Company News

June 19, 2000

Current regulatory NDA review status of ELASPOL(R) in Japan.

For further information

The NDA for ELASPOL(R) injection has been submitted to Japanese MHW for the indication of acute lung injury (ALI) associated with systemic inflammatory response syndrome (SIRS) , and it's approval was expected by the end of this year (Year 2000). However, at the interview meeting with Evaluation Center (Pharmaceutical and Medical Devices Evaluation Center of National Institute of Health Science) held on May 30 , an additional clinical trial was required to be performed with the methodology commonly employed for overseas clinical trials on acute respiratory failure.

ALI associated with SIRS is a serious disease condition that aggravates pulmonary functions rapidly resulting in death in approximately 30% of the patients. There exists no effective therapy at present other than mechanical ventilation that is only supplementary to the aggravated pulmonary functions. ELASPOL(R) improves pulmonary functions of such patients and helps earlier discharge from painful respirators and intensive care unit. The Japanese clinical trials were performed with the methodology taking into account the medical practice in Japan , and MHW has agreed to Ono's thoughts in respect of the efficacy and clinical benefits of the drug. However the authority has an opinion that the approval of world's first drug for ALI requires the results of trial performed along with the methodology of global standard as much as possible.

The requirement of MHW does not refer to the efficacy or clinical benefits of the drug, but is based on the difference in medical practice between Japan and overseas where clinical trials are performed. Ono has accepted a small scale clinical trial to be performed under the supervision of MHW, recognizing the drug potential as "the world's first innovative new drug from Japan".
However we expect that it delays the product launch in Japan by about 1 to 1.5 years. Meanwhile the requirement of MHW will have no negative impact whatsoever on overseas development of the drug , including out-licensing the drug to Eli Lilly.

SUPPLEMENTAL COMMENTARY

1. Dialogue with Eli Lilly

The Evaluation Center at the interview meeting of May 30, 2000 required that an additional clinical study should be performed before ELASPOL(R) is approved. We visited Lilly headquarters on June 2 to explain the details of the Center's requirement. In response to our explanation, we were informed that there would be no change in Lilly's in-licensing policy for ELASPOL(R) and that they were willing to provide Ono with assistance in obtaining the regulatory approval in Japan.

We are pleased to announce that Ono and Lilly have recently signed a definitive license agreement to develop, manufacture and market ELASPOL(R).

2. Prospect of Approval in Japan

The Evaluation Center has agreed to Ono's views on the efficacy and clinical benefits of ELASPOL(R). It is anticipated to take approximately another one year to perform the additional clinical trial, but we have no doubt that the drug will be approved.

3. Outline of Additional Trial

There is a difference between Japan and US and European countries in a primary endpoint adopted for clinical trials with this kind of drug. Improvement in pulmonary functions was chosen as a primary endpoint for the clinical

trial performed in Japan. For the planned additional clinical study, as commonly done in overseas, discharge from mechanical ventilator will be adopted as a primary endpoint. A small scale open study enrolling 20 to 30 patients will be conducted.

However, recent clinical trials with other drugs in the United States have been performed with predetermined criteria for 'discharge from mechanical ventilator' and therefore our planned additional study in Japan will be done along with this US methodology as much as possible.

4. Reasons for Japanese Study Not Evaluating Discharge from Ventilator as Primary Endpoint

When we started a Phase III clinical trial with ELASPOL(R) in Japan, no one in the world was performing a clinical study with efficacy evaluation on 'discharge from mechanical ventilator' as a primary endpoint. Even in the United States, it was not until recent years that such clinical studies were performed.

We chose 'improvement in pulmonary functions' as a primary endpoint for the phase III study which was the best possible method we could pursue at that time. We conducted the study with discharge from mechanical ventilators in the way then clinically adopted in Japan and we therefore used this endpoint as a secondary one for the trial.

5. Difference in Medical Practice between Japan Where Clinical Trials Were Performed and US/Europe

In the United States, respiratory therapists take care of mechanical ventilators. Discussions are underway, led by the National Institutes of Health (NIH), to improve usage of mechanical ventilators and establish the standard criteria. Such underlying background has enabled to perform clinical trials with standardized criteria in the United States in these days. On the other hand, medical practice is not ready yet to establish such standardized criteria in Japan because surgeons, internists and anesthesiologists are in charge of the care of ventilators in the respective ways they consider appropriate.

However the authority has an opinion that, from the standpoint of generating the world's first drug in acute lung injury from Japan, supplemental clinical data should be obtained along with the global standard method as much as possible.

6. Impact on This Fiscal Year's Prospect and Mid-term Sales Performance Because of Delay in Expected Launch of the Product.

Although we had targeted the product launch within Calendar Year 2000, we thought that ELASPOL(R) would only contribute to the sales from our fiscal 2002 (starting April 1, 2001), and was not included in the prospective total sales of this fiscal year which is Yen 129,000 million (2.3% increase over fiscal 2000). Accordingly, there is no negative impact on sales performance of this fiscal year.

Meanwhile, we expect that the impact on mid-term sales performance would be minor because delay in approval would be slightly over 1 year behind our original schedule.

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