Basic Information

Basic Information on the Pharmaceutical Industry

Overview of Domestic Pharmaceutical Market and NHI Drug Prices

Trends in National Medical Expenses

Without medical system reforms, Japan's national medical expenses will increase at an annual rate of approximately 2 to 4 percent going forward. In fiscal 2016 (the year ended March 2017), national medical expenses[1] totaled ¥41.3 trillion, a ¥0.2 trillion or 0.4 percent decrease from the previous year. The accelerating pace of aging of Japan's society presents serious challenges to efficiently managing the increase in medical expenses for the elderly.

1. Source: Trends of recent medical expenditure (FY 2016) by Ministry of Health, Labour and Welfare

Promotion of the Use of Generics

The Japanese government is promoting the use of generics[2] with the primary objective of reducing the cost burden on patients and improving the finances of the health insurance system. Various measures have been carried out under the action program announced in October 2007 to promote the worry-free use of generics. In April 2013, the new "Roadmap to Further Promote the Use of Generics" was formulated. A Cabinet decision in June 2017 set the new goal of raising the volume market share of generics, which was 65.8 percent[3] as of September 2017 to 80 percent by the end of September 2020. The government is also aiming to double the number of biosimilars by the end of March 2021.

2. Drugs approved after the expiry of the patents for original drugs with the same active ingredients and efficacy
3. Preliminary results of the Drug Price Survey

National Health Insurance (NHI) Drug Price Revision

The Ministry of Health, Labour and Welfare (MHLW) generally reviews drug reimbursement prices every two years and sets new standard prices (reimbursement prices) so that the official prices of pharmaceuticals prescribed under the health insurance system approximate their actual market price. MHLW does this by investigating the prices and volumes of all prescription drug transactions during a given period. In fiscal 2018 (the year ending March 2019), drug reimbursement prices are set to decline by 1.65 percent overall on a medical expense basis and 7.48 percent on a reimbursement price basis (-6.17 percent from revision of actual market prices and -1.31 percent from fundamental reform of the drug pricing system).

Repricing Based on Market Expansion

Under this repricing rule introduced in 1994, drugs priced by the cost calculation method with annual sales exceeding ¥10.0 billion and more than 10 times the original forecast at the time of price revision, or with annual sales exceeding ¥15.0 billion and more than two times the original forecast, are subject to a price reduction of up to 25.0 percent. Drugs priced by methods other than the cost calculation method (including the similar efficacy comparison method) with annual sales exceeding ¥15.0 billion and more than two times the original forecast at the time of the price revision are subject to a price reduction of up to 15.0 percent. In addition, the prices of drugs that have pharmacological action similar to the drug subject to this repricing rule are reduced by the same rate. In the NHI drug pricing system fundamental reforms of fiscal 2018, the NHI listing of new drugs that takes place four times a year will be used as an opportunity for repricing of drugs with annual sales exceeding ¥35.0 billion. The purpose of this change is to respond more quickly when sales expand rapidly due to an additional indication or other reasons.

NHI Drug Price Revision Rate (%)

	2008	2010	2012	2014*	2016	2018
Industry Average	(5.2)	(6.5)	(6.25)	(2.65)	(7.8)	(7.48)
Chugai	(7.2)	(6.8)	(6.0)	0.8	(5.5)	(6.7)

*Includes provision for increase in consumption tax
Source: Chugai data

Special Market-Expansion Repricing

In the reforms to the drug pricing system in fiscal 2016, an additional repricing rule for drugs with very high annual sales was introduced as a special measure from the standpoint of balancing reward for innovation with the sustainability of the National Health Insurance system. This rule lowers prices by up to 25.0 percent for drugs with annual sales of ¥100.0-150.0 billion and more than 1.5 times the original forecast, and lowers prices by up to 50.0 percent for drugs with annual sales exceeding ¥150.0 billion and more than 1.3 times the original forecast. In addition, the prices of drugs that have pharmacological action similar to the drug subject to the special repricing rule and were comparator drugs at the time of the NHI price listing are reduced by the same rate. In 2016, four active ingredients and six products were subject to the additional repricing rule. In fiscal 2018, two active ingredients and four products are subject to the rule. In the NHI drug pricing system fundamental reforms of fiscal 2018, the NHI listing of new drugs that takes place four times a year will be used as an opportunity for repricing of drugs that meet the conditions in this system.

Premium to Promote the Development of New Drugs and Eliminate Off-Label Use

As part of the NHI drug pricing system reforms of fiscal 2010 (the year ended March 2011), a new pricing scheme was implemented on a trial basis to promote the creation of innovative medical products and solve the drug lag[4] problem. In this scheme, at the time of the NHI drug price revisions, prices are maintained on drugs for which no generics are available (provided that they have been in the NHI price list for no more than 15 years), and which satisfy certain conditions.

This premium pricing for new drugs was continued on a trial basis in subsequent NHI drug pricing system reforms. However, in the NHI drug pricing system fundamental reforms of fiscal 2018, the requirements for companies and products will be revised and will be listed in the drug repricing rules.

Companies that do not respond appropriately to development requests from MHLW will continue to be excluded from eligibility for premium pricing. In addition, indicators have been set for (A) creation of innovative drugs, (B) drug lag countermeasures, and (C) development of novel drugs ahead of other countries, and the pricing premiums may vary according to the level of achievement or fulfillment of these indicators. Healthcare-related ventures are expected to play an important role in the creation of innovative drugs, and will be evaluated accordingly, irrespective of the company indicators.

Regarding the product requirements, the percentage price difference requirement will be abolished, and the price premium will be limited to novel drugs during their patent period, and drugs that are truly innovative and useful. More specifically, it will be limited to orphan drugs, drugs for which development was publicly requested, drugs to which the premium was applied because of their usefulness at the time they were newly listed, and drugs with novel mechanisms of action that are innovative or useful (limited to the top three first-in-class drugs within three years from listing).

In fiscal 2018, 314 active ingredients and 560 products are set to receive premium pricing (publicly announced).

Among new drugs subject to premium pricing, including those for which generics (including biosimilars) have been launched or 15 years have elapsed since their drug price listing, the cumulative amount of premium pricing is deducted from the NHI drug price in the subsequent initial drug price revision. Furthermore, a reduction or other adjustment due to the actual market price of the new drug during the fiscal year is made to the NHI drug price less the cumulative amount.

4. The inability of Japanese patients to gain access to global standard or most advanced treatments because the drugs are not developed in Japan

Response to Requests from the MHLW Review Committee on Unapproved Drugs and Indications with High Medical Needs (As of February 1, 2018)

Development request	Product	Indication	Development status
First development request	Xeloda	Advanced or recurrent gastric cancer	Approved in February 2011
	Tarceva	Advanced or recurrent pancreatic cancer	Approved in July 2011
	Avastin	Advanced or recurrent breast cancer	Approved in September 2011
	CellCept	Pediatric renal transplant	Approved in September 2011
	Herceptin	Q3W dosage metastatic breast cancer overexpressing HER2	Approved in November 2011
		Neoadjuvant breast cancer overexpressing HER2	
	Kytril	Gastrointestinal symptoms associated with radiotherapy	Approved in December 2011
	Pulmozyme	Improvement of pulmonary function in patients with cystic fibrosis	Approved in March 2012
	Bactramin	Treatment and prevention of pneumocystis pneumonia	Approved in August 2012
	Avastin	Ovarian cancer	Approved in November 2013
Second development request	Avastin	Recurrent glioblastoma	Approved in June 2013 (Malignant glioma)
	Herceptin	Q1W dosage postoperative adjuvant breast cancer overexpressing HER2	Approved in June 2013
	CellCept	Lupus nephritis	Approved in May 2016
Third development request	Tamiflu	Additional dosage for neonates and infants younger than 12 months	Approved in March 2017
	Xeloda	Adjuvant chemotherapy in rectal cancer	Approved in August 2016
	Avastin	Additional dosage and administration for ovarian cancer	Submitted company opinion and waiting for evaluation by committee
Fourth development request	Copegus	Improvement of viraemia associated with genotype 3 chronic hepatitis C or compensated cirrhosis related to hepatitis C when administered in combination with sofosbuvir	Approved in March 2017
	Xeloda	Neuroendocrine tumor	Submitted company opinion and waiting for evaluation by committee

Solving the Drug Lag Problem

In January 2005, MHLW established the Investigational Committee for Usage of Unapproved Drugs as one means of helping solve the drug lag problem. The committee is charged with investigating the clinical necessity and the appropriateness of usage of drugs already approved in Europe and the United States, but not yet approved in Japan. The aim of these investigations is to promote the development of those drugs in Japan. In February 2010, MHLW established the Review Committee on Unapproved Drugs and Indications with High Medical Needs. This committee evaluates the medical necessity of drugs and indications that are not yet approved in Japan and investigates matters such as the applicability of filings for approval based on evidence in the public domain. As a result of continuous efforts to strengthen the review function of the Pharmaceutical and Medical Devices Agency, an independent administrative institution responsible for reviewing drugs and medical devices for approval, the median total review time for new drugs fiscal 2016 was 11.6 months.

