

# AU InforMed

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Guest Editors: Justin Carter, Caroline Dunn, Andrei Znamenski, Pharm.D. Candidates 2022, Bernie R. Olin, Pharm.D.



## Key Inforbits

- Ivermectin Use in COVID-19
- Ivermectin Toxicities
- Approved Products, Doses, and Indications for Ivermectin
- Current COVID-19 treatment and prevention recommendations

## Ivermectin: Use in COVID-19?

Ivermectin is an antiparasitic agent that is U.S. Food and Drug Administration (FDA) approved in humans for the treatment of onchocerciasis, intestinal strongyloidiasis, head lice, and rosacea.<sup>1</sup>

Ivermectin has become a topic of controversy due to an increase in interest for its use in the prevention and treatment of COVID-19. Ivermectin has been shown to have antiviral activity *in vitro* and *in vivo* against a broad range of viruses. It was hypothesized that ivermectin could be a potential option for therapy with COVID-19 after one *in vitro* study found that ivermectin had significant antiviral activity when administered to Vero/hSLAM cells infected with COVID-19. The authors concluded that the results from their experiment should prompt further investigation for ivermectin use *in vivo* and that there is a need for developing a more effective dosing regimen in order to obtain similar concentrations of ivermectin found in the *in vitro* study.<sup>2</sup>

Unfortunately, individuals and groups have taken a shred of experimental data and translated that into clinical recommendations. The Front Line COVID-19 Critical Care Alliance (FLCCC), a group of physicians, is one of several groups that have developed COVID-19 treatment guidelines independent of recommendations from major healthcare authorities. These organizations have been formed since early in 2020 with the intent of developing treatment protocols to prevent the transmission of COVID-19 and improve treatment outcomes.

These alliances often include a national and international network of providers; however, most, if not all of the groups have not been acknowledged or supported by recognized medical



authorities. Some have published protocols for prevention, early treatment, and late phase hospital care. Protocols recommend ivermectin 0.4 to 0.6 mg/kg per dose by mouth daily for at least 5 days or until recovery for treatment and 0.2 mg/kg twice a week for chronic prevention.<sup>3</sup> Groups generally recommend the use of ivermectin tablets for oral administration and does not support or recommend the use of veterinary products. Treatment recommendations often are not supported by quality clinical trial data and may include a disclaimer that their protocol is solely for educational purposes on potentially beneficial COVID-19 therapies. The FLCCC has attempted to publish its own study on ivermectin use in the *Frontiers* journal, but the article was removed during the provisional acceptance phase due to a series of strong unsupported claims based on studies with insufficient statistical significance, and with inconsistent use of control groups.<sup>4</sup> One meta-analysis referenced by this group suggested clinical benefit and mortality benefit with ivermectin for COVID-19 treatment, however their analysis included data from trials that used active comparators with unclear ascertainment of infection and disease severity, and with uncertain assessment of outcomes.<sup>5</sup>

<b>Statements on Ivermectin use for COVID-19<sup>6-10</sup></b>	
<b>National Institutes of Health (NIH)</b>	The NIH Covid-19 guideline panel indicates that there is insufficient data to recommend for or against the use of ivermectin for the treatment of COVID-19 and that “results from adequately powered, well-designed, and well conducted clinical trials are needed to provide more specific, evidence-based guidance”
<b>World Health Organization (WHO)</b>	The WHO addressed the use of ivermectin in patients with COVID-19 in the fourth version of the WHO living guide after recognizing an increase in international attention for the therapy. The statement addresses the use of ivermectin for the treatment of COVID-19 but not for prophylaxis. The organization recommends not to use ivermectin in patients with COVID-19 except in the context of a clinical trial. The reasoning for this recommendation is due to the low certainty of available evidence. Subsequently published updates to the WHO living guide have continued to include this recommendation.
<b>Centers for Disease Control and Prevention (CDC)</b>	The CDC released a statement through their Health Alert Network (HAN) on August 28, 2021 in response to the use of ivermectin for treatment and prevention of COVID-19. The statement included that ivermectin is FDA indicated to treat certain infections in humans caused by internal and external parasites, and that it is generally safe and well tolerated. However, it warns that ivermectin is not authorized or approved by the FDA for prevention or treatment of COVID-19. Clinicians and public health practitioners are cautioned to be aware that the NIH has determined that there is insufficient data to recommend ivermectin use for COVID-19, and to advise against the use of medications that are formulated or intended for veterinary use.
<b>Infectious Diseases Society of America (IDSA)</b>	The IDSA COVID-19 guidelines advise against the use of ivermectin outside of a clinical trial in COVID-19 treatment in both hospitalized patients and the outpatient setting. The guideline panel additionally made the statement that sufficiently designed clinical trials are needed to make informed decisions for treatment recommendations.

