Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memorandum

Date:	May 19, 2020
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Product Names:	Hydroxychloroquine and Chloroquine
Subject:	All adverse events in the setting of COVID-19
Application Type/Number:	NDA 009768, ANDA multiple
Applicant:	Concordia, Teva, Sandoz, Watson Labs, Mylan, Zydus, Hikma, IPCA Labs, Alkaloida, APPCO, Lupin, Amneal, Laurus Labs, Accord Healthcare, Natco
OSE RCM #:	2020-1000
TSI #:	2150

1 INTRODUCTION

The purpose of this review is for the Division of Pharmacovigilance II (DPV II) to provide the Division of Antiviral (DAV) Drug Products a high-level overview of the postmarketing safety data related to the use of hydroxychloroquine and chloroquine in the setting of coronavirus disease 2019 (COVID-19). The data reviewed for this evaluation were from the FDA Adverse Event Reporting System (FAERS) database, published medical literature, American Association of Poison Control Centers National Poison Data System (AAPPC-NPDS), and other safety reports forwarded from DAV.[a]

1.1 BACKGROUND

On March 28, 2020, FDA authorized the emergency use of hydroxychloroquine and chloroquine supplied from the Strategic National Stockpile to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible.

On April 13, 2020, the Division of Anti-infective (DAI) products opened a priority Tracked Safety Issue (TSI) 2150 to assess the risk of cardiac toxicity with hydroxychloroquine and chloroquine with or without azithromycin when used for the treatment of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

On April 24, 2020, FDA issued a Drug Safety Communication (DSC) cautioning against the use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of arrhythmias. The DSC described reports of serious cardiac events, including QT prolongation, in patients receiving hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines, for the prevention or treatment of COVID-19.[1]

On May 6, 2020, DAV consulted the Office of Surveillance and Epidemiology (OSE) to review clinical trials, observational studies, and postmarketing surveillance data published or available after the March 28, 2020 EUA for hydroxychloroquine and chloroquine in the setting of COVID-19 and comment on implications of these data regarding known and potential risks of the authorized use. DPV's analysis focused on the available safety data reporting the use of hydroxychloroquine or chloroquine for the treatment or prevention of COVID-19 in any setting.

On May 6, 2020, the Division of Applied Regulatory Science (DARS) and DPV opened a Newly Identified Safety Signal (Safety Signal ID 1004045) in the pre-evaluation stage to track an emerging signal of methemoglobinemia with hydroxychloroquine in the setting of COVID-19.

On May 12, 2020, the DPV and the DARS met with the Office of New Drugs (OND), specifically, DAI, DAV, and the Division of Rheumatology and Transplant Medicine (DRTM),

[a] DPV reviewed these safety reports that were forwarded from DAV prior to their entry into FAERS; therefore, these cases were not yet assigned a FAERS Case ID at the time of this memo.

to discuss emerging safety data from the National Poison Data System, with hydroxychloroquine and methemoglobinemia in the setting of COVID-19.

2 METHODS AND MATERIALS

2.1 CASE SELECTION CRITERIA

Reports retrieved from the search strategies described in Tables 1-3 were screened for cases of adverse events associated with hydroxychloroquine or chloroquine used for the prevention or treatment of COVID-19.

2.2 FAERS SEARCH STRATEGY

DPV II searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	Recurring daily searches†
Time period of search	December 1, 2019 – May 6, 2020
Search type	Drug Safety Analytics Dashboard (DSAD)
Product terms	**Product Active Moiety (PAM):** hydroxychloroquine, chloroquine
MedDRA search terms (Version 23.0)	**Preferred Terms (PTs**): *Asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, Suspected COVID-19, SARS-CoV-2 carrier, Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2, SARS-CoV-2 test, SARS-CoV-2 test false negative, SARS-CoV-2 test positive, COVID-19 prophylaxis, COVID-19 treatment, Coronavirus test positive, Coronavirus infection*
Other criteria (text string search)	**Reported Reason for Use:** Coronavirus infection, Corona virus infection, Coronavirus test positive **Reporter Narrative:** Coronavirus, Corona virus, Novel coronavirus, ncov, 2019-ncov, 2019 ncov, Hubei, Wuhan, COVID, SARS-COV-2, SARS COV 2, T705, T-705, Emergency use authorization, EUA **Medical History Comments:** SARS-COV-2, SARS COV2, ncov, 2019-ncov, Corona virus, Coronavirus, COVID
* See Appendix A for a description of the FAERS database. † Searches recurring daily Tuesday through Friday with a 1-day prior completion date and on Monday with a 3-day prior completion date.	