Annual Drug Price Survey and Annual NHI Drug Price Revision

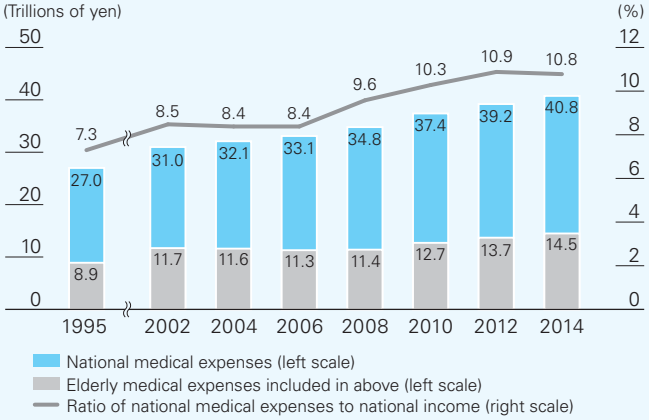
Due to the growing public financial burden of the current situation, in which drug prices are maintained for up to two years even if the market price declines, it was decided in the NHI drug pricing system fundamental reforms of fiscal 2018 that drug price surveys and drug price revisions will be carried out even in interim years when there would ordinarily be no price revisions. Fiscal 2018 and fiscal 2020 (the year ending March 2021) are price revision years even under the current system, and it is expected that the prices of all drugs will be revised in conjunction with the consumption tax rate increase in October 2019. Therefore, the interim-year price revisions under the new rules will take place starting from fiscal 2021 (the year ending March 2022). The scope of items subject to interim-year price revisions will be deliberated by the Central Social Insurance Medical Council (Chuikyo) and other organizations.

Reduction Due to Cost-Effectiveness Assessment

Seven pharmaceutical products, including Kadcyla sold by Chugai, were subject to cost-effectiveness assessments, which are currently being implemented on a trial basis. The results of the comprehensive assessment were reflected in drug prices at the time of the fiscal 2018 price revisions (price adjustments). The extent of these price adjustments is the portion corresponding to the amount of the corrective premium applied at the time of the drug's initial pricing. Price adjustments will be made according to the incremental cost effectiveness ratio (ICER).[5] The corrective premium will be maintained if the ICER is less than ¥5 million, but will be reduced by up to 90 percent if the ICER is ¥5 million or more. The percentage of the reduction may be moderated if ethical and social factors are taken into consideration.

5. The ICER indicates the extent to which additional investment would be necessary to obtain the additional benefit from replacing existing drug (technology) B with new drug A.

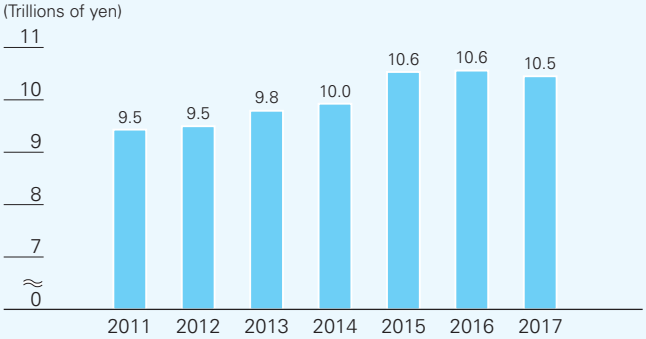
Trends of Medical Care Expenditure



Source: Overview of Estimates of National Medical Care Expenditure, FY2015 by Ministry of Health, Labour and Welfare

Note: National income is based on the actual results of the System of National Accounts announced by the Cabinet Office.

Prescription Drug Market



Oncology

Overview of Disease and Treatment Methods

Leading Cause of Death in Japan

Cancer has been the single most common cause of death in Japan since 1981. In 2016, 372,986 people[1] died of cancer, accounting for 28.5 percent[1] of all deaths in that year and the highest number since government surveys began in 1899.

1. Source: Outline of Vital Statistics (2016) by Ministry of Health, Labour and Welfare

Establishment of the Basic Act for Anticancer Measures and Improvement in the Healthcare Environment

In June 2006, the Diet enacted the Basic Act for Anticancer Measures, which stipulates the obligation of national and local governments to promote measures to fight cancer. The basic principle of the law is to develop cancer treatment systems in every region of the country so that patients can receive standard therapy based on scientific knowledge and in accordance with their wishes ("the availability of standard therapy" for cancer patients). The law includes provisions for (1) improvement of cancer prevention and treatment technologies, (2) development of oncologists and "hub" institutions that specialize in cancer, and (3) enhanced provision of information to patients. As a result of the enactment of this law, progress has been made in the training of oncologists and medical staff such as nurses and pharmacists. Other advances include greater efforts to establish networks

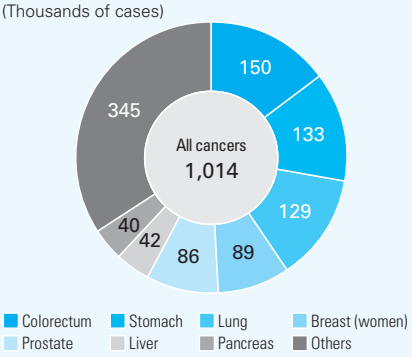
among local medical institutions by designating interregional hub cancer centers. Moreover, an increasing percentage of medical institutions are adopting multidisciplinary team care in which oncologists, nurses, pharmacists and nutritionists work together to provide care tailored to the condition of each individual patient. In December 2013, the Cancer Registration Law was enacted, requiring hospitals nationwide to provide information on each cancer patient. The law is aimed at shedding light on the current state of cancer treatment by centralizing patient information in a single database and using that resource to improve early detection and treatment. Furthermore, it is projected that achieving the overall goal of reducing the age-adjusted cancer mortality rate by 20 percent over 10 years from 2007 in the Basic Plan to Promote Cancer Control Programs (approved by the Cabinet in June 2007), will be difficult. Therefore, in December 2015, the Plan for Acceleration of Cancer Control Programs was formulated. This plan specified concrete measures that should be implemented intensively in a short period of time.

