SUMMARY OF EVIDENCE

Meglumine acridone acetate

Section 1.

General information of the proposed health technology

Product name	Cycloferon®
Generic name	Meglumine acridone acetate
FDA approved indication	Not Philippine FDA-registered
Indication/s	• In adults, recommended during combined therapy of: influenza and acute viral infections; herpes infections; HIV infections (stages 2A-3B); neural infections; chronic viral hepatitis A, B, C, D; and, acute enteric infections • In children over 4 years old, recommended during combined therapy of: influenza and acute viral infections; herpes infections; viral hepatitis A, B, C, D; and, HIV infections
Proposed indication:	Treatment of COVID-19
Dosage formulation/ strength	• 12.5% solution for injection, ampules • 0.15 g enteric-coated tablet
Route of administration	• Intramuscular (IM) • Intravenous (IV) • Oral
Dosage regimen	• IM/IV: Administered once daily following the basic scheme for ten (10) days. • Oral: Once a day dosing, half an hour before meals for 10 days. - Children (4 – 6 years old): 0.15 g per dose - Children (7 – 11 years old): 300 to 450 mg or 2 to 3 pills per dose

	- Adults and children >12 years old: 450 to 600 mg or 3 to 4 pills per dose
Therapeutic class	Immunomodulating factor
Anatomical Therapeutic Chemical (ATC) classification	L03AX
Pharmacological action	Interferon-reducing

Section 2.
Context of the health technology

Background

The World Health Organization (WHO) declared the novel coronavirus disease (COVID-19) caused by severe acute coronavirus 2 (SARS-COV-2) a global pandemic. The most common symptoms are fever, sore throat, malaise and dry cough. The symptoms are usually mild and begin gradually. It can spread from person-to-person through small droplets when coughing or sneezing. As of 12 April 2020, it has affected 160 countries with at least 4,171,859 cases and 285,690 deaths worldwide [1]. Locally, there are 11,086 COVID-19 cases with 726 deaths and a case fatality rate of 6.5% [2].

Currently, there are no known treatments for COVID-19. As a response to increasing number of COVID-19 cases, the WHO announced a global testing of effective treatments across several countries called the "SOLIDARITY Trial." Globally, there have been separate studies and trials on the treatment for COVID-19 using existing drugs in the market that are indicated for the treatment of influenza.

Locally, by virtue of Department Memorandum (DM) No. 2020-0108, the Department of Health endorsed the treatment guidelines for COVID-19 issued by the Philippine Society of Microbiology and Infectious Diseases (PSMID) on 31 March 2020. The guidelines listed the following drugs that may be used in hospitalized, probable or confirmed COVID-19 cases with moderate to high-risk pneumonia:

[1]Johns Hopkins University, *COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University*, https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 (accessed on 12 May 2020)
[2]Department of Health. (2020), *COVID-19 Tracker*, https://www.doh.gov.ph/covid19tracker (accessed on 12 May 2020)

1) **hydroxychloroquine, chloroquine, lopinavir/ritonavir, tocilizumab (off-label use)**
2) **compassionate use of remdesivir**

A Russian pharmaceutical company has expressed their intent to donate sufficient amount of meglumine acridone acetate (MA) (Cycloferon®) to the Philippines as a treatment for COVID-19. The parenteral preparation of meglumine acridone acetate, which was donated to the Institute of Tropical Medicine in Hanoi, was claimed to be effective during the SARS-COV epidemic in 2003. This drug is not currently registered with the Philippine Food and Drug Administration (FDA) and there is no conclusive guidance on the use of this drug for COVID-19.

Policy Question

Should the Philippine government accept the donation and introduce MA as an add-on to the DOH-PSMID-recommended treatment regimens for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31*?

Research Questions:

1. What is the market entry status of MA across different countries? What are the current country TGs or CPGs which recommend the use of MA in treating patients with COVID-19?

2. What is the clinical efficacy/ effectiveness and safety of MA as an add-on to the DOH-PSMID-recommended treatment regimens for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31*? [primary] What is the clinical efficacy/ effectiveness and safety of MA as an add-on to supportive treatment for patients with influenza *versus the DOH-PSMID recommended guidelines as of March 31*? [secondary]

3. Does MA as an add-on to the DOH-PSMID-recommended treatment regimens represent value for money for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31*?