2.3 LITERATURE CASE SEARCH STRATEGY

DPV II searched the medical literature with the search strategy described in Table 2.

Table 2. Literature Case Search Strategy	
Date of search	Recurring daily searches
Database	Embase
Search terms	Drug search for "hydroxychloroquine" and "chloroquine"
Time period of search	January 1, 2020 – May 6, 2020

In addition, weekly PubMed and EMBASE Early Alerts for COVID-19 and safety-related articles were reviewed (March 15, 2020 – April 30, 2020).

2.4 AAPCC-NPDS Search Strategy

In an effort to identify exposures to hydroxychloroquine or chloroquine, DPV set up a case-based definition with daily alerts in the NPDS database using the search strategy described in Table 3.

Exposure calls received by Poison Control Centers (PCCs) are managed by healthcare professionals with specialized toxicology training needed to assess, triage to the most appropriate level of care, provide recommendations, and follow up on toxic emergencies.

Table 3. NPDS Search Strategy*	
Date of Search	March 27, 2020 through May 6, 2020
Type of Search	Prospective case-based definition (toxicosurveillance) Anomaly IDs 2258 and 2266 with daily alerts†
Search Restrictions	Call type: Exposure Case status: Open, Closed Species: Human Product Type: Contains at least one Single Substance Only: No
Product Codes‡	All chloroquine and hydroxychloroquine products Complete list of product codes: (b) (4) [redacted]
Reason for Exposure	All excluding Intentional – Suspected suicide and Unintentional Therapeutic error†
Outcomes	All outcomes

*See **Appendix B** for a description of the NPDS database
†Anomaly ID 2258 was used from March 27, 2020 to April 14, 2020 (all outcomes included). Anomaly ID was used from April 15, 2020 to May 6, 2020 (modified alert to exclude reason for exposure of "Intentional – Suspected suicide" and "Unintentional Therapeutic error").
‡**These product codes must be redacted for public release.**
AAPCC = American Association of Poison Control Centers

2.5 OTHER SAFETY REPORTS

DPV II reviewed hydroxychloroquine safety reports forwarded from DAV through April 24, 2020.

3 RESULTS

Table 4 provides the total number of cases identified from each source that met the selection criteria (see Section 2) and describes characteristics of these cases. The most frequently reported preferred terms (PTs) can be found in Appendix C. The majority of PTs are either 1) known and labeled adverse events for hydroxychloroquine or chloroquine, 2) known and labeled adverse events for concomitant medications, or 3) known effects of COVID-19 (e.g., respiratory failure, liver impairment, pulmonary embolism). **Table 5** describes cases that reported serious adverse events with the use of hydroxychloroquine or chloroquine in the setting of COVID-19. Cases in **Table 5** were assessed for a causal association with hydroxychloroquine or chloroquine using elements from a modified World Health Organization (WHO) – Uppsala Monitoring Centre (UMC) Causality Categories described in Appendix D.[2] We categorized the cases as probable, possible, unlikely, or unassessable based on the strength of the evidence for a causal association. We excluded cases we classified as unlikely or unassessable from further analysis. **Table 6** describes the most frequently reported dosages in patients receiving hydroxychloroquine or chloroquine in the setting of COVID-19.

Table 4. All Hydroxychloroquine and Chloroquine Cases Reporting Adverse Events in the Setting of COVID-19 from December 1, 2019 – May 6, 2020 (n=385)

	Hydroxychloroquine (n=347)	Chloroquine (n=38)
Source*		
FAERS	291	21
Literature	25	13
NPDS	20	3
Other Safety Reports	11	1
Sex	(n=331)	(n=37)
Male	230	22
Female	101	15
Age (years)	(n=324)	(n=24)
Range	18-96	34-83
Median	63.5	61
Mean	61.8	57.9
Country of Origin		
US	97	5
Foreign	250	33

Table 4. All Hydroxychloroquine and Chloroquine Cases Reporting Adverse Events in the Setting of COVID-19 from December 1, 2019 – May 6, 2020 (n=385)		
	Hydroxychloroquine (n=347)	**Chloroquine (n=38)**
Fatal Cases	77	10

* FAERS – includes any case identified in either FAERS alone OR both FAERS and the literature. Literature – includes cases only identified in the literature. Other safety reports– includes cases that were forwarded by DAV and were not yet entered into FAERS at the time of this memo.

