;*
⇓ *Potential decreased exposure of COVID drug;*
↔ *No significant effect;*
♥ *One or both drugs may cause QT and/or PR prolongation.*

	Drugs should not be co-administered.
	Potential interaction which may require a dose adjustment or close monitoring.
	Potential interaction likely to be of weak intensity. Additional acts/monitoring or dosage adjustment unlikely to be required.
	No clinically significant interaction expected.

[1] Currently, the *Johnson & Johnson*, holder of *Janssen Pharmaceutica* owner of the drug **Darunavir**, highlighted the lack of evidence to support use of Darunavir-based treatments for SARS-CoV-2 (https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus).

[2] Some data on drug interactions of **Remdesivir** are not available yet.

[3] An increase in IL-6, as well as other cytokines, can improve plasmatic concentration of administered drugs reducing hepatic metabolism (CYP-mediated), a treatment with **Tocilizumab** (anti-IL6R) could reduce plasmatic concentrations of other previous co-treatments due to hepatic metabolism normalization[2].

[4] No studies have been performed yet in humans to assess drugs-interactions.

Notes:

- Ritonavir is a strong inhibitor of CYP 3A and 2D6 *per se*, independently to co-administered antiviral.
- Atazanavir can increase **midazolam** plasmatic concentration until 4-fold.
- Also refer to **SmPC** for further information.

1. Aitken, A. E., Richardson, T. A. & Morgan, E. T. Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu. Rev. Pharmacol. Toxicol.* **46**, 123–149 (2006).
2. Kim, S., Östör, A. J. K. & Nisar, M. K. Interleukin-6 and cytochrome-P450, reason for concern? *Rheumatology International* **32**, 2601–2604 (2012).

By E. Russo and L. Iannone (School of Pharmacology, University of Catanzaro, Mater Domini University Hospital, Catanzaro, Italy)