

March 19th, 2020

Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2

Dear Health Care Professional,

On behalf of the Janssen Pharmaceutical Companies of Johnson & Johnson, our thoughts are with all affected by the outbreak of the coronavirus (SARS-CoV-2). Considering the large public health and humanitarian implications, we are committed to global efforts to care for those affected, contain the current outbreak and develop measures to tackle future outbreaks.

We support broad access to information, and we strongly believe that the development of evidence-based intervention guidelines for COVID-19 is critical. We are therefore writing to inform you of important information relating to REZOLSTA[®], (a fixed-dose combination of 800 mg darunavir (DRV), and 150 mg cobicistat, a CYP3A inhibitor) which is approved for the treatment of HIV-1 infection, in combination use with other antiretroviral agents. The recommended dosage of REZOLSTA[®] is one tablet taken once daily orally with food. Of note, DRV should not be administered without a boosting agent (ritonavir or cobicistat) as previous studies of unboosted DRV resulted in subtherapeutic drug levels and was associated with a higher rate of adverse events.

It has been brought to our attention that despite lack of published evidence, HIV protease inhibitors are being considered as therapeutic options for COVID-19. We believe this use is based on limited, unpublished virologic and clinical data in the treatment of patients infected with severe acute respiratory syndrome (SARS) coronavirus.

- **Janssen has no clinical nor pharmacological evidence to support the inclusion of DRV/cobicistat in treatment guidelines for COVID-19, nor are there published data on the safety and efficacy profile of DRV/cobicistat in treatment of COVID-19.**
- **There are no published clinical studies that have evaluated the efficacy and safety of DRV, DRV/cobicistat or DRV/cobicistat/emtricitabine/tenofovir alafenamide for the treatment of novel coronavirus.**
- **Results from a single center, open label, randomized, and controlled trial conducted at Shanghai Public Health Clinical Center (SPHCC) of darunavir and cobicistat (DRV/c) in treating laboratory-confirmed 30 COVID-19 patients showed that DRV/c was not effective.**
- **In addition, there are no published *in-vitro* studies with DRV and coronavirus. Based on preliminary, unpublished results from a previously reported *in-vitro* experiment, it is not likely DRV will have significant activity against SARS-CoV-2 when administered at the approved safe and efficacious dose for the treatment of HIV-1 infection.***



- **Additionally, structural analyses show very few interactions of DRV with the active site of the SARS-CoV-2 protease.***

Many Janssen compounds, including DRV, are in the process of being evaluated *in-vitro* for potential antiviral activity against SARS-CoV-2. Janssen has also provided DRV based medicines to support several ongoing clinical studies in China. We have received unpublished results from one clinical study (listed above). These results show that five days of darunavir and cobicistat was not effective in treating COVID-19.

As soon as this data is published and further preclinical and / or clinical data become available, we will provide an update.

In this situation, our priority – acknowledging that there is no current evidence that DRV is efficacious for the treatment of COVID-19 – is to ensure current provision of these life-saving medicines to patients living with HIV.

We remain open to collaborating with governments, healthcare professionals and others to ensure rigorous collection and transparent sharing of data that will allow evidence generation to guide the use of effective medicines and support the best outcomes for patients affected by COVID-19. We do however want to ensure that investigational treatments with the highest probability of success are being prioritized for use in experimental settings and would therefore appreciate your help in **sharing this information with relevant stakeholders** particularly those involved in developing clinical treatment guidelines or managing patients affected by COVID-19.

There is no higher priority than patient health for Janssen. Since January, we have been deeply engaged in a multipronged response to the SARS-CoV-2 outbreak.

Janssen is leading collaborative efforts to screen compounds in discovery and development within our organization and across the broader pharmaceutical industry to accelerate the development of therapies. In mid-January 2020, Janssen also initiated a high priority project to develop a SARS-CoV-2 vaccine candidate leveraging our AdVac[®] and PER.C6[®] technologies. We are partnering with multiple organizations to support the development of collaborative research programs and fast-track the development solutions for COVID-19.

Due to the importance of this information, we are in the process of informing local health authorities, regulatory bodies and other healthcare stakeholders. Should you have any questions pertaining to the information outlined in this letter, please contact Rui Marques (r.

Sincerely,

A handwritten signature in black ink, appearing to read "Aran Maree".

Aran Maree, MD
Chief Medical Officer
Janssen Pharmaceutical Companies of Johnson & Johnson



Manuel Salavessa, MD
Medical Affairs and Regulatory Director

Supporting Documents enclosed:

- Medical Information Factsheet*
REZOLSTA eMPC

Cautions Concerning Forward-Looking Statements

This letter contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding darunavir/cobicistat and development of potential preventive and treatment regimens for COVID-19. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of the Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 29, 2019, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

Darunavir, Darunavir/Cobicistat, Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide Use in Coronavirus

SUMMARY

- Janssen does not believe there is sufficient clinical and pharmacological evidence at this time to support the inclusion of darunavir (DRV)/cobicistat in treatment guidelines for COVID-19, nor is there sufficient data on the safety and efficacy profile of DRV/cobicistat in the treatment of COVID-19.
- There are no clinical studies that evaluated the efficacy and safety of darunavir, darunavir/cobicistat or darunavir/cobicistat/emtricitabine/tenofovir alafenamide for the treatment of COVID-19. In addition, there are no published *in-vitro* studies with darunavir and COVID-19.
- Currently, darunavir/cobicistat is being tested *in-vitro* for potential antiviral properties against coronavirus.¹
- Results from a single-center, open-label, randomized, controlled trial conducted at Shanghai Public Health Clinical Center (SPHCC) of darunavir and cobicistat (DRV/c) in treating laboratory-confirmed 30 COVID-19 patients showed that DRV/c was not effective.
- For additional information regarding the lack of evidence to support use of darunavir-based treatments for SARS-CoV-2, please visit <https://www.janssen.com/lack-evidence-support-use-darunavir-based-treatments-sars-cov-2>.