Table 5. Possibly/Probably Associated Hydroxychloroquine and Chloroquine Cases Reporting Serious Adverse Events in the Setting of COVID-19 from December 1, 2019 – May 6, 2020 (n=211) *		
	Hydroxychloroquine	**Chloroquine**
Serious Cardiac AEs*	**(n=90)**	**(n=19)**
Labeled Cardiac AEs*	(n=85)	(n=19)
QT prolongation	62	18
VA, VF, VT	11	3
Bradycardia	7	1
Tachyarrhythmia	4	0
Tachycardia (excluding VT, tachyarrhythmia)	4	0
TdP	4	0
AV block	3	1
Arrhythmia (excluding VA, VF, VT, tachyarrhythmia)	3	0
QRS prolonged	2	1
Cardiovascular collapse (in overdose)	1	0
Unlabeled Cardiac AEs*	(n=5)	(n=0)
Atrial fibrillation/atrial flutter	4	0
Myocardial infarction	1	0
Concomitant Treatments of Interest‡	(n=76)	(n=16)
Azithromycin	55	12
LPV/r	5	0
Azithromycin + LPV/r	7	1
Other QT prolonging drugs	24	3
Fatal Cardiac Cases§	17	8
Serious Non-Cardiac AEs of Interest*	**(n=101)**	**(n=12)**
Labeled Non-Cardiac AEs*	(n=86)	(n=11)
Psychiatric Disorders	(n=3)	(n=4)*
Hallucinations/psychosis	3	2
Other neuropsychiatric changes (mania, abnormal behavior)	0	3
Blood and Lymphatic System Disorders	(n=17)*	(n=0)
Hemolytic anemia/G6PD deficiency related issues	5	0
Pancytopenia/thrombocytopenia/anemia/leukopenia	12	0
Agranulocytosis	1	0
Hepatobiliary Disorders	(n=63)	(n=4)
Hepatitis/increased liver enzymes/hyperbilirubinemia	60	4
Hepatic failure	3	0
Nervous System Disorders	(n=0)	(n=2)
Seizure	0	2
Musculoskeletal and connective tissue disorders	(n=3)	(n=0)
Rhabdomyolysis	3	0
Immune System Disorders	(n=1)	(n=0)
	1	0

Table 5. Possibly/Probably Associated Hydroxychloroquine and Chloroquine Cases Reporting Serious Adverse Events in the Setting of COVID-19 from December 1, 2019 – May 6, 2020 (n=211) *		
	Hydroxychloroquine	**Chloroquine**
Exacerbation of psoriasis	(n=0)	(n=1)
Eye disorders	0	1
Visual impairment		
Unlabeled Non-Cardiac AEs*	(n=18)	(n=2)
Acute kidney injury/Renal failure	5	1
Methemoglobinemia	4	0
Hypokalemia	4	1
Hyponatremia	2	0
Oropharyngeal edema	1	0
Anuria	1	0
Hyperglycemia	1	0
Hypoacusis	1	0

* A case may have more than one AE. Some cases reported both a cardiac and non-cardiac AE. The FDA reviewer assessed the reported AEs were probably/possibly associated with HCQ or CQ use.

‡ A case may have more than one concomitant treatment.

§ Fatal cardiac cases are considered those cases reporting death and a cardiac AE. Cases were not individually evaluated to determine if the cardiac AE was the cause of death.

Abbreviations: AE = adverse event, CQ = chloroquine, HCQ = hydroxychloroquine, LPV/r = lopinavir/ritonavir, VA = ventricular arrhythmia, VF = ventricular fibrillation, VT = ventricular tachycardia, TdP = Torsades de Pointes, AV = atrioventricular

Key Findings:

- The majority of the cases (69%) involved males with a median age in the early 60s.
- Of the 385 cases reporting use of hydroxychloroquine or chloroquine in the setting of COVID-19, 377 cases reported use for treatment and 8 cases reported use for prophylaxis.
- 28% of the cases were from the U.S. Of the 97 U.S. cases for hydroxychloroquine, 5 reported use of hydroxychloroquine through the EUA.
- Eleven cases reported both a cardiac and non-cardiac AE.
- Of all serious adverse events (cardiac and non-cardiac), QT prolongation was the most commonly reported adverse event for both hydroxychloroquine and chloroquine.
- Of the 109 hydroxychloroquine and chloroquine cases with a serious cardiac adverse event:
    - 80 (73%) reported QT prolongation.
    - 4 (4%) reported Torsades de Pointes (TdP)
    - 92 (84%) reported concomitant use of at least one other medication that prolongs the QT interval. 75 (69%) reported concomitant use of azithromycin.
    - 14 (13%) reported ventricular arrhythmia, ventricular tachycardia or ventricular fibrillation.
    - 25 (23%) had a fatal outcome. Fatal cardiac cases were considered those cases reporting death and a cardiac AE.
        - 9/25 had a cardiac event that was assessed to have possibly or probably contributed to death.
        - 22/25 reported use of a concomitant QT-prolonging medication.

