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Ministry of Food and Drug Safety

Press Release

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Divisions	· 허가총괄담당관 · 의약품안전국 의약품정책과 · 코로나19위기대응지원본부 · 화학치료제심사반 총괄검토팀 · 화학치료제심사반 비임상·임상심사팀
Directors	· 이수정 (☎043-719-2341) · 채규한 (☎043-719-2610) · 최영주 (☎043-719-2911) · 김영림 (☎043-719-3051)
Researchers	· 도원임 (☎043-719-2318) · 김영주 (☎043-719-2640) · 김소희 (☎043-719-2927) · 최경숙 (☎043-719-3053)

Advisory Committee Meeting Outcomes on Candidate COVID-19 Treatment Napabeltan

☐ The Ministry of Food and Drug Safety (MFDS, Minister Kim Ganglip) describes as follows the marketing authorization process of ChongKunDang's Napabeltan, which was repurposed for COVID-19 treatment efficacy and effectiveness.

1 Drug Repurposing Approval and Review Status

☐ On March 17, the Ministry held a meeting of the COVID-19 Treatment and Vaccine Safety and Efficacy Assessment Advisory Committee (hereinafter "Advisory Committee") to review the clinical trial results of Napabeltan developed by ChongKunDang.

○ The Advisory Committee meeting was attended by five external experts including an infectious disease specialist and a clinical data expert as well as four internal experts from the Overall Evaluation Team and Clinical Review Team of the Chemical Therapeutics Review Division in the COVID-19 Emergency Response Support Headquarters under the Ministry.

2 Clinical Trial Results

<<Overview>>

☐ Submitted clinical trial data included the results of one (1) phase II

clinical trial conducted in Russia, in which a total of 104 patients at 13 clinical trial institutions in Russia underwent *open and randomized assignment** and were divided into two groups: patients who only received COVID-19 *standard treatment*** (control group, 51 participants) and patients who received standard treatment and were administered with the test product (test group, 53 participants).

* Participants' information is disclosed to clinical trial researchers and other participants (open assignment); participants are randomly assigned in order to eliminate researchers' bias in treatment assignment (randomized assignment).

** Standard treatment: COVID-19 treatment option recommended by health authorities

<< Efficacy >>

○ The clinical trial was conducted based on *time to clinical improvement* between the test group and control group after Napabeltan had been administered to the test group for 10 days.

* Time to clinical improvement: Based on the COVID-19 clinical status in the score of one to seven, a patient shows a decrease of at least two scores or has been discharged not long after the treatment.

** Measuring the score of one to seven: one (no need for hospitalization and no difficulty engaging in normal activities) to seven (death)

○ The test results failed to demonstrate efficacy as the test and control groups showed no meaningful difference in time to clinical improvement (11 days for both), which was the main indicator of efficacy, and in time from positive to negative conversion (virus negative conversion time) of SARS-CoV-2 (4 days for both).

* Among the 104 randomly assigned participants, one participant not administered with the clinical product and another not tested for efficacy were excluded from the analysis. A total of 102 participants (52 from the test group and 50 from control group) were analyzed.

○ However, additional analysis on 36 patients who were graded as 7 or more in the *National Early Warning Score* showed that there was a difference between test group (18 participants) and control group (18

participants) in time to clinical improvement, 11 and 14 days respectively.

* National Early Warning Score (NEWS): evaluation criteria based on 7 clinical variables (respiratory rate, oxygen saturation, assisted oxygen, temperature, systolic blood pressure, heart rate, and level of consciousness)

<< Safety >>

○ According to the submitted clinical trial results, frequent adverse reactions among the test group included phlebitis, hyponatremia, respiratory failure, none of which was unexpected.

3 Advisory Meeting Outcomes

□ Based on the phase II clinical trial results of Napabeltan, the Advisory Committee held a meeting to review the therapeutic effect of the candidate drug.

<< Conclusion on Efficacy >>

○ Based on the following findings, the Advisory Committee concluded that additional clinical trials are needed to demonstrate the COVID-19 treatment efficacy and effect of repurposed Napabeltan because the submitted phase II clinical trial results cannot sufficiently demonstrate the therapeutic effect of Napabeltan.

- The clinical trial failed to demonstrate the effectiveness of the test drug because the test and control groups did not show a meaningful difference in time to clinical improvement, which is the primary efficacy endpoint,
- and, although the additional analysis showed statistical significance among the patients with a score of 7 or more on the NEWS chart, it has been concluded that the therapeutic effect of Napabeltan has not be sufficiently demonstrated for the following reasons.
- In order to demonstrate clinical improvement effect among the subjects (patients with a score of 7 or more on the NEWS chart), the effect must have been intentionally solicited before conducting the clinical trial and its statistical review. However, clinical improvement effect was unsolicited in

the clinical trial, which led to the conclusion that the clinical trial results should be used only for reference.

- Also, it was also considered that the clinical trial's objectivity and reliability was limited due to the "open assignment".

<< Opinion on Approval for High-risk Patients >>

○ The Advisory Committee has concluded that it is not appropriate to approve Napabeltan only based on the phase II clinical trial results and advised that additional clinical results that can demonstrate therapeutic effect should be submitted for approval and review.

4 Future Plan for Approval and Review

☐ Following the meeting outcomes of the Advisory Committee, the Ministry decided not to hold a meeting of the Central Pharmaceutical Advisory Committee (CPAC), which should be the next step in advisory procedures for COVID-19 vaccines and treatments, to make sure that the phase III clinical trial for Napabeltan is thoroughly planned and prepared.

☐ The MFDS will continue to do its utmost to ensure rigorous review and approval processes for COVID-19 vaccines and treatments while at the same time guaranteeing objectivity and transparency across all approval and review processes by taking into account multidisciplinary advice from experts.