Changes in Treatment Methods

Cancer treatment is increasingly being based on a multidisciplinary approach that combines surgery, radiation therapy and chemotherapy. In particular, the field of anticancer agents is evolving, and highly innovative medicines such as molecular targeted drugs have been introduced. This has brought a dramatic improvement in treatment outcomes in colorectal, lung and breast cancer, gynecological cancers, kidney cancer, brain tumors, malignant melanoma, hematological malignancy and other forms of cancer. Advances are being made in personalized healthcare, which involves testing patients with companion diagnostics when administering molecular targeted drugs to identify patients in whom the drug is likely to have the desired effect with minimal strain on the body and few side effects. In addition to enabling physicians to propose the optimal treatment tailored to each patient, this approach offers a number of other benefits. For example, it can reduce national healthcare expenditures by reducing the administration of drugs when their effect cannot be determined. When performing a diagnosis, there may be a number of different molecular targeted drugs available for the same disease, and there are some cases in which looking at the molecules expressed in the target tissues is insufficient for diagnosis; therefore, it is also becoming important to conduct exhaustive biomarker measurements such as multiplex testing. Moreover, the Council to Promote the Realization of Genomic Medicine, established by the Japanese government in January 2015, MHLW and pharmaceutical industry organizations have launched studies for the realization of genomic medicine. The provision of optimal treatments based on each patient's genetic profile is thus becoming a reality. In addition, cancer immunotherapy, which takes advantage of the body's own immune cells to fight cancer, is another important emerging field of treatment. Immune checkpoint inhibitors, one type of immunotherapy now in use, are a promising new direction in cancer treatment. Cancer has the ability to suppress immune functions to avoid attack from the immune system. By blocking the immune "brakes" (the binding of PD-1 to PD-L1) known as the immune checkpoint, immune cells can be awakened to attack cancer cells. In clinical trial results, immune checkpoint inhibitors have shown promise for long-term survival and cure, even in advanced cancer. Expectations are growing for their high therapeutic effect and potential for treating a wide range of cancers. On the other hand, some patients do not respond to cancer immunotherapy, so screening to select patients for whom this therapy is likely to be effective and combination therapy with existing anticancer agents are also being examined.

Projected Cancer Incidence (2017)

(Thousands of cases)



Source: National Cancer Center Cancer Information Service, "Cancer Registries/Statistics"

Note: Projections were performed with a model incorporating age, calendar year at diagnosis, and their interactions as independent variables, utilizing frequency of incidence of cancer by age bracket from Monitoring of Cancer Incidence in Japan (1975-2013 nationwide estimates) and cancer mortality figures from the Outline of Vital Statistics (1975-2015 estimates). The total may not add up because projections have been performed by cancer type and figures have been rounded.

Reference: *Japanese Journal of Clinical Oncology* 2014, 44: 36-41

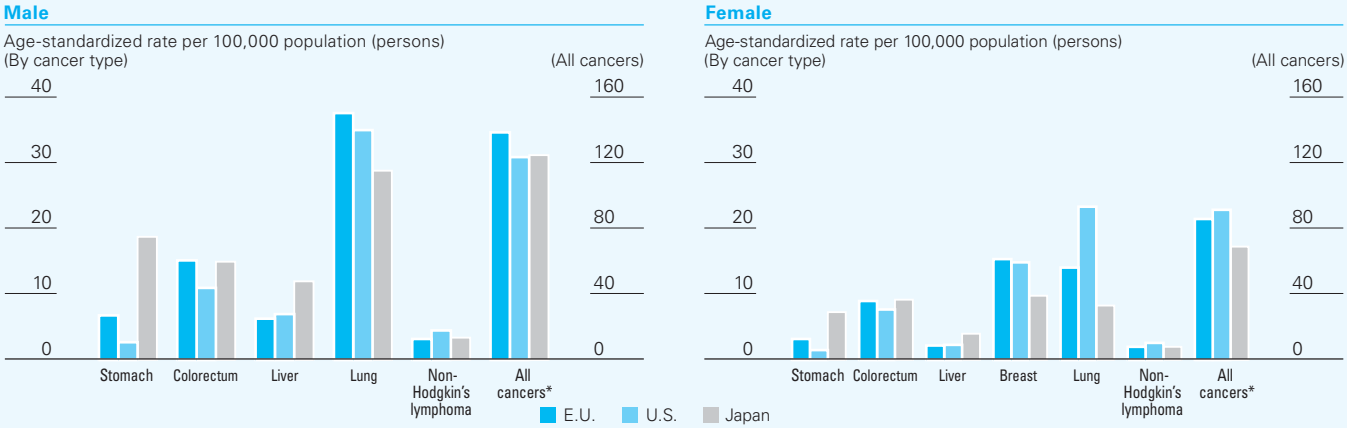
Avastin (RG435)

Anti-VEGF humanized monoclonal antibody (Generic name: bevacizumab)

Basic Information

Avastin is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). It is the first therapeutic agent in the world that inhibits angiogenesis (the growth of the network of blood vessels that supply nutrients and oxygen to the cancer). Unlike conventional anticancer agents that act directly on cancer cells, Avastin acts on the cancer microenvironment. In Japan, Avastin was launched in 2007 for the treatment of

International Comparison of Cancer Mortality Rates (2012)



* Excluding non-melanoma skin cancer

Source: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 06/03/2018.

unresectable advanced or recurrent colorectal cancer. In 2009, Chugai obtained approval for a new dosage and administration for colorectal cancer and the additional indication of unresectable advanced or recurrent non-squamous non-small cell lung cancer (NSCLC), followed in 2011 by inoperable or recurrent breast cancer. Chugai also obtained approval for the additional indications of malignant glioma and ovarian cancer in 2013, and advanced or recurrent cervical cancer in May 2016.

Review of 2017 Performance

Sales of Avastin increased ¥1.0 billion, or 1.1 percent, year on year to ¥93.1 billion. Avastin has built a solid position in the treatment of colorectal cancer and lung cancer, but the competitive environment in the field of lung cancer has been changing due to the introduction of immune checkpoint inhibitors and other products. On the other hand, in the field of gynecologic oncology, sales were solid for both ovarian cancer and cervical cancer owing to the synergy between these two indications. In development, Chugai had been conducting a phase II clinical trial in Japan for the potential treatment of malignant pleural mesothelioma, but development was discontinued in light of the development situation overseas. A phase III multinational study of Avastin in combination with Tecentriq in NSCLC, renal cell carcinoma and ovarian cancer patients is under way.

Herceptin

Anti-HER2 humanized monoclonal antibody
(Generic name: trastuzumab)

Basic Information

Herceptin is a humanized monoclonal antibody that targets human epidermal growth factor receptor type 2 (HER2), [2] which contributes to tumor cell growth. The earliest PHC-based anticancer agent, Herceptin has built a solid reputation as an essential treatment for HER2-positive breast cancer since its launch in 2001.

Overexpression of HER2 is found in about 20 percent of breast cancers. Such cancer is diagnosed as HER2-positive. HER2-positive breast cancer progresses rapidly, and has been associated with a poor prognosis. However, treatment outcomes have improved significantly with the emergence of Herceptin and other medicines that target HER2. In 2011, Herceptin obtained approval for the additional indication of advanced or recurrent gastric cancer overexpressing HER2, not amenable to curative resection, bringing personalized healthcare to the field of gastric cancer.

Review of 2017 Performance

Sales of Herceptin decreased ¥0.5 billion, or 1.5 percent, year on year to ¥33.6 billion. In addition to the extension of the dosage period in first-line treatment of HER2-positive advanced or recurrent breast cancer in combination with Perjeta, Herceptin is used for more than 90 percent of lymph-node positive patients undergoing postoperative adjuvant chemotherapy for HER2-positive breast cancer. For gastric cancer, although Herceptin maintained its established position in first-line treatment, sales decreased slightly due to competition in second-line treatment.

2. A diagnostic test can determine if a patient's breast or gastric cancer cells have overexpression of a protein called HER2. Herceptin, Perjeta and Kadcyla target HER2 and are administered only to patients whose tumors are identified as HER2-positive.

