FOOD AND DRUGS AUTHORITY

SAFETY MONITORING PLAN FOR MEDICINES FOR THE TREATMENT OF COVID-19

Version 10.4 May 2020

Table of Contents

Glossary

Adverse reactions

Adverse Reaction is a response to a medicinal product which is noxious and unintended including lack of efficacy and which occurs at any dosage and can arise from:

- The use of product within the terms of the marketing authorization
- The use of product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse and medication errors;
- Occupational exposure

Serious adverse reactions

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life threatening
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event or reaction

Suspected unexpected serious adverse reactions

A Suspected Unexpected Serious Adverse Reaction (SUSAR), is a serious adverse reaction (SAR) for which a reasonable causal relationship with the medicine use is suspected but not confirmed. Unexpected in this context means not consistent with the applicable product information i.e. summary of product characteristics (SmPC).

Emergency Use Authorization (EUA) or Emergency Use Listing (EUL)

This is a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics for use primarily during public health emergencies of international concern (PHEIC) but also in other public health emergencies if appropriate. The approval of any medicine(s) or diagnostics for EUA is not intended to interfere with ongoing clinical trials. This means that the clinical development should proceed as planned after the initial submission and subsequent updates.

Background

The first cases of the outbreak of the Coronavirus disease (COVID-19) were reported in Wuhan, China in late December 2019 and rapidly spread to other cities in China and the rest of the world. The World Health Organization (WHO) declared Covid-19 as a pandemic on 11th March 2020. Ghana recorded the first two cases of COVID-19 on 12th March 2020.

About 80% of patients with COVID-19 present with mild disease and the overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to 79 years and 14.8% in those aged greater than 80 years.

Since COVID-19 is a new disease, therefore there are no Food and Drugs Authority (FDA)-approved treatments or vaccines at the moment but a few drugs have shown in-vitro activity against the virus and promising results in small studies in countries most affected by the pandemic, particularly China and France. There are however, a number of ongoing clinical trials to find safe and effective treatment for COVID-19.

The Ministry of Health has developed the Provisional Standard Treatment Guidelines for Novel Coronavirus Infection to use medicines, namely, Hydroxychloroquine, Chloroquine, Azithromycin (or Doxycycline), Remdesivir and Tocilizumab for the treatment of patients with COVID-19 based on current information. There are also a number of drugs for supportive treatment using existing therapies based on the 7th edition 2017 Standard Treatment Guidelines.

Objective

The objective of the safety monitoring plan is to outline procedures for active pharmacovigilance during treatment of COVID-19 to ensure that healthcare professionals report all suspected adverse reactions associated with these medicines to facilitate early detection of safety signals to promote patient safety.

Why enhanced pharmacovigilance during treatment of COVID-19?

Although some of the drugs (i.e. azithromycin, chloroquine and hydroxychloroquine) have been used in Ghana for the treatment of infections with susceptible bacteria, malaria and rheumatoid arthritis respectively, they haven't been used in COVID-19 so there is lack of information on the effect of these drugs in the treatment of this disease.

First of all, azithromycin has been used in combination with hydroxychloroquine in the treatment of COVID-19 patients during a study in France with better outcome compared with hydroxychloroquine alone.[1] However, azithromycin, hydroxychloroquine and chloroquine are all known to cause QT prolongation. The combination of chloroquine or hydroxychloroquine with azithromycin should therefore be avoided in patients with comorbid cardiovascular disease conditions.

Large clinical trials are under way to generate robust data needed to establish the efficacy and safety of chloroquine or hydroxychloroquine in combination with azithromycin the treatment of COVID-19.

The use of chloroquine or hydroxychloroquine are also associated with hypoglycemia and also intravascular haemolysis in persons with G6PD deficiency.