<b>American Medical Association (AMA), American Pharmacists Association (APhA), and American Society of Health-System Pharmacists (ASHP)</b>	On September 1st, 2021, the AMA, APhA, and ASHP issued a joint statement on the use of ivermectin. These groups strongly oppose the ordering, prescribing, or dispensing of ivermectin to prevent or treat COVID-19 outside of a clinical trial. They urge physicians, pharmacists, and other prescribers to warn patients against the use of ivermectin outside of FDA-approved indications and guidance, whether intended for use in humans or animals, as well as purchasing ivermectin from online stores.
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<b>Approved Products, Doses, and Indications for Ivermectin in Humans<sup>1</sup></b>	
Onchocerciasis ( <i>Generic Ivermectin 3mg tablet or Stromectol 3mg tablet</i> )	150 mcg/kg by mouth for 1 dose
Intestinal Strongyloidiasis ( <i>Generic Ivermectin 3mg tablet or Stromectol 3mg tablet</i> )	200 mcg/kg by mouth for 1-2 days
Head lice ( <i>Topical - Generic Ivermectin 0.5%, Generic Ivermectin 1%, or Soolantra 1%</i> )	Apply a sufficient amount to cover entire dry scalp and hair for 1 dose
Rosacea ( <i>Topical - Generic Ivermectin 0.5%, Generic Ivermectin 1%, or Soolantra 1%</i> )	Apply to affected area once daily



## Ivermectin Toxicities



The doses of ivermectin used in COVID-19 are higher than established and approved maximum doses. Organizations such as the Front Line COVID-19 Critical Care Alliance (FLCCC) are recommending doses two to three times greater than the FDA approved doses of 150-200 mcg/kg.<sup>1,3</sup> Ivermectin toxicities can include gastrointestinal effects (nausea, vomiting, abdominal pain, and diarrhea), headache, blurred vision, dizziness, tachycardia, hypotension, visual hallucinations, altered mental status, confusion, loss of coordination and balance, central nervous system depression, and seizures. It also has the potential to increase the sedative effects of other medications such as benzodiazepines and barbiturates.<sup>1</sup> There is limited data available on higher doses of ivermectin, but one systematic review and meta-analysis observed the safety data from 6 trials to compare the rate of adverse events in higher doses of ivermectin compared to known safe doses. Doses of up to 0.8 mg/kg were observed to have no significantly different rate of adverse events compared to doses 0.2 mg/kg and lower. They did note that ocular adverse events, specifically blurred vision, although being transient, were of the greatest concern. However, the authors concluded that they did not have enough data to support a recommendation for doses of ivermectin higher than approved doses.<sup>11</sup> UpToDate's COVID-19 management recommendations note that gastrointestinal and neurologic side effects have been reported in individuals who obtained ivermectin at high doses or uncertain doses without prescriptions such as with veterinary medications.<sup>4</sup>

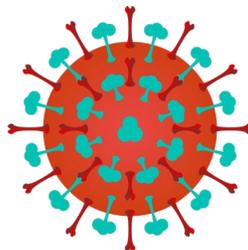
Ivermectin is also used in veterinary practice for the prevention of heartworm disease, and for the treatment of certain internal and external parasites in various animal species. Some

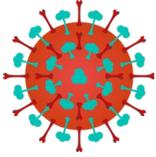
veterinary formulations of ivermectin such as pour-on, injectable, and paste are available for purchase without the authorization of a veterinarian. Due to the increase in misinformation about the role of ivermectin in COVID-19, concern has grown about the potential of humans self-treating with veterinary products. The FDA released a statement that veterinary products are not reviewed for safety in humans and could potentially contain inactive ingredients that are not safe for human consumption. Furthermore, ivermectin products formulated for animal use are often for large animals like horses and cows. These doses are highly concentrated and can be toxic for humans.<sup>11</sup>

Ivermectin Veterinary Products <sup>12</sup>
Ivermectin for Injection: 10 mg/mL (1%)
Ivermectin Oral Paste: 1.87% (18.7 mg/g) in 6.08 g syringes
Ivermectin Liquid: 1% (10 mg/mL) in 50 mL and 100 mL bottles
Ivermectin Oral Tablets: 68, 136, and 272 mcg
Ivermectin Oral Chewable Tablets: 55 or 165 mcg
Ivermectin Topical Parasiticide Pour-on for Cattle: 5 mg/mL

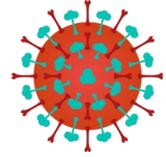
The American Association of Poison Control Centers released a bulletin on poison control reports submitted for Ivermectin comparing 2019, 2020, and 2021. From January 1, of 2021 to August 31, there have been 1,143 ivermectin poison control reports; 459 of those cases occurred in August alone. Of these cases, none were reported to result in death, but approximately 103 resulted in a moderate to major effect. There were 137 of those cases categorized as unable to be followed but were judged as a potentially toxic exposure.<sup>13</sup> The majority of cases were in adults (20-79 years) with an even distribution among sexes.