Perjeta (RG1273)

HER2 dimerization inhibitory humanized monoclonal antibody
(Generic name: pertuzumab)

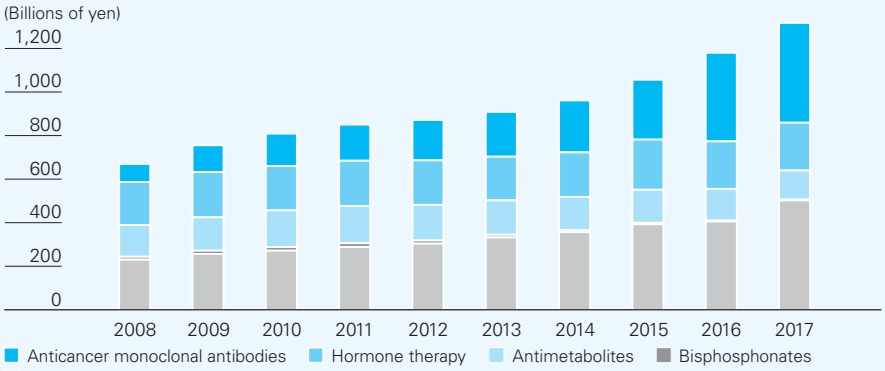
Basic Information

Perjeta is a humanized monoclonal antibody and is the first molecular targeted therapy that inhibits the dimerization of HER2. The combination of Perjeta and Herceptin, which also targets HER2, provides a more comprehensive blockade of HER signaling pathways associated with the proliferation of tumor cells. Chugai launched Perjeta for the indication of HER2-positive inoperable or recurrent breast cancer in September 2013, after obtaining approval in June 2013.

Review of 2017 Performance

Sales of Perjeta increased ¥1.7 billion, or 14.3 percent, year on year to ¥13.6 billion, exceeding projections. In the clinical practice guidelines for breast cancer, which were updated in July 2015, the combination therapy of Herceptin and Perjeta with docetaxel was the only therapy to receive a Grade A recommendation as a first-line therapy for HER2-positive metastatic or recurrent breast cancer, and uptake as a first-line treatment was steady. In development, Chugai filed an application in October 2017 for approval for the expected indication of adjuvant chemotherapy for HER2-positive early breast cancer. However, development for the potential treatment of advanced or recurrent gastric cancer was discontinued in view of the results of phase III multinational studies.

Anticancer Agent Market in Japan



Source: JPM 2008-2017

The scope of the market is defined by Chugai.

Kadcyla (RG3502)

Anti-HER2 antibody-tubulin polymerization inhibitor conjugate
(Generic name: trastuzumab emtansine)

Basic Information

Kadcyla is an antibody-drug conjugate of the anti-HER2 humanized monoclonal antibody trastuzumab (product name: Herceptin) and the potent chemotherapeutic agent DM1, joined together with a stable linker. Chugai filed an application for approval for the treatment of HER2-positive inoperable or recurrent breast cancer in January 2013, obtained approval in September 2013 after priority review, and launched the product in April 2014.

Review of 2017 Performance

Sales of Kadcyla decreased ¥0.3 billion, or 3.6 percent, year on year to ¥8.0 billion. Kadcyla was launched three years ago, and many patients who had been receiving first-line treatment with Kadcyla proceeded to the next line of treatment as their disease progressed. In addition, regarding patients receiving first-line treatment with Herceptin and Perjeta plus a chemotherapeutic agent, the number who switched to Kadcyla after their cancer worsened fell slightly due to an increase in cases in which only the chemotherapeutic agent was changed. In development, a phase III multinational study for the potential treatment of HER2- positive breast cancer (adjuvant chemotherapy) is under way.

Rituxan

Anti-CD20 monoclonal antibody
(Generic name: rituximab)

Basic Information

Rituxan is a monoclonal antibody targeting the CD20 antigen found on the surface of lymphocytes. As a standard therapy for CD20-

positive, B-cell non-Hodgkin's lymphoma (hematological cancer), it has substantially improved clinical outcomes in combination with chemotherapy or in monotherapy. In Japan, Rituxan is marketed jointly by Chugai and Zenyaku Kogyo Co., Ltd. In recent years, the usefulness of Rituxan has been recognized in treating CD20-positive, B-cell lymphoma in immunosuppressed patients, ANCA-associated vasculitis, refractory childhood-onset nephrotic syndrome, suppression of antibody-related rejection in ABO-incompatible kidney and liver transplantation, and idiopathic thrombocytopenic purpura (ITP). It has also become a valuable treatment option for patients with autoimmune diseases and other conditions.

Review of 2017 Performance

Sales of Rituxan increased ¥1.3 billion, or 4.0 percent, year on year to ¥33.4 billion. The number of patients diagnosed with B-cell non-Hodgkin's lymphoma who are using Rituxan has increased, and the use of Rituxan in patients with ITP, for which it recently obtained approval, also contributed to sales growth.

Alecensa (AF802/RG7853)

ALK inhibitor
(Generic name: alectinib)

Basic Information

Alecensa, an oral, small molecule targeted molecular therapy created by Chugai, inhibits the activity of the tyrosine kinase anaplastic lymphoma kinase (ALK) with *EML4-ALK* fusion gene expressed in about 2 to 5 percent of NSCLC. It was designated as an orphan drug in Japan in September 2013 for the treatment of *ALK* fusion gene-positive unresectable, recurrent/advanced NSCLC. In October 2013, Chugai filed an application for approval. Following approval in July 2014, Alecensa was launched first in Japan in September 2014. In addition to being the first product from Chugai research to be granted breakthrough therapy designation by the U.S. Food and Drug Administration (FDA), Alecensa received its second such designation as a first-line treatment in 2016, and it is expected to contribute to the treatment of patients around the world. In December 2015, Alecensa obtained approval in the United States for the indication of ALK-positive metastatic (advanced) NSCLC in patients whose disease has progressed on or who are intolerant to crizotinib.

Review of 2017 Performance

Market penetration proceeded further with the announcement of positive results leading to the early discontinuance for benefit of a study comparing the efficacy and safety of Alecensa and a competing product on patients in Japan (J-ALEX study). Sales increased ¥4.8 billion, or 40.3 percent, year on year to ¥16.7 billion, exceeding expectations due to a high rate of continuation of treatment. All-case registration surveillance is currently being conducted for Alecensa, and Chugai is promoting appropriate use and gathering safety information. Outside Japan, Alecensa obtained approval in Europe in February 2017 for the indication of ALK-positive, metastatic NSCLC in patients whose disease has progressed on or who are intolerant to crizotinib. A study evaluating the efficacy and safety of Alecensa in direct comparison with a competing product in overseas patients (ALEX study) showed the superiority of Alecensa, and applications for approval as first-line treatment were filed in the United States and Europe in March 2017. Approval as a first-line treatment was obtained in the United States in November 2017 and in Europe in December 2017. Overseas sales of Alecensa (exports to Roche) increased 275.7 percent, or ¥10.2 billion, year on year to ¥13.9 billion.

Xeloda

Antimetabolite, 5-FU derivative
(Generic name: capecitabine)

Basic Information

Xeloda is a 5-fluorouracil (5-FU) anticancer agent developed at the research laboratories of the former Nippon Roche. Orally administered Xeloda is absorbed by the body, then gradually metabolized by certain highly active enzymes in liver and tumor tissue, and is eventually converted into active 5-FU within tumor tissue. Xeloda has obtained approval for the treatment of inoperable or recurrent breast cancer, colorectal cancer and gastric cancer.

Review of 2017 Performance

Sales of Xeloda decreased ¥0.1 billion, or 0.8 percent, year on year to ¥12.2 billion. Backed by Chugai's initiatives to promote adverse drug reaction management, Xeloda has established a top position in postoperative adjuvant chemotherapy performed to inhibit recurrence after surgery for colon cancer. In gastric cancer, prescriptions have increased for postoperative adjuvant chemotherapy, for which Xeloda obtained approval in November 2015.