Section 3.

Details of supporting evidence on the use of the proposed HT

3.1. Clinical evidence

Currently, MA is not included in any treatment or clinical practice guidelines, nor it is registered in all the reviewed countries for the treatment of COVID-19 , even in its source country Russia. Further, there are no ongoing clinical trials testing the clinical

efficacy and safety of MA for COVID-19, to date. Considering other indications, our review showed that it is registered in Russia only, specifically for cases of immunocompromised patients, neuroinfection, HIV, viral hepatitis, herpes, and cytomegalovirus infection.

The submitted dossier stated that MA has been presented in the Republic of Belarus, Georgia, Moldova, Kazakhstan, Kyrgyzstan, Uzbekistan, Mongolia, Tajikistan, Laos, Armenia, Turkmenistan, Azerbaijan; however, we are unable to verify the claimed registration status due to limitations in accessing databases of international drug regulatory bodies. The countries where this is supposedly being marketed are all in the global south (developing countries), and there was no mention of it being marketed in the global north (e.g., US, Singapore) where health systems are more robust.

No relevant studies were found with regard to the clinical efficacy and safety of MA for COVID-19. Expanding the evidence review on its use for influenza, three studies (Romantsov et. al. (2010), Romantsov et. al. (2009), Sologub et. al. (2009)) were retrieved and translated from Russian to English using Google® Translate. The salient points and critical appraisal of the studies are tabulated below:

Romantsov et al., 2010	• MA was able to normalize the body temperature on the 4th day in patients with acute respiratory tract viral infection. • The major flaw of the study is the lack of a control group, therefore, relative treatment effects cannot be established. Likewise, it failed to report Baseline characteristics, allocation concealment, blinding, intention to treat and complete follow up.
Romantsov et al., 2009	• The study explored the possibility of improving the natural resistance of children on acute respiratory tract viral infection using meglumine acridone acetate as compared with placebo. • Results showed that in children aged 4-16 years old, there is marked reduction in symptoms of intoxication, duration of catarrhal episodes of the upper respiratory tract and absence of adverse drug reactions. • The study has multiple gaps which include failure to report, effective allocation concealment, baseline characteristics, blinding, and accounting of patient assignment to outcome reporting.
Sologub et al., 2009	• This study has two (2) sub studies: - **Sub study 1:** When compared with symptomatic basic treatment, the reported

	outcomes [i.e., temperature intensity and duration of fever (average duration ranging from 1.8 to 3.0 days versus 5 days), lesser duration (in mean days) of catarrhal events and symptoms in influenza patients (on average, 2-2.5 days lesser than the control), and lesser number of adverse events] favored MA. - **Sub study 2:** When compared with multivitamins, the reported outcome "incidence of illness" favored meglumine acridone acetate; however the interpretations and clinical impact for the reported outcomes "efficiency index" and "safety index" were unclear as their definitions were not mentioned in the report. • The studies mentioned the use of envelopes for randomization and the use of table of random numbers. There was, however, limited discussion on the methods and the lack of completeness of presented data on the outcomes.

None of these three studies reported mortalities or other clinically relevant outcomes for influenza such as clinical recovery and length of hospital stay. Further, despite the reported favorable outcomes MA for the treatment of influenza in all of the three (3) studies, the studies cannot support such claims due to low internal validity of the studies.

3.2. Economic Evaluation

No data available

Section 4.

Ethical, Legal, Social, and Health System Impact

No evidence available.

Section 5.

Recommendation

The HTA Council ***does NOT recommend the acceptance of the donation of meglumine acridone acetate*** due to the following reasons:

1. It is not included in any CPG for COVID-19 and it is also not registered for the management of COVID-19 even in its country source, Russia. Its registered indication in Russia for the treatment of influenza and acute viral respiratory infections.
2. There were no reports of it being marketed in the global north (e.g., United States Singapore) where health systems are more robust.
3. There are no published completed and on-going clinical trials regarding its clinical efficacy and safety for COVID-19, to date. The three studies were indicated for influenza and while the outcomes of the studies are favourable, the overall low internal validity of the studies cannot support such claim.
4. There may be logistical and financial burden to dispose the donated medicine if there will be no users.

For inquiries, you may contact the HTA Unit:

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