Secondly, there is limited information on the safety of remdesivir, the clinical trial during the Ebola outbreak along with other treatments in the Democratic Republic of Congo in 2019 was discontinued because it wasn't effective in prevention of deaths in patients. In this study, 175 patients were treated with redemsivir, one had hypotension followed by cardiac arrest.[2] Remdesivir has been shown to be active against SARS-CoV-2 and other types of coronavirus (i.e. SARS-CoV and MERS-CoV) in laboratory studies. Preliminary data from randomized, controlled trial clinical trials in hospitalized patients with advanced COVID-19 and lung involvement who received remdesivir recovered faster than similar patients who received placebo.[3]

There were reports that COVID-19 patients treated with remdesivir reported significant gastrointestinal symptoms and elevated liver enzymes.

It is recommended that regular laboratory assessments, including hepatic tests are performed in patients receiving remdesivir and any observed liver function-related laboratory abnormalities and adverse reactions are treated appropriately and followed to resolution. Additionally, measurement of estimated glomerular filtration rate (eGFR) should be performed while patients are receiving remdesivir, particularly subjects with known renal impairment at the start of therapy.

Finally, tocilizumab has been used for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have used one or more disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, that did not provide enough relief). There are ongoing clinical trials to access the safety and efficacy of tocilizumab in COVID-19. Meanwhile, a Chinese study with 20 patients treated with tocilizumab showed nineteen have been discharged on average 13.5 days and the rest are recovering well.[4]

With the foregoing, it is therefore critical that the pharmacovigilance system is enhanced with appropriate risk minimization measures to support the continued safe and effective use of these medicines to gather local data on the safety of these medicines for prompt identification of safety concerns during this pandemic as this information will help guide the safe and most effective use of these medicines in Ghana.

What to report?

All suspected adverse reactions including Suspected Unexpected Serious Adverse Reactions (SUSARs) should be reported within 24 hours, including cases where any of the medicines is suspected to be ineffective. In addition, information on patients treated with any of the medicines during pregnancy should also be reported with follow up on

the outcome of the pregnancy.

To assist the FDA in the assessment of suspected adverse reaction reports, as much information as possible should be provided in the initial report, particularly the underlisted information if available:

- suspected drug
- the age and gender of the patient
- description of the adverse reaction (including indication of seriousness)
- patient's medical history (including any previously diagnosed/recently diagnosed conditions) e.g. diabetes, heart disease, chronic liver disease, asthma, HIV, active tuberculosis.
- any concomitant medications, whether supportive or already prescribed
- outcome of the reaction (resolved, revolving, death)
- state whether medicine was discontinued as a result of the adverse reaction

For product issued with EUA in accordance the Guidelines for Emergency Use Authorization of Medical Products,[5] the Marketing Authorization Holder shall comply with the FDA's safety monitoring requirements.

How to report?

The most efficient way to report adverse reactions to the FDA in the pandemic is via our online reporting system at http://adr.fdaghana.gov.gh/ or the Med Safety App (which can be downloaded from the App Store and Google Play Store).

Reports can also be made by completing the Adverse Reaction Reporting Form (attached as Appendix 1) or by calling Mobile no: 0244310297 or send an email to drug.safety@fdaghana.gov.gh

When to report?

Adverse reactions are to receive immediate attention and reported within 24 hours of detection.

The FDA will follow up on the Heads or the Institutional Contact Persons of the Treatment Centres and report weekly in the format provided in Appendix 2 accompanied by completed adverse reaction reporting forms where applicable.

Training for healthcare professionals

All training programmes to be organized for healthcare professionals on the use of the recommended drugs for COVID-19 will include a session on pharmacovigilance and how to report adverse reactions. Adverse reaction reporting forms will be distributed to all Treatment Centres to be announced by the Ministry of Health.

The pharmacovigilance system in the treatment centres will be established with the support of the Heads of the institutions and the Institutional Contact Person. Where there are no Institutional Contact Persons, the Head of the Institution will be contacted to appoint one to help establish and maintain a system for the diagnosis, management and reporting of adverse reactions.