Tarceva

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor
(Generic name: erlotinib)

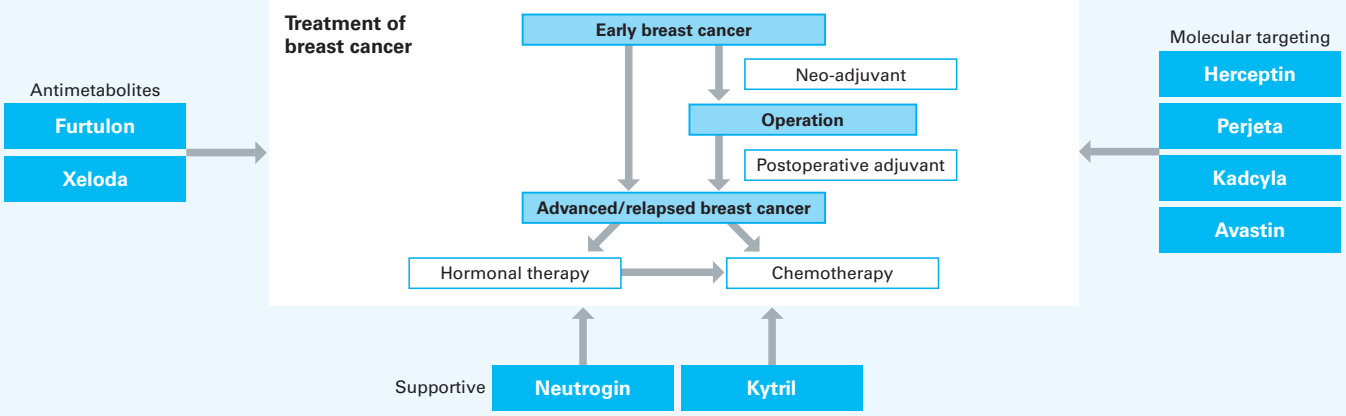
Basic Information

Tarceva is an oral targeted small molecule drug that inhibits the activation of epidermal growth factor receptor (EGFR) tyrosine kinase, which is associated with the growth, progression and metastasis of cancer. In Japan, Tarceva had been used for second-line or later treatment of NSCLC since its launch in 2007, but the approval of an additional indication in June 2013 allowed its use in first-line treatment of patients with *EGFR* mutations, in whom high efficacy is expected. About 10 percent of NSCLC patients in Europe and about 30 percent in Asia diagnose positive for *EGFR* mutations. In 2011, Tarceva obtained approval for the additional indication of pancreatic cancer not amenable to curative resection.

Review of 2017 Performance

Sales of Tarceva decreased ¥1.0 billion, or 8.7 percent, year on year to ¥10.5 billion. In NSCLC, uptake of Tarceva in first-line treatment in patients with *EGFR* mutations is progressing due to evidence of efficacy in patients with brain metastases, but sales decreased compared with the previous year due to the impact of competing products in the second-line setting.

Extensive Contribution to Cancer Treatment (Breast Cancer)



Zelboraf

BRAF inhibitor
(Generic name: vemurafenib)

Basic Information

Zelboraf, in-licensed from Roche, is an oral, small molecule drug that selectively inhibits a mutated form of the BRAF protein which is thought to occur in approximately half of all malignant melanoma cases. Chugai filed an application for approval of Zelboraf for the treatment of unresectable melanoma with *BRAF* mutation in April 2014, obtained approval in December 2014 and launched the product in February 2015. Roche Diagnostics K.K. filed an application for approval of a companion diagnostic to detect the *BRAF* mutation, and obtained approval in December 2014.

Review of 2017 Performance

Sales decreased ¥0.3 billion, or 75 percent, year on year to ¥0.1 billion as a result of changes in the competitive environment.

Neutrogin

Recombinant human granulocyte colony-stimulating factor (G-CSF)
(Generic name: lenograstim; overseas product name: Granocyte)

Basic Information

Neutrogin is a recombinant human granulocyte colony-stimulating factor (G-CSF) created by Chugai. One common side effect of anticancer drugs is neutropenia, a decrease in the white blood cell count that heightens the risk of developing serious infections. Neutrogin stimulates the differentiation and growth of neutrophils, enabling the safer use of chemotherapy, thus helping to improve treatment outcomes. Neutrogin is also essential in hematopoietic stem cell transplantation, which is performed for illnesses that affect production of normal blood cells, such as leukemia.

Review of 2017 Performance

Despite intensified competition overseas, sales of Neutrogin increased ¥0.1 billion, or 0.8 percent, year on year to ¥12.3 billion due to the positive effect of exchange rates (weak yen relative to the euro).

Aloxi

5-HT_3 receptor antagonist
(Generic name: palonosetron)

Akynzeo

NEPA
(Generic name: oral combination of netupitant and palonosetron)

Basic Information

These products are small molecules for the prevention of chemotherapy-induced nausea and vomiting. Chugai has been granted exclusive marketing rights by the Helsinn Group of Switzerland for Aloxi in the U.K. and Akynzeo in the U.K. and Ireland. Aloxi is a best-in-class 5-HT_3 receptor antagonist, and Akynzeo is an oral capsule that combines this receptor antagonist with netupitant, a novel NK1 receptor antagonist. Aloxi was launched in the U.K. in January 2015. Akynzeo was launched in the U.K. in September 2015 and in Ireland in December 2015.

Review of 2017 Performance

Sales in the U.K. for Aloxi and Akynzeo totaled ¥0.4 billion. All MRs in charge of promoting these products also handle Granocyte, which is creating synergy.

Tecentriq (RG7446)

Engineered anti-PDL1 monoclonal antibody
(Generic name: atezolizumab)

Tecentriq is an engineered anti-PDL1 monoclonal antibody in-licensed from Roche. One way that tumor cells evade the immune system is by expressing a protein called programmed death-ligand 1 (PD-L1) on their surface, which is believed to shield them from immune system attacks by binding to T cells. Tecentriq restores and maintains the immune response of T cells by binding to PD-L1, and is expected to demonstrate efficacy against cancer cells. Its mode of action differs from conventional treatments that attack cancer cells directly. Since it takes advantage of the patient's own immune response, it is also promising for use in combination with existing drugs and for various cancer types. Chugai filed an application in February 2017 for approval as a treatment for NSCLC, and obtained approval in January 2018 for the treatment of unresectable advanced or recurrent NSCLC. New phase III multinational studies started for adjuvant chemotherapy of renal cell carcinoma in January 2017 and for the treatment of ovarian cancer and prostate cancer in March 2017. In addition, Chugai is participating in phase II and phase III multinational studies for the treatment of NSCLC as well as phase III multinational studies for the expected indications of postoperative adjuvant chemotherapy of NSCLC, small cell lung cancer, urothelial carcinoma, postoperative adjuvant chemotherapy of muscle invasive urothelial carcinoma, breast cancer and renal cell carcinoma (in combination with Avastin).

GC33 (RG7686)

Anti-glypican-3 humanized monoclonal antibody
(Generic name: codrituzumab)

GC33, a humanized monoclonal antibody created by Chugai, targets glypican-3 (GPC3), which is specifically expressed in hepatocellular carcinoma. The project involves joint research between Chugai and Tokyo University, as well as pathological proteomics work by PharmaLogicals Research Pte. Ltd., a former subsidiary of Chugai. GC33 did not meet the primary endpoint in a phase II multinational monotherapy study started in March 2012. A phase I clinical study for the potential treatment of hepatocellular carcinoma in combination with Tecentriq started in August 2016.

ERY974

Anti-glypican-3/CD3 bispecific antibody

ERY974 is the first T-cell redirecting antibody (TRAB) developed by Chugai. TRAB is a bispecific antibody that creates a short bridge between CD3 on T cells and tumor antigen on tumor cells to activate T cells in a tumor antigen-dependent manner, and is expected to demonstrate strong cytotoxicity against tumor cells. GPC3, a tumor antigen targeted by ERY974, is reported to be expressed in multiple types of tumor cells including hepatocellular carcinoma, gastric cancer and esophageal cancer. A phase I clinical study started overseas in August 2016.

GA101 (RG7159)

Glycoengineered type II anti-CD20 monoclonal antibody
(Generic name: obinutuzumab; overseas product name: Gazyva/Gazyvaro (E.U.))

GA101 is a type II glycoengineered monoclonal antibody in-licensed from Roche that, like Rituxan, targets CD20. In November 2012, Chugai entered into an agreement with Nippon Shinyaku Co., Ltd. to co-develop and co-market this agent in Japan. In August 2017, Chugai filed an application for approval for the treatment of CD20-positive B-cell follicular lymphoma (FL).

