

Annex to WHO Regulatory Update – 5

Descriptive analysis¹ of COVID19-related spontaneous reports from Vigibase

Interim results (17 April 2020)

(Prepared in collaboration with the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring)

Vigibase, the WHO global Individual case safety reports (ICSR) database is managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC). Vigibase has been receiving an increasing number of ICSRs related to the COVID19 disease treatment from countries.

Between 1 and 29 March 2020, 26 case safety reports were submitted to Vigibase and included one or more of the following drugs: lopinavir, ritonavir, hydroxychloroquine, oseltamivir, remdesivir, interferon-beta. The drugs were reported as suspected or interacting in these 26 cases. Eight of these cases reported serious adverse events.

All 26 case reports were from Europe and related to 7 females, with a median age of 60.5 years, and 17 males with a median age of 70.5 years. The sex of the patient was not indicated in two reports. The age range of the patients in the reports was 41 - 83 years.

Hydroxychloroquine: One report described the use of hydroxychloroquine, 600 mg daily in a 47-year-old male. MedDRA preferred terms (PTs) reported in the case were: vision blurred, accommodation disorder and headache. All are well-known adverse effects of the drug. Hydroxychloroquine was withdrawn. There were additional cases where hydroxychloroquine was reported together with other drugs (see below).

Remdesivir: 6 reports concerned treatment with remdesivir where, in 5 cases, this was the only reported drug. One case reported death as an adverse event. In one case where treatment was combined with hydroxychloroquine, several concomitant drugs were reported including cardiotropics, antihypertensives, antidiabetics and antibacterials. Where reported (n= 2), the dosage was 100mg daily. One additional report included remdesivir alongside lopinavir-ritonavir (see below).

Reported adverse events, actions taken and outcome (when available) were:

- Hepatic enzyme increased (drug continued)
- Rash pustular (drug continued, outcome: not recovered)
- Diarrhoea
- Blood creatinine increased, Death (drug continued)
- Acute kidney injury, Septic shock (drug withdrawn)
- Transaminases increased

Neither summary of products characteristics nor product label are available for remdesivir. The

¹ **Disclaimer:** Data in the reports are not complete and none of the reports in this analysis contained narratives. With the limited data available at this stage of the pandemic and the uncertainty over other confounders, this report is no more than a preliminary overview of cases and reported ADRs. Any signals detected in the future will be communicated separately.

EMA's Summary on Compassionate use for remdesivir indicates that transient elevation of hepatic enzymes were recorded in healthy volunteers after repeated dosing.

Lopinavir-ritonavir: The use of lopinavir-ritonavir was reported in 19 cases, several of them in combination with other drugs with a putative efficacy against COVID 19. 4 cases reported lopinavir-ritonavir alone with a dose (where noted), of 1 tablet per day. In the drug list of one of the cases there was the presence of anaesthetic, cardiotropic and other drugs compatible with assisted respiration in ventilator, heart failure and thromboembolic disease.

Reported adverse events, actions taken and outcome (when available) were:

- Diarrhoea, vomiting (drug withdrawn, outcome: recovered)
- Nausea vomiting (drug withdrawn)
- Acute kidney injury (drug withdrawn, outcome: not recovered)
- Therapeutic response unexpected, Off-label use

Lopinavir-ritonavir with other drugs: 12 cases are reported with a combination of lopinavir-ritonavir and hydroxychloroquine and in one of the cases with the addition of tocilizumab, interferon beta and antibacterial treatment. Dosing, where noted, was 1-2 tablets of lopinavir-ritonavir and 400-500 mg hydroxychloroquine daily. Reported adverse events, actions taken and outcome (when available) were:

- Diarrhoea (N=5) (drug withdrawn in one case with recovery, unchanged dose in one case, outcome recovered)
- Diarrhoea, Abdominal pain (n=2, outcome in one case, recovery)
- Nausea (outcome: recovering)
- Vomiting, Nausea (lopinavir-ritonavir withdrawn, outcome: recovered)
- Nausea, Diarrhoea, Decreased appetite, Asthenia (L/R withdrawn)
- Diarrhoea, Rash, Gastroesophageal reflux disease (L/R withdrawn, outcome: recovering)
- Off label use, Therapeutic response unexpected

3 cases are reported with a combination of lopinavir-ritonavir, with an addition of oseltamivir, remdesivir or interferon beta respectively. In the case with lopinavir-ritonavir + remdesivir, the dosing reported was 1 tablet of the former and 200 mg remdesivir daily. Two of the reports include concomitant antibacterials and one a concomitant antidiuretic. Reported adverse events, actions taken and outcome (when available) were:

- Lopinavir-ritonavir + oseltamivir - hepatocellular injury (drugs withdrawn, outcome: recovering)
- Lopinavir-ritonavir + remdesivir - hepatic enzyme increased (drugs withdrawn, outcome: not recovered)
- Lopinavir-ritonavir + interferon beta - therapeutic response unexpected, off-label use

The EU summary of product characteristics for Kaletra® (lopinavir-ritonavir originator product) includes diarrhoea, vomiting, nausea, abdominal pain, rashes, gastroesophageal reflux disease, decreased creatinine clearance, hepatitis, and increased liver enzyme levels as acknowledged adverse effects of the drug.

Summary: During the month of March 2020, 26 reports in relation to treatment for COVID 19 with drugs included in the WHO SOLIDARITY trial were retrieved from Vigibase, the Global individual case safety reports database as presented. Further updates will follow.