ZENYAKU KOGYO CO.,LTD.
6-15,Otsuka5-chome,Bunkyo-Ku,Tokyo,Japan

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CHUGAI PHARMACEUTICAL CO., LTD.
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Zenyaku Kogyo Co., Ltd.
Chugai Pharmaceutical Co., Ltd.

Anti-CD20 Monoclonal Antibody Rituxan® Approved for Suppression and Treatment of Antibody-mediated Rejection in Organ Transplantation

TOKYO, December 22, 2023 -- Zenyaku Kogyo Co., Ltd. (Japanese-only website) and Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced today that Zenyaku obtained regulatory approval from the Ministry of Health, Labour and Welfare (MHLW), for an anti-CD20 monoclonal antibody Rituxan® intravenous injection 100 mg and 500 mg [generic name: rituximab (genetical recombination)] (hereafter, “Rituxan”) for “suppression and treatment of antibody-mediated rejection in organ transplantation.”

Antibody-mediated rejection[*2] after organ transplantation is a major cause of malfunction or extinction of the transplanted organ. Therefore, if the production of causative antibodies is suppressed or removed before transplantation, and the antigen-antibody reaction at the time of transplantation is suppressed (desensitization), transplantation will be possible even for blood type incompatible transplantation[*3], which have a high risk of antibody-mediated rejection, and for cases in which the recipient has antibodies[*4] specific to human leukocyte antigen (HLA). If a rejection reaction occurs, treatment by suppressing the antigen-antibody reaction is expected to maintain or restore transplanted organ function.

Rituxan is an anti-CD20 monoclonal antibody that specifically binds to CD20, a protein expressed on B cells, excluding hematopoietic stem cells and plasma cells. It attacks target B cells using the immune system equipped with the human body, and damages cells. This mechanism of action suppresses the differentiation of B cells into antibody-producing cells, and is expected to suppress antibody production for transplanted organs.

The development of Rituxan for "suppression and treatment of antibody-mediated rejection in organ transplantation" had started based on the results of the "34th Meeting on Unapproved and Off-label Drugs with High Medical Needs (held on March 23, 2018)."
The study was triggered by the 3rd call for requests for unapproved and off-label drugs with high medical needs that began from August 2013. At that time, the Japan Society of Transplantation submitted development requests for "treatment of antibody-mediated rejection in kidney transplantation" and "preoperative desensitization in anti-donor antibody-positive kidney transplantation."

Based on the results of usage survey[*5] conducted by the Japan Society of Transplantation, clinical trials were conducted for suppression of antibody-mediated rejection in kidney transplantation[*6] and treatment of antibody-mediated rejection[*7]. In addition, in a specific clinical

study[*8] conducted by the transplant medical technology development research project of the Japan Agency for Medical Research and Development, suppression and treatment of antibody-mediated rejection for liver, heart, lung, pancreas and small intestine transplantation were investigated. Based on the data obtained from these studies, Zenyaku submitted an application for partial changes to the manufacturing and sales approval items on April 6, 2023, which led to the current approval.

Zenyaku and Chugai will continue working closely together so that Rituxan may contribute to the suppression and treatment of antibody-mediated rejection in organ transplantation.

*1 Approved indication or effect
- Suppression of antibody-mediated rejection in the following organ transplantation:
  Kidney, liver, heart, lungs, pancreas, small intestine
- Treatment of antibody mediated rejection in the following organ transplantation:
  Kidney, liver, heart, lungs, pancreas, small intestine
  Rituxan was approved for suppression of antibody mediated rejection in ABO blood type incompatible transplantation in kidney and liver, in 2016. By the additional approval this time, the indication will not be limited to ABO blood type incompatible transplantation, and also heart, lung, pancreas, and small intestine have been added as eligible organ transplantation.

*2 About antibody-mediated rejection
Antibody-mediated rejection is a type of rejection in which the transplanted organ is damaged by an antigen-antibody reaction between antibodies possessed by the recipient (the person receiving the transplant) and antigens from the transplanted organ derived from the donor (the person donating the organ).

*3 About blood type incompatible transplantation
The following combinations of recipient and donor are blood type incompatible transplants.
- If the recipient is type O and the donor is type A, B, or AB
- If the recipient is type A and the donor is type B or AB
- If the recipient is type B and the donor is type A or AB

*4 Antibodies against HLA（human leukocyte antigen）
HLA is expressed in almost all cells except red blood cells. Anti-HLA antibodies are produced during transplantation, blood transfusion, or pregnancy, and may be involved in antibody-mediated rejection.

*5 The results of the National survey on suppression[1)] of antibody-mediated rejection and treatment[2)], the results of usage survey regarding suppression of antibody-mediated rejection in liver[3)] and small intestine transplantation[4)], and regarding treatment of antibody-mediated rejection in liver [5)], heart[6)], lung[7)], pancreatic transplantation[8)] and small intestine transplantation[4)] have been published.

*6 Phase III study for evaluating efficacy and safety of desensitization based on IDEC-C2B8 in living donor kidney transplantation recipients with pre-formed anti-HLA antibody and/or

donor-specific antibody. Phase III study for evaluating efficacy, safety and pharmacokinetics of pre-transplant administration of FK506 or FK506E(MR4) for 7 to 28 days in living donor kidney transplantation recipients. (jRCT2080224107)

*7 Phase III study for evaluating efficacy and safety of a combination treatment of IDEC-C2B8 with steroid pulse therapy and plasmapheresis for antibody-mediated rejection after kidney transplant (jRCT2080224105)

*8 Research on the development of new treatments for antibody-mediated rejection in organ transplantation (jRCTs031180264)

Sources

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Contact:	
Zenyaku Holdings Co., Ltd. General Affairs Department, Public Relations Section Tel: +81-3-3946-1123	Chugai Pharmaceutical Co., Ltd., Corporate Communications Dept., Media Relations Group Tel: +81-3-3273-0881 Investor Relations Group Tel: +81-3-3273-0554