PRE-CLINICAL DATA

In a previously reported experiment, preliminary *in-vitro* data show that DRV inhibited viral replication of SARS-CoV-2 at a concentration of 300 μM , a concentration that is much higher than what is usually achieved with oral administration of DRV/cobicistat.² As explained by the investigator of this *in-vitro* experiment, this does not imply efficacy *in-vivo*.³ In fact, when DRV/cobicistat is administered at the indicated dose (800/150 mg once daily tablets) to treat HIV infection, the mean trough concentration of DRV in plasma is 3.4 μM , 88-fold lower than the 300 μM concentration at which antiviral activity against SARS-CoV-2 has been reported. Based on these data, it is unlikely that DRV will have significant activity against SARS-CoV-2.

Furthermore, based on structural analyses it is unlikely that DRV will have significant antiviral activity against SARS-CoV-2. The HIV protease is a dimeric aspartic protease and DRV binds at its active site.⁴ The crystal coordinates of the compound binding to HIV protease are deposited in the Protein Data Bank (PDB-code 1T3R). The crystal structure of HIV protease with DRV reveals a tight extensive hydrogen bonding network, explaining the high potency of DRV against HIV, where it has been demonstrated over many years to be a safe and effective therapy. Researchers at Shanghai Tech University have resolved a high-resolution crystal structure of the SARS-CoV-2 main 3C-like (3CL) protease, a cysteine protease (PDB-code 6LU7). Janssen did an *in-silico* docking experiment of DRV in this crystal structure of SARS-CoV-2 protease and found several docking poses. However, all these poses showed very few interactions of DRV with the catalytic center in the active site of the protease, unlike the many strong interactions observed for DRV bound to HIV protease. These results are consistent with the much lower *in-vitro* activity of DRV against SARS-CoV-2 as compared to HIV.

Janssen is collaborating with other partners to generate robust data on the *in-vitro* antiviral activity of DRV against SARS-CoV-2 to provide evidence-based guidance on the further evaluation of DRV/cobicistat for the treatment of COVID-19.

Additionally, Janssen is leading collaborative efforts to screen compounds in discovery and development within our organization and across the broader pharmaceutical industry accelerate the development of therapies. In mid-January 2020, Janssen also initiated a high priority project to develop a SARS-CoV-2 vaccine leveraging our AdVac and PER.C6 technologies. Janssen expanded our collaboration with the Biomedical Advanced Research and Development Authority (BARDA) to further expedite our investigational coronavirus vaccine program⁵ and screening for compounds with antiviral activity against SARS-CoV-2.⁶ In addition to these efforts, Janssen is partnering with multiple organizations to support the development of collaborative research programs and fast-track the development of diagnostics and therapeutics for COVID-19 to complement the ongoing global activities on vaccines.

CLINICAL DATA

A single-center, open-label, randomized, controlled trial was conducted at Shanghai Public Health Clinical Center (SPHCC) of darunavir and cobicistat (DRV/c) in treating laboratory-confirmed 30 COVID-19 patients.⁷ The primary endpoint (viral clearance rate at day 7 after randomization) showed that DRV/c was not effective. (NCT04252274)

LITERATURE SEARCH

A literature search of MEDLINE[®], DERWENT[®], EMBASE[®] (and/or other resources, including internal databases) pertaining to darunavir and coronavirus was conducted on 17 March 2020.

REFERENCES

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3. Li Lanjuan, "Li Lanjuan's response to the data of two new crown referrals is questioned: only experimental data and no results released", interview by Beijing News. 2020. Available at: https://view.inews.qq.com/a/20200214V0UJ3M00?uid=100092361387&chlid=news_news_top&jumpType=104&devid=a3f6f62afccf2705&qimei=a3f6f62afccf2705&shareto=wx&from=groupmessage&isappinstall=0.
4. King NM, Prabu-Jeyabalan M, Nalivaika EA, et al. Structural and thermodynamic basis for the binding of TMC114, a next-generation human immunodeficiency virus type 1 protease inhibitor. *J Virol*. 2004; 78(21): 12012-12021.
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6. Janssen Pharmaceutical Companies of Johnson & Johnson. Press Release (Posted February 18, 2020). Johnson & Johnson to Expand Partnership with U.S. Department of Health & Human Services to Accelerate the Discovery of Potential COVID-19 Treatments. Available at: <https://www.jnj.com/johnson-johnson-to-expand-partnership-with-u-s-department-of-health-human-services-to-accelerate-the-discovery-of-potential-covid-19-treatments>.
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