RG7596

Anti-CD79b antibody-drug conjugate
(Generic name: polatuzumab vedotin)

RG7596 is an antibody-drug conjugate of an anti-CD79b monoclonal antibody and the microtubule inhibitor MMAE, joined together with a linker. In-licensed from Roche, the conjugate is designed to deliver MMAE directly into B cells via CD79b, which is expressed on B cells, so that the inhibitor can act. RG7596 is expected to demonstrate a cytostatic effect on tumor cells while limiting impact on normal cells. A phase III multinational study for the treatment of diffuse large B-cell lymphoma (DLBCL) started in November 2017.

RG7604

PI3K inhibitor
(Generic name: taselisib)

RG7604 is a PI3K inhibitor in-licensed from Roche. A phase I clinical study started in Japan in September 2014 for the treatment of solid tumors. This drug is a small molecule

anticancer agent that selectively inhibits PI3K. It has been shown to exhibit stronger inhibitory activity against PI3Kα mutations compared with RG7321, development of which was discontinued in 2015.

RG7440
AKT inhibitor
(Generic name: ipatasertib)

RG7440 is an AKT inhibitor in-licensed from Roche. Phase III multinational studies started in June 2017 for the treatment of prostate cancer and in January 2018 for the treatment of breast cancer.

CKI27
Raf/MEK inhibitor

CKI27 is a Raf and MEK dual inhibitor created by Chugai. Phase I clinical studies in Japan and overseas have been completed. An investigator-initiated clinical study is ongoing overseas, and study results were announced at the 2017 ASCO Annual Meeting.

RG7421
MEK inhibitor
(Generic name: cobimetinib)

RG7421 is an MEK inhibitor in-licensed from Roche. Chugai started a phase I clinical study for the treatment of solid tumors in Japan in July 2017.

CEA-TCB (RG7802)
Anti-CEA/CD3 bispecific antibody

CEA-TCB, a bispecific antibody in-licensed from Roche, is expected to activate T-cells and attack tumor cells by cross-linking CD3 on T-cells to carcinoembryonic antigen (CEA) on tumor cells. With a novel structure engineered to bind simultaneously with one arm to CD3 on T-cells and two arms to CEA on tumor cells, it exhibits higher tumor selectivity and stronger binding to CEA. CEA is reported to be overexpressed in a variety of cancers, including colorectal cancer.

CEA-TCB-mediated intra-tumor T-cell proliferation may yield efficacy in tumor types that are not responsive to current cancer immunotherapies because there are few T-cells in the tumor. In addition, combination immunotherapy of CEA-TCB with Tecentriq is expected to yield a potent antitumor effect in various CEA-positive cancers by inducing further T-cell activation. Chugai has decided to start development of CEA-TCB in Japan.

Bone and Joint Diseases/Autoimmune Diseases

Osteoporosis

Osteoporosis is a disease in which the bones become weak due to advanced age or other factors, increasing the risk of fractures. Osteoporosis patients may incur fractures through normal daily activities. Among these, compression fractures of the spine and femoral neck fractures can decrease quality of life by leaving patients bed-ridden and can also increase mortality risk. About 13 million people in Japan suffer from osteoporosis, including one in every two women age 65 and older. However, the treatment rate stands at around only 20 percent of the estimated number of sufferers because there are virtually no noticeable symptoms until a fracture occurs. The availability of superior new drugs that have higher efficacy, safety and convenience has brought promise for improvement in the quality of life of patients.

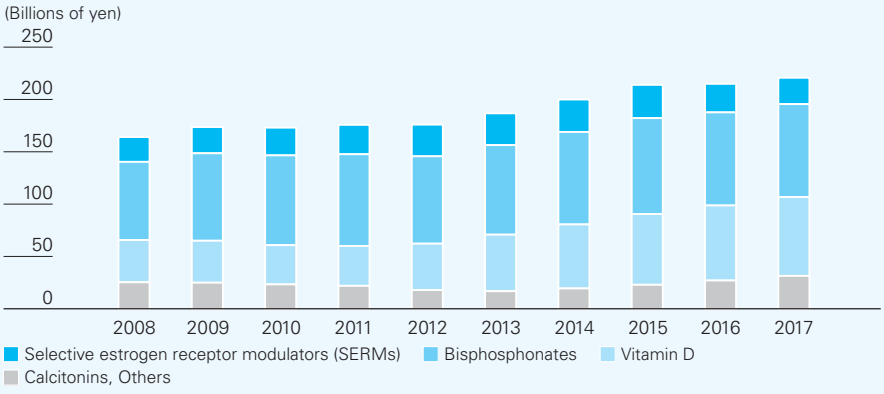
Treatment Methods

Osteoporosis treatments include bisphosphonates, which are bone resorption inhibitors, active vitamin D_3 derivatives, which improve bone metabolism, human parathyroid hormone (PTH), a humanized anti-RANKL antibody, and selective estrogen receptor modulators (SERMs).

Regulatory Trends

National guidelines for osteoporosis treatment were revised in October 2006. Subsequently, advances have been made in basic and clinical research into osteoporosis: evaluation of fracture risk and criteria for the initiation of drug treatment have been reviewed; and osteoporosis caused by lifestyle-related diseases has been addressed. In the interim, Edirol and other medicines have been approved for insurance coverage. Revisions issued in December 2011 added preventive and diagnostic items in light of the importance of early prevention to broaden the overall scope of osteoporosis treatment. Since then, the 2012 revised diagnostic criteria for primary osteoporosis and revised management and treatment guidelines for steroid-induced osteoporosis have been adopted, Bonviva IV Injection and other medicines have been launched and covered by insurance, and revised guidelines were issued in July 2015.

Osteoporosis Market in Japan



Source: JPM 2008-2017

The scope of the market is defined by Chugai.

Edirol
Active vitamin D_3 derivative
(Generic name: eldecalcitol)

Basic Information

Edirol is a vitamin D_3 preparation born out of Chugai's many years of research in vitamin D. Chugai started sales of Edirol in April 2011 as the successor drug to Alfarol for the indication of osteoporosis with a stronger effect in regulating bone metabolism. Under an agreement signed in May 2008, Edirol has been co-developed and is currently co-marketed with Taisho Pharmaceutical Co.,

Ltd. Clinical trials have confirmed that Edirol has a similar safety profile to alfacalcidol with a statistically significant greater effect in preventing fractures. In the 2015 osteoporosis prevention and treatment guidelines, Edirol received a Grade A recommendation, the only one for an active vitamin D_3 preparation, for its effectiveness in increasing bone density and preventing vertebral fractures.

Review of 2017 Performance

Sales of Edirol increased ¥2.9 billion, or 10.9 percent, to ¥29.6 billion. It has become the most widely used active vitamin D_3 preparation because of its superior efficacy in increasing bone mass and preventing fractures compared with existing products. Recognition and understanding of Edirol as a base treatment has also broadened. As a result, its use by medical institutions is increasing, as are prescriptions, primarily for new cases. In China, an application has been filed for approval of Edirol as a treatment for osteoporosis.

Bonviva

Bisphosphonate anti-resorptive agent
(Generic name: ibandronate)

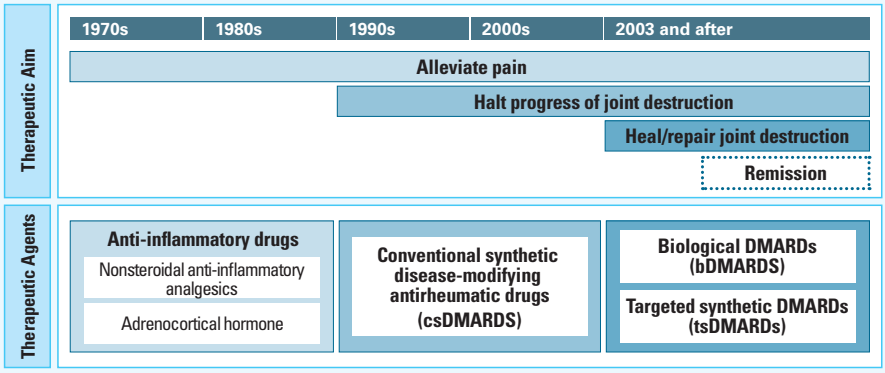
Basic Information

Bonviva is a bisphosphonate in-licensed from Roche. Bonviva IV Injection was launched in August 2013. Under an agreement signed in September 2006, Bonviva is being co-developed and co-marketed with Taisho Pharmaceutical Co., Ltd. Bisphosphonates in Japan are administered in drip infusions, but Bonviva IV Injection is given in a rapid intravenous injection once a month. This is expected to significantly reduce the burden on patients at the time of administration. In addition, Bonviva Tablet administered once monthly demonstrated non-inferiority to Bonviva IV Injection in a phase III clinical trial (the MOVEST study). Chugai obtained approval in January 2016 and began sales in April 2016. By enabling drug selection according to patient lifestyle, monthly Bonviva IV Injection and Bonviva Tablet are expected to help improve patient adherence, convenience for healthcare providers and the rate of continuation of treatment.