- Of the 113 hydroxychloroquine and chloroquine cases with a serious non-cardiac adverse event of interest:
    - Hepatitis/increased liver enzymes/hyperbilirubinemia was the most commonly reported adverse event (59% of cases). These are labeled events for hydroxychloroquine and chloroquine.
    - The most commonly reported unlabeled adverse event was acute kidney injury/renal failure (5%).
    - Methemoglobinemia was reported in 4 cases (4%), two of these cases were fatal. Methemoglobinemia is currently not labeled for hydroxychloroquine or chloroquine.

Table 6. Hydroxychloroquine/ Chloroquine Dosage	
Reported Dosage	(n=256)
1200 mg/day, then 400 mg/day	3
1000 mg/day	4
800 mg/day x 1, then 400 mg/day	33
800 mg/day	16
600 mg/day	39
400 mg/day	109
250 mg/day	2
200 mg/day	11
800 mg*	4
600 mg*	3
400 mg*	9
200 mg*	6
1 teaspoon of powder	2
Miscellaneous†	15
*** Frequency was not reported** **† One case each reported doses ranging from 100 mg to 2200 mg**	

Key Findings:

- The most frequently reported dose was 400 mg/day (43%), which is consistent with FDA-approved dosing for labeled indications.
- Of the 256 cases that reported hydroxychloroquine or chloroquine doses, 6 were for prophylaxis and 250 for treatment.

4 REVIEWER'S COMMENTS

In addition to the key findings listed in Section 3, two emerging safety signals were identified:

- **Cardiac toxicity with hydroxychloroquine and chloroquine:** Hydroxychloroquine and chloroquine are labeled for several cardiotoxic events including QT prolongation, ventricular arrhythmias, TdP, and conduction disorders. Both labels advise caution with use of hydroxychloroquine or chloroquine with other drugs that have the potential to prolong the QT interval.[3,4] In our evaluation of hydroxychloroquine and chloroquine use in the setting of prevention or treatment of COVID-19, QT prolongation was the most

frequently reported serious adverse event for both hydroxychloroquine and chloroquine. Notably, 84% of hydroxychloroquine and chloroquine cases reporting a serious cardiac adverse event also reported concomitant use of at least one other QT prolonging medication; 69% of the cases with a serious adverse cardiac event reported concomitant azithromycin use, with or without other QT prolonging medications. Fourteen cases were identified with ventricular arrhythmia, ventricular tachycardia or ventricular fibrillation; seven of these had a fatal outcome. Two of the ventricular arrhythmia cases also reported TdP, one of which was fatal. Two additional cases reported TdP, neither of these were fatal. On April 13, 2020, a priority TSI was opened for cardiac toxicity with use of hydroxychloroquine and chloroquine in the setting of COVID-19. Additionally, the DSC emphasized the potential for hydroxychloroquine and chloroquine to prolong the QT interval and interact with other QT prolonging medications as well as to cause potentially fatal heart rhythms, such as ventricular tachycardia. DPV II will continue to actively monitor for cases in the available data sources for this emerging safety signal.

- **Methemoglobinemia with hydroxychloroquine:** Hemolysis in individuals with G6PD deficiency is labeled for hydroxychloroquine; however, the adverse event methemoglobinemia is not specifically described. Four cases of methemoglobinemia occurring with hydroxychloroquine use in the treatment of COVID-19 were identified in the NPDS database. All patients had evidence of hemolysis; two of these patients were confirmed not to have G6PD deficiency. Cases of methemoglobinemia with hydroxychloroquine use in the treatment of COVID-19 have not been identified in either the FAERS or literature searches. During the May 12, 2020 meeting, DPV, DARS, DAI, DAV and DRTM agreed that continued surveillance is most appropriate at this time given the small number of methemoglobinemia cases and limited information in the context of years of experience with hydroxychloroquine in the autoimmune disease population. Data with enough details to ascertain if methemoglobinemia is only observed in patients who are critically ill or if it also occurs in patients taking hydroxychloroquine in the setting of moderate COVID-19 disease are needed. In addition, DPV and OND agreed to include cases of hemolysis in ongoing surveillance. DPV, DARS, and OND plan to reassess this emerging signal if more compelling data become available.