Review of Safety Reports Received

Adverse reaction reports received during the COVID-19 pandemic will be submitted for review by the Technical Advisory Committee on Safety of Medicines. The assessment of these reports will be prioritized to ensure that any new safety concerns are managed appropriately, with information communicated as quickly as possible for continued safe and effective use of these products.

References

1. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. March 2020:105949. doi:10.1016/j.ijantimicag.2020.105949
2. Mulangu S, Dodd LE, Davey RT, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med*. 2019;381(24):2293-2303. doi:10.1056/NEJMoa1910993
3. National Institute of Allergy and Infectious Diseases. NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19. https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19. Published 2020. Accessed May 10, 2020.
4. Xiaoling Xu. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. *Open Repos*. 2020. http://www.chinaxiv.org/abs/202003.00026. Accessed May 10, 2020.
5. FDA. *FOOD AND DRUGS AUTHORITY GUIDELINES FOR EMERGENCY USE AUTHORIZATION OF MEDICAL PRODUCTS*. https://fdaghana.gov.gh/images/stories/pdfs/downloads/drugs guidelines/BPD/Guidelines for Emergency Use Authorization of a Medical Product ---.pdf. Accessed April 13, 2020.

Appendices

Appendix 1: Adverse reaction reporting form

SMC/SMD/GEN- 09/1.0

ADVERSE REACTION REPORTING FORM

(Please complete all sections as much as possible)

(A) PATIENT DETAILS

Age/Date of Birth (dd/mm/yyyy): / / Wt (kg): .....
Gender: M ( ) F ( ) If female, Pregnant Yes ( ) No ( ) Age of pregnancy.....
Name/Folder Number ..... Telephone No:.....
Hospital/Treatment Centre.....

(B) DETAILS OF ADVERSE REACTION AND ANY TREATMENT GIVEN (Attach a separate sheet and all relevant laborator tests/data when necessary)

Date reaction started (dd/mm/yyyy): / / Date reaction stopped (dd/mm/yyyy): / /

(C) OUTCOME OF ADVERSE REACTION:

Recovered ( ) Not yet recovered ( ) Unknown ( )
Did the adverse reaction result in any untoward medical condition? Yes ( ) No ( ) If yes, Specify.....
SERIOUSNESS: Death ( ) Life threatening ( ) Disability ( ) (specify)..... Hospitalization
Others (specify).....

(D) SUSPECTED PRODUCT(S) (Attach sample or product label if available)

Brand name	**Generic name**	**Batch Number**	**Expiry date**	**Manufacturer**
Reasons for use (Indication):		**Dosage Regimen:**	**No. of days given:**	**Route of Administration:**

Date started: (dd/mm/yyyy) / / Date stopped: (dd/mm/yyyy) / /
Did the adverse reaction subside when the drug was stopped (de-challenge)? Yes ( ) No ( )

Was the product prescribed? Yes ☐ No ☐ | **Source of Drug:**

Was product re-used after detection of adverse reaction (re-challenge)? Yes ( ) No ( )
Did adverse reaction re-appear upon re-use? Yes ( ) No ( )

(E) CONCOMITANT DRUGS: INCLUDING COMPLEMENTARY MEDICINES, CONSUMED AT THE SAME TIME AND/OR 3 MONTHS BEFORE

(Attach a separate sheet when necessary)

Name of Drug	**Daily dose**	**Date started**	**Date stopped/ Ongoing**	**Reason(s) for use**

(F) REPORTER DETAILS

Name of Reporter: .....Profession.....
Institution's Address:.....
Signature: .....Tel.....E-mail.....
Date (dd/mm/yyyy) : / /

Confidentiality: Identities of the reporter and the patient will remain strictly confidential

Appendix 2: Weekly reporting format

No	Name of Facility	Region	Contact Person	Telephone No.	Cumulative No. of Patients	No. Patients Treated	No. of adverse reaction reports	Treatment Physician	Telephone No.	Comments