Review of 2017 Performance

Sales of Bonviva increased ¥1.4 billion, or 19.2 percent, to ¥8.7 billion. Bonviva IV Injection is particularly convenient for patients who have difficulty taking existing oral formulations, and recognition of the drug's usefulness is increasing as a product that can be expected to improve adherence to treatment.

Changes in Rheumatoid Arthritis Drug Therapy



With the advent of biologics, the aim of therapy for rheumatoid arthritis has shifted to achieving and maintaining remission.

Rheumatoid Arthritis/ Osteoarthritis

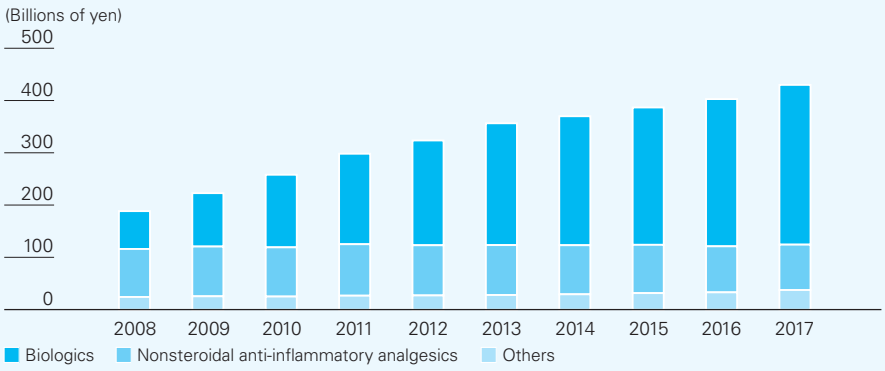
Rheumatoid arthritis (RA) is a systemic disease characterized by painful inflammation and deformation of joints leading to dysfunction. Without appropriate treatment, the patient's condition deteriorates over time. It is estimated that there are about 700,000 patients in Japan suffering from RA, of whom some 330,000 are currently receiving drug treatment. The number of patients is increasing as the average age of the population rises. On the other hand, there are only several hundred patients in Japan with systemic juvenile idiopathic arthritis (sJIA), a form of RA suffered by children below 16 years of age, but sJIA is considered even more difficult to treat than adult forms of the disease. The most common joint disease is osteoarthritis. It leads to degeneration of the cartilage in the joints and surrounding areas, causing joint pain and reduced mobility in daily life. The prevalence of this disease increases with age, with knee osteoarthritis in particular affecting at least 60 percent of people 40 years of age or older, primarily women.

Treatment Methods and Market Conditions

In drug therapy for RA, methotrexate (MTX), an anti-rheumatic drug, is mainly used in treatment, but with the introduction of biologics, the goal of treatment has now been extended to remission. Research in recent years suggests that the administration of biologics at the early onset stage is effective in inhibiting bone and joint damage. The global market for these agents is forecast to reach $25.6 billion* by 2020. The market is also changing. In 2013, a new oral formulation was launched in the United States and Japan, and a biosimilar was launched in Europe. In 2014, a biosimilar was also launched in Japan.

Recently, there has been an increase in drugs offering greater convenience in administration. In addition to drip infusions, which were the only formulations previously available, subcutaneous formulations have been added, and new formulations that improve convenience, such as a dosage form that can be injected simply by pushing a button, are increasing. In Japan, Europe and the United States, the subcutaneous market is estimated to be larger than the intravenous market.

Rheumatoid Arthritis Market in Japan



The scope of the market is defined by Chugai.

New oral drugs called targeted synthetic DMARDs are also gaining attention. There are signs that their efficacy will be similar to that of biological agents, broadening the range of treatment options for RA.

Steroid drugs, which had been the only treatment available for sJIA, can cause growth impairment and other adverse reactions. Accordingly, the approval and launch of Actemra in April 2008 provided a significant advance in therapy.

The main drug therapies for osteoarthritis include non-steroidal anti-inflammatory analgesics, steroids and hyaluronic acid preparations, with intraarticular administration of hyaluronic acid preparations used as a treatment in the early and middle stages. Intraarticular administration of hyaluronic acid preparations has also demonstrated effectiveness in improving periarthritis of the shoulder and knee joint pain associated with rheumatoid arthritis.

* Source: Evaluate Pharma®

Regulatory Trends

In October 2005, MHLW released the Report of the Rheumatism and Allergy Countermeasure Committee. The report calls for the following measures to prevent RA from becoming severe: (1) promotion of early diagnosis and the development of highly effective treatment methods; (2) establishment of medical service systems to provide appropriate care; and (3) improvement of the patient environment, including consultation opportunities and access to information. In Europe, revised treatment recommendations in 2013 added Actemra and Abatacept to the biologic drugs recommended in first-line therapy, which were previously limited to anti-TNF agents. In 2015, a proposed update of clinical practice guidelines was announced at the American College of Rheumatology, with biologics including Actemra added as first-line therapy along with anti-TNF agents. Moreover, the updated European League Against Rheumatism (EULAR) recommendations that were announced in June 2016 state the superiority of biologics in interleukin-6 (IL-6) inhibitor therapy in cases where MTX and other therapies cannot be used.

In recent years, academic societies and other players have been aggressively promoting research, diagnosis and treatment of osteoarthritis as an underlying cause of "locomotive syndrome," a term proposed in the field of orthopedics to designate the condition of individuals at high risk of suffering loss of motor function due to advanced age that leaves them requiring nursing care and bedridden.

Castleman's Disease

Castleman's disease is a lymphoproliferative disease characterized by symptoms such as systemic lymphadenopathy, fever and general fatigue, as well as various abnormal laboratory test values including anemia, hypergammaglobulinemia and hypoalbuminemia. It has been confirmed that these manifestations result from the excessive production of IL-6, one of the cytokines that causes inflammation. Castleman's disease is very rare, affecting approximately 1,500 people in Japan.

Large-Vessel Vasculitis

Large-vessel vasculitis belongs to a group of autoimmune diseases called vasculitis syndromes. It refers to vasculitis in the aorta and the major aortic branches to the limbs and head and neck, and includes Takayasu arteritis and giant cell arteritis (temporal arteritis).

Takayasu arteritis leads to inflammation of the aortic arch and its branch vessels. It affects women more than men, at a ratio of 9:1, and age of onset is between 20 and 50 years. It occurs most commonly in Asia, including Japan, and the Middle East. Initial symptoms include reduced head and cerebral blood flow-related conditions such as dizziness, lightheadedness and headaches, as well as neck pain, chest pain and vascular pain along the limb arteries.

Giant cell arteritis is a granulomatous vasculitis occurring primarily in the aorta and aortic branches, mainly the temporal arteries. It also affects women more than men, at a ratio of 1.6:1, and the age of onset is 55 years or older. It occurs most commonly in Western countries and is rare in Japan. Common initial symptoms include headache, systemic conditions such as fever, and loss of vision.

Systemic Sclerosis

Systemic sclerosis (SSc) is a rare, chronic disorder characterized by blood vessel abnormalities, as well as degenerative changes and scarring in the skin, joints and internal organs. The incidence rate of SSc is difficult to measure, but it is estimated to affect approximately 2.5 million people worldwide, and has the highest fatality rate of any rheumatic disease.