5 REFERENCES

[1] U.S. Food and Drug Administration. Drug Safety Communication: FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. Accessed on May 12, 2020.
[2] The Use of the WHO-UMC System for Standardized Case Causality Assessment. The Uppsala Monitoring Centre. Available at: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf. Accessed May 12, 2020.
[3] Plaquenil (hydroxychloroquine sulfate) [package insert]. Concordia Pharmaceuticals, Inc. St. Michael, Barbados. January 2019.
[4] Chloroquine phosphate [package insert]. NATCO Pharma Limited. Kother, India. February 2018.

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.2 APPENDIX B. NATIONAL POISON DATA SYSTEM (NPDS)

The National Poison Data System (NPDS) is a database managed by the American Association of Poison Control Centers (AAPCC) and derived from a nationwide network of Poison Control Centers (PCCs) that receives calls from individuals, healthcare professionals, and other interested persons regarding exposures to prescription drugs, over-the-counter medications as well as unapproved products. Within NPDS, calls for exposures may result in documentation of an event, provision of information, or advice regarding medical management, and AAPCC staff managing these calls undergo training in the efforts to standardize documentation across centers.

Documentation of calls includes detail on the drug(s), patient characteristics, route of exposure, reported reasons for exposure, level of care received (e.g. admitted to critical care unit vs. treated and released), medical outcomes (e.g., death, no effect) and other more curated variables, such as "relatedness" of the reported exposure to the outcomes of interest. Reasons for use are categorized into groups by AAPCC, and include such categories as "intentional", "unintentional," the former encompassing the subgroups of intentional misuse, abuse, suspected suicide or unknown intent.

PCC call data should not be interpreted as representing the complete incidence of national exposures or cases of misuse/abuse related to any substance. These data only capture events if the exposure resulted in a call to a PCC. PCC data rely on information electively shared by patients and healthcare personnel, and most substance classification is based on history alone and does not involve any biologic confirmation. Reported exposures may be unconfirmed ingestions, i.e., the product may not have been ingested at all by the patient. Drug exposures resulting in unattended or out-of-hospital death are unlikely to generate a call to a PCC, and therefore, fatal poisonings are expected to be substantially under-reported in PCC call data. Follow-up and medical outcomes are not available for all calls. It is possible that changes in PCC rates in part reflect changes in public and professional awareness of the risks associated with specific drugs, and awareness of the abuse potential of a drug among call center personnel could also increase the likelihood of an exposure being coded as intentional abuse. Call rates may also be influenced by general changes in use of PCCs over time. AAPCC is not able to completely verify the accuracy of every report made to member centers.

6.3 APPENDIX C. MOST FREQUENTLY REPORTED MEDDRA PREFERRED TERMS (PTS) FOR FAERS REPORTS FOR HYDROXYCHLOROQUINE AND CHLOROQUINE FROM DECEMBER 1, 2019 – MAY 6, 2020 (N=312)

Table 1. Most Frequently Reported MedDRA Preferred Terms (PTs) Reporting ≥ 2% of Total	
Event-Preferred Terms (PTs)	**Percent of Total**
OFF LABEL USE	41.22
ELECTROCARDIOGRAM QT PROLONGED	20
CORONAVIRUS INFECTION	11.84
HEPATITIS	11.02
PRODUCT USE IN UNAPPROVED INDICATION	11.02
CONDITION AGGRAVATED	8.98
DRUG INTERACTION	8.57
ACUTE RESPIRATORY DISTRESS SYNDROME	4.49
TRANSAMINASES INCREASED	4.08
ACUTE KIDNEY INJURY	3.67
DEATH	3.67
CARDIO-RESPIRATORY ARREST	3.27
HEPATITIS ACUTE	3.27
HEPATOCELLULAR INJURY	3.27
PNEUMONIA	3.27
PYREXIA	2.86
CARDIAC ARREST	2.45
DIARRHOEA	2.45
DYSPNOEA	2.45
ACUTE RESPIRATORY FAILURE	2.04
BRADYCARDIA	2.04
CORONAVIRUS TEST POSITIVE	2.04
HYPERBILIRUBINAEMIA	2.04
INTENTIONAL PRODUCT USE ISSUE	2.04
MALAISE	2.04
MULTIPLE ORGAN DYSFUNCTION SYNDROME	2.04
VENTRICULAR FIBRILLATION	2.04
VENTRICULAR TACHYCARDIA	2.04

6.4 APPENDIX D. WHO-UMC CAUSALITY ASSESSMENT CATEGORIES

Categorization[b]	Assessment Criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Cannot be assessed because information is insufficient or contradictory

*All points should be reasonably complied with

[b] The Use of the WHO-UMC System for Standardised Case Causality Assessment. The Uppsala Monitoring Centre. Available at: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf. Accessed November 18, 2019

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