

Approval of In Vitro Diagnostics for the novel coronavirus infection  
(Fujirebio Inc. application item)

May 13, 2020

Medical Device Evaluation Division,  
Pharmaceutical Safety and Environmental Health Bureau,  
Ministry of Health, Labour and Welfare (MHLW)

1. Product Overview

[Product name]: ESPLINE SARS-CoV-2

[Applicant]: Fujirebio Inc.

[Application date]: April 27, 2019 (Application for marketing approval)

[Purpose of use]: Detection of SARS-CoV-2 antigen in nasopharyngeal swabs  
(diagnostic aid for SARS-CoV-2 infection)

\* This product is a kit for detecting SARS-CoV-2 antigen in nasopharyngeal swabs using immunochromatography with enzyme immunoassay as the measurement principle. Liquids containing a test sample are dropped into the cassette, and within about 30 minutes, the presence or absence of the indicator line on the cassette is checked to determine positive or negative test result.

By using this product, it is possible to make a quick and definite diagnosis of positive cases at the place where the sample was collected. However, at present, when the result is negative, the risk of infection cannot be discarded, and in order to make a definitive diagnosis of non-infection, it is necessary to carry out an additional PCR test at a laboratory.

2. Summary of Approval Review

(1) Clinical performance

Regarding the clinical performance of this product, the results of two studies mentioned below were mainly submitted. In addition, study results using domestic test samples were submitted as reference data.

1) Domestic clinical performance study

The result of the clinical performance study based on the comparison with RT-PCR method conducted in Japan (n = 72 cases) showed a negative agreement rate of 98% (44/45 cases), and a positive agreement rate of 37% (10/27 cases). When comparing the positive agreement rate of the positive samples with the converted

RNA copy numbers (estimated values) in the RT-PCR test samples, the positive agreement rate was found to be 83% (5/6 cases) in the samples of more than 100 copies/test.

## 2) Study using domestic test samples

The result of the study based on the comparison with RT-PCR method using domestic test samples (n = 124 cases) showed a negative agreement rate of 100% (100/100 cases) and a positive agreement rate of 66.7% (16/24 cases). When comparing the positive agreement rate of the positive samples with the converted RNA copy numbers (estimated values) in the RT-PCR test samples, the agreement rate was found to be 100% (12/12 cases) in the samples of more than 1,600 copies/test, 93% (14/15 cases) in the samples of more than 400 copies/test, and 83% (15/18 cases) in the samples of more than 100 copies/test.

In the approval review, although the studies were conducted with a limited number of cases, this product had a positive agreement rate of about 80 to 90% in the samples of more than certain amounts of virus (approximately 80% in more than 100 copies/test and 90% in more than 400 copies/test), and a negative agreement rate of almost 100%.

Based on its clinical performance, this product is expected to be clinically useful, although less sensitive than the RT-PCR method, for diagnosing the infection based on a positive test result in patients with certain symptoms or other conditions. In addition, at present, there is no in-vitro diagnostics capable of rapid and simple detection of SARS-CoV-2 antigen in the country, and the prompt expansion of testing capacity at clinical sites is urgently needed. Therefore, it was considered acceptable to introduce this product into clinical practice on the following assumptions: i) put an approval condition that requests the verification of clinical performance in actual clinical practice in post-marketing; ii) provide information on the possibility of false negatives in the package insert; and iii) for negative cases of this product, indicate that PCR tests should be performed to confirm assessment.

## (2) Cross-reactivity

This product showed a reaction with recombinant human coronavirus antigen SARS-CoV, but showed no reaction with recombinant human coronavirus antigen (MERS-CoV, HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1), and inactivated influenza virus (Influenzavirus H1N1, Influenzavirus H3N2 and

Influenzavirus B)<sup>1</sup>.

Since this product did not react with the major antigens that may have cross-reactivity other than SARS-CoV, considering the urgency of developing this product, it was considered acceptable to introduce it into the clinical practice on the assumption that the reactivity with SARS-CoV be notified in the package insert, and that required additional cross-reactivity tests be promptly conducted.

### (3) Stability

Regarding the stability of this product, long-term stability test results under the actual storage conditions have not been submitted, but the effective period was provisionally set based on similar diagnostics of the applicant company.

In the approval review, considering the urgency of developing this product, it was considered acceptable to provisionally set the effective period on the assumption that a long-term stability test of this product will be carried out in post-marketing.

### (4) Others

The precautions required for using this product will be specified on the package insert.

### (5) Expert consultation

Expert consultation was held, and the review considerations from (1) to (4) were supported. Regarding (1), there was an opinion that the package insert should clearly warn of the necessity to carry out additional PCR tests for the definitive diagnosis of non-infection, and this was addressed.

## 3. Conclusion

Based on the above approval review, we have approved the marketing of this product by putting the following approval conditions:

[Approval date]: May 13, 2020

[Approval conditions]:

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<sup>1</sup> In addition, no reaction was shown with the culture solutions of human coronavirus (HCoV-229E (ATCC VR-740), HCoV-NL63 (Amsterdam I), HCoV-OC43 (ATCC-VR1558), HCoV-OC43 (Tokyo/SGH-36/2014) and HCoV-HKU1 (Tokyo/GH-15 /2014)).

- Since the data at the time of approval is extremely limited, the marketing approval holder is to carry out further studies to evaluate the clinical performance of this product in post-marketing.
- The marketing approval holder is to perform a stability test under the actual storage conditions in post-marketing.