Zenyaku Kogyo Co., Ltd.
Chugai Pharmaceutical Co., Ltd.

Anti-CD20 Monoclonal Antibody Rituxan® Approved for Treatment of Frequently Relapsing or Steroid-Dependent Nephrotic Syndrome in Childhood That Has not yet Become Intractable

TOKYO, March 27, 2025 -- 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 additional indication of an anti-CD20 monoclonal antibody Rituxan® intravenous injection 100 mg and 500 mg [generic name: rituximab (genetical recombination)] (hereafter, "Rituxan"), which is co-marketed by both companies, for "frequently relapsing or steroid-dependent nephrotic syndrome" in childhood that has not yet become intractable.

Nephrotic syndrome is a collective term for a condition characterized by generalized edema resulting from severe proteinuria and hypoalbuminemia, caused by damage to the glomerular slit diaphragm in the nephrons that make up the kidneys[1]. Idiopathic nephrotic syndrome that develops in childhood is the most common cause of chronic kidney disease in children and is designated as an intractable disease of unknown etiology[2]. About 80-90% of these cases are classified as steroid-sensitive nephrotic syndrome, which quickly goes into remission with steroids, the first-line treatment. However, approximately 50% of these cases are further classified as either "frequently relapsing nephrotic syndrome," which relapses relatively quickly despite steroid treatment, or "steroid-dependent nephrotic syndrome," which relapses when steroids are reduced or discontinued[3].
For "frequently relapsing or steroid-dependent nephrotic syndrome," the introduction of immunosuppressive drugs is recommended to reduce the side effects of long-term steroid use[4]. However, there are patients who become refractory and cannot be weaned off steroids despite using immunosuppressive drugs, remaining frequently relapsing or steroid-dependent, as well as those who transition into adulthood[2], and the emergence of serious side effects from long-term administration of immunosuppressive drugs has become a problem[4].

Rituxan is an anti-CD20 monoclonal antibody that specifically binds to the CD20, a protein expressed on B cells, excluding hematopoietic stem cells and plasma cells. It attacks and damages target B cells using the immune system equipped with the human body. B cells are suggested to influence the pathogenesis and disease activity of nephrotic syndrome[5] [6] [7], and by eliminating B cells with Rituxan, a therapeutic effect on nephrotic syndrome is

expected.

Rituxan was approved in August 2014 for the indication of “refractory nephrotic syndrome (in cases of frequent relapse or steroid dependence)” with onset in childhood, and in September 2024 for “refractory nephrotic syndrome (in cases of steroid resistance)” with onset in childhood.
For “frequently relapsing or steroid-dependent nephrotic syndrome” that has not yet become refractory, an investigator-initiated clinical trial[*2] demonstrated that the primary endpoint of relapse-free period was significantly prolonged in the rituximab group compared to the placebo group (hazard ratio: 0.266 [95% confidence interval: 0.120-0.592], p = 0.0006 [stratified log-rank test]), showing rituximab's effect in suppressing relapse. While there was no significant difference in the incidence of adverse events between the rituximab and placebo groups, there was a tendency for a higher incidence of side effects in the rituximab group. The observed adverse events and side effects were similar to those previously reported for the drug's approved indications both domestically and internationally. Based on these results, Zenyaku filed an application for partial changes to the manufacturing and marketing approval items on April 26, 2024, which led to the current approval.

Zenyaku and Chugai will continue working closely together so that Rituxan can further contribute to the treatment of nephrotic syndrome.

*1 Indications or effects of Rituxan for nephrotic syndrome (underlined part: scope of the current approval)
○The following nephrotic syndrome:
・Frequently relapsing or steroid-dependent nephrotic syndrome
・Refractory nephrotic syndrome (in cases showing frequent relapse, steroid dependence, or steroid resistance)

*2 Multicenter, double-blind, placebo-controlled, randomized parallel-group comparative study of IDEC-C2B8 for childhood-onset nephrotic syndrome (JSKDC10) [8) 9)]

Sources
1. Chapter I General Remarks, 1. Disease Concept and Etiology. Supervised by the Japanese Society for Pediatric Nephrology, created by the Research Project for Rare and Intractable Diseases “Establishment of Diagnosis and Research System for Rare and Intractable Diseases in Pediatric Nephrology” (Health and Labour Sciences Research Grant). Pediatric Nephrotic Syndrome Guidelines 2020, SHINDAN TO CHIRYO SHA, Inc., 2020, pp2-4.
2. Iijima K, Sako M, Nozu K. VII. Pediatric Idiopathic Nephrotic Syndrome. Journal of the Japanese Society of Internal Medicine. 2020; 109(5): 926-932.

3. Chapter I General Remarks, 5. Prognosis. Supervised by the Japanese Society for Pediatric Nephrology, created by the Research Project for Rare and Intractable Diseases “Establishment of Diagnosis and Research System for Rare and Intractable Diseases in Pediatric Nephrology” (Health and Labour Sciences Research Grant). Pediatric Nephrotic Syndrome Guidelines 2020, SHINDAN TO CHIRYO SHA, Inc., 2020, pp15-16.
4. Chapter II Treatment, 2. Specific Topics. Supervised by the Japanese Society for Pediatric Nephrology, created by the Research Project for Rare and Intractable Diseases “Establishment of Diagnosis and Research System for Rare and Intractable Diseases in Pediatric Nephrology” (Health and Labour Sciences Research Grant). Pediatric Nephrotic Syndrome Guidelines 2020, SHINDAN TO CHIRYO SHA, Inc., 2020, pp39-48.
5. Tani Y, Kida H, Abe T, et al. B lymphocyte subset patterns and their significance in idiopathic glomerulonephritis. Clin Exp Immunol. 1982; 48(1): 201-204.
6. Yokoyama H, Kida H, Tani Y, et al. Immunodynamics of minimal change nephrotic syndrome in adults T and B lymphocyte subsets and serum immunoglobulin levels. Clin Exp Immunol. 1985; 61(3): 601-607.
7. Garin EH, Diaz LN, Mu W, et al. Urinary CD80 excretion increases in idiopathic minimal-change disease. J Am Soc Nephrol. 2009; 20(2): 260-266.
8. Nagano C, Sako M, Kamei K, et al. Study protocol: multicenter double-blind, randomized, placebo-controlled trial of rituximab for the treatment of childhood-onset early-stage uncomplicated frequently relapsing or steroid-dependent nephrotic syndrome (JSKDC10 trial). BMC Nephrol. 2019; 20(1): 293.
9. Japan Registry of Clinical Trials (jRCT) Clinical Research Submission and Publication System. [Internet: March 2025]. Available at: https://jrct.mhlw.go.jp/en-latest-detail/jRCT1091220380

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 E-mail: pr@chugai-pharm.co.jp Investor Relations Group Tel: +81-3-3273-0554 E-mail: ir@chugai-pharm.co.jp