Poison Control Center Cases for Ivermectin	
2019	402
2020	435
2021 (January 1st thru August 31st)	1,143





# Current COVID-19 Recommendations



CDC Recommendations for <u>Treatment</u> of COVID-19 <sup>14-24</sup>	
<b>Glucocorticoids</b>	<b>REGEN-CoV (casirivimab/imdevimab)</b>
<ul style="list-style-type: none"> <li>● Agent: dexamethasone</li> <li>● Recommended for patients requiring supplemental oxygen or if hospitalized</li> <li>● Not recommended for non-hospitalized patients that do not require supplemental oxygen</li> <li>● Recommended for the duration of supplemental oxygen use in non-hospitalized patients not to exceed 10 days of dexamethasone therapy</li> </ul>	<ul style="list-style-type: none"> <li>● Anti-SARS-CoV-2 monoclonal antibodies</li> <li>● Recommended for patients with mild-moderate COVID-19 who are at high risk for disease progression</li> </ul>
<b>Bamlanivimab/etesvimab</b>	
<ul style="list-style-type: none"> <li>● Anti-SARS-CoV-2 monoclonal antibodies</li> <li>● Authorized for post-exposure prophylaxis for adults and pediatrics patients (12 years and older) at risk for progression to severe COVID-19, and are not fully vaccinated or expected to have mounted an adequate immune response</li> </ul>	
<b>Veklury (remdesivir)</b>	<b>Actemra (tocilizumab)</b>
<ul style="list-style-type: none"> <li>● Inhibits the SARS-CoV-2 RNA-dependent RNA polymerase to halt viral replication</li> <li>● Recommended for hospitalized patients that require supplemental oxygen</li> </ul>	<ul style="list-style-type: none"> <li>● Inhibits IL-6 receptors leading to a reduction in cytokine and acute phase reactant production</li> <li>● Recommended for hospitalized patients with systemic inflammation and increasing oxygen demand</li> </ul>
<b>Olumiant (baricitinib)</b>	<b>Xevudy (sotrovimab)</b>
<ul style="list-style-type: none"> <li>● Inhibitor of Janus kinase enzymes. This prevents the activation of transcription and reduces IgA, IgG, IgM, and CRP levels</li> <li>● Recommended for hospitalized patients with systemic inflammation and increasing oxygen demand</li> </ul>	<ul style="list-style-type: none"> <li>● Anti-SARS-CoV-2 monoclonal antibody</li> <li>● Authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years and older) who are at high risk for progression to severe COVID-19, including hospitalization or death</li> </ul>

## CDC Recommendations for Prevention of COVID-19<sup>17</sup>

- GET VACCINATED!!
- Wear a mask
- Stay 6 feet away from others
- Avoid crowds and spaces with poor ventilation
- Wash hands often with soap and water for at least 20 seconds
- Cover coughs and sneezes → wash hands
- Clean and disinfect highly touched surfaces daily
- Monitor your health daily

**Summary:** Ivermectin is an antiparasitic drug used in both humans and animals that has been a topic of controversy regarding its use for the prevention and treatment of COVID-19. Multiple health authorities do not recommend the use of ivermectin for prevention or treatment of COVID-19 due to insufficient evidence available. Ivermectin is FDA-approved in humans for only four disease states, all with different doses and formulations: Onchocerciasis, Intestinal Strongyloidiasis, Head Lice, and Rosacea. Toxicities that can be seen with ivermectin include gastrointestinal effects, headache, blurred vision, dizziness, tachycardia, hypotension, visual disturbances, altered mental status, confusion, loss of coordination and balance, central nervous system depression, and seizures. The consensus of COVID-19 treatment recommendations from health authorities such as the NIH, WHO, and CDC include the use of glucocorticoids, casirivimab/imdevimab, remdesivir, tocilizumab, and baricitinib. The CDC also has recommendations for the prevention of COVID-19 which include getting vaccinated (a priority), wearing a mask, staying 6 feet away from others, avoiding crowds and spaces with poor ventilation, washing your hands often with soap and water for at least 20 seconds, covering coughs and sneezes and then washing your hands, cleaning and disinfecting surfaces daily that are highly touched, and monitoring your health daily.

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also a love of humanity.”

-Hippocrates [Greek physician, 460 – 370 BCE]

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