Actemra (MRA/RG1569)

Humanized anti-human IL-6 receptor monoclonal antibody
(Generic name: tocilizumab)

Basic Information

Actemra, created by Chugai and the first therapeutic antibody originating in Japan, blocks the activity of IL-6, a type of cytokine. It was launched in Japan in June 2005 as a treatment for Castleman's disease. In April 2008, Chugai obtained approval in Japan for the additional indications of RA, polyarticular juvenile idiopathic arthritis (pJIA) and sJIA. In May 2013, Chugai launched a new subcutaneous formulation that improves convenience for patients in addition to the existing drip infusion formulation. This subcutaneous formulation includes the first auto-injector in the Japanese RA market.

Actemra is marketed globally through Roche. In Europe, where the medicine is known as RoActemra, sales for the treatment of RA started in 2009. Chugai's marketing subsidiary co-promotes RoActemra with Roche in the United Kingdom, France and Germany. In the United States, Actemra obtained approval in January 2010 for the treatment of adult patients with moderate to severe active RA who have had an inadequate response to one or more TNF antagonist therapies, and obtained approval in October 2012 as a first-line biologic treatment. In Taiwan and South Korea, where Chugai has marketing rights, Actemra obtained approval in July 2011 and April 2012, respectively. Following its launch in Japan, the subcutaneous formulation obtained approval in the United States in October 2013 and in Europe in April 2014, and has been launched in both markets. RoActemra was also approved for early RA in Europe in September 2014.

Furthermore, Actemra obtained approval for the additional indication of treatment of sJIA in the United States in April 2011 and in Europe in August 2011. Actemra also received breakthrough therapy designation from the U.S. FDA in 2015 as a potential treatment for SSc and in 2016 as a treatment for giant cell arteritis. In Japan, Actemra received orphan drug designations as a treatment for large-vessel vasculitis in June 2014 and systemic scleroderma in March 2016.

Review of 2017 Performance

In 2017, sales of Actemra in Japan increased ¥2.9 billion, or 9.6 percent, to ¥33.1 billion, due to steady uptake of both the drip infusion and subcutaneous formulations. Sales of the subcutaneous formulation accounted for more than 40 percent of the total.

Sales of Actemra outside Japan (to Roche) increased ¥0.6 billion, or 1.0 percent, to ¥60.9 billion. At the same time, Roche's

global sales increased 14.0 percent year on year with steady market penetration. In particular, market uptake of the subcutaneous formulation drove growth in the United States and key countries of Europe.

In development, Chugai obtained approval in Japan in June 2017 for an additional dosage and administration of Actemra Subcutaneous Injection, reducing the dose interval to one week in patients with RA who respond inadequately to the previously approved bi-weekly dosing regimen. Actemra also obtained approval for the additional indication of giant cell arteritis in the United States in May 2017 and in Europe in September 2017, and for the additional indications of Takayasu arteritis and giant cell arteritis in Japan in August 2017. In the United States, Actemra obtained approval in August 2017 for the additional indication of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome. A phase III multinational joint study for the treatment of systemic scleroderma is under way.

RG7845

BTK Inhibitor

RG7845 is an oral, small molecule Bruton's tyrosine kinase (BTK) inhibitor in-licensed from Roche. BTK, a non-receptor tyrosine kinase expressed in B cells and bone marrow, is involved in arteritis and joint destruction associated with RA. RG7845 is expected to improve RA symptoms because it selectively and reversibly binds to the BTK molecule, thereby having an inhibiting effect on its activity. A phase I clinical trial started in June 2017.

Suvenyl

Agent for joint function improvement
(Generic name: sodium hyaluronate)

Basic Information

Suvenyl, a drug that improves joint function through injection into the joint cavity, is a high molecular weight sodium hyaluronate drug that alleviates knee osteoarthritis, shoulder periarthritis and knee joint pain caused by RA. With physical and chemical properties close to that of hyaluronic acid found in the body, Suvenyl has been recognized for its superior performance, including its anti-inflammatory and analgesic effects.

Review of 2017 Performance

Sales decreased ¥0.5 billion, or 5.4 percent, to ¥8.8 billion, due to the impact from competing products and generics. In China, phase III clinical studies are under way for the potential treatment of knee osteoarthritis and shoulder periarthritis.

Neuromyelitis Optica

Neuromyelitis optica (NMO), also known as Devic's disease, is a neurological autoimmune disorder characterized by severe optic neuritis and transverse myelitis. The disease affects 0.3 to 4.4 in 100,000 people, and there are about 4,000 patients in Japan. It is an incurable disease that typically appears around the age of 40 years and affects women more than men, at a ratio of 9:1. Symptoms include loss of vision (blindness) and impairment of motor function and sensation. In some cases, the disease results in death. However, as there are no approved treatments available, NMO is an orphan disease with high unmet medical need. It is believed to occur when aquaporin-4 (AQP4) in the central nervous system is attacked by autoantibodies called anti-AQP4 antibodies.

SA237

Anti-IL-6 receptor humanized monoclonal antibody
(Generic name: satralizumab)

SA237, created by Chugai, is a next-generation therapeutic antibody that has shown success in blocking IL-6 receptors for an extended period of time. Chugai created SA237 by applying its novel antibody technology (Recycling Antibody® technology) that enables a single antibody molecule to block the target antigen repeatedly. Preclinical studies have verified that this extends the duration of the blocking action on IL-6 receptors more than four times longer than Actemra, and an extension of serum half-life has been demonstrated in clinical trials. Because IL-6 promotes the production of the anti-AQP4 antibodies that cause NMO, this drug is expected to improve (reduce recurrence of) the symptoms of this disease as it inhibits the production of those antibodies by blocking the IL-6 signal. A phase III multinational study for the potential treatment of NMO is under way. In addition to its designation as an orphan drug by the U.S. FDA, SA237 was also granted orphan drug designation in Europe in 2016. Furthermore, in June 2016, Chugai concluded a license agreement that grants Roche exclusive rights for the development and marketing of SA237 worldwide, with the exception of Japan, South Korea and Taiwan.

Renal Diseases

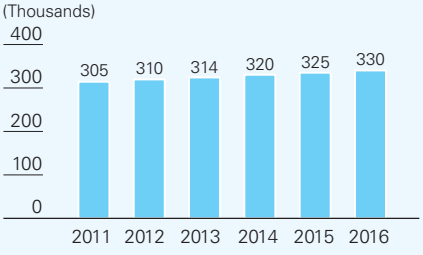
Renal Anemia

Complications of Renal Dysfunction

For dialysis patients and end-stage renal disease patients, the treatment of various complications of advanced renal dysfunction, such as renal anemia, secondary hyperparathyroidism, and abnormal calcium and phosphorus metabolism, is a major issue. Of these complications, renal anemia is one of the most frequent, occurring not only in renal disease patients undergoing dialysis but also in pre-dialysis renal disease patients. Renal anemia, in turn, is thought to be a factor not only in reducing quality of life, but also in the progress of organ damage, including decreased cardiac function.

The importance of treating renal anemia and chronic kidney disease - mineral and bone disorder (CKD-MBD) was indicated in the Guideline for Renal Anemia in Chronic Kidney Disease (2015) and the Clinical Practice Guidelines for the Management of CKD-MBD (2012) issued by the Japanese Society for Dialysis Therapy and in the Evidence-based Practice Guidelines for the Treatment of CKD (2013) issued by the Japanese Society of Nephrology.

Number of Dialysis Patients in Japan



Source: Overview of Regular Dialysis Treatment in Japan (as of December 31, 2016) by Statistical Survey Committee, The Japanese Society for Dialysis Therapy

Erythropoiesis-Stimulating Agent (ESA)

Erythropoietin (EPO) is a hemopoietic factor produced mainly in the kidneys. It speeds up erythrocyte production using erythroid progenitor cells found in bone marrow. An erythropoiesis-stimulating agent (ESA) is effective in treating renal anemia caused primarily by the decline in EPO production due to CKD, and is thought to help improve quality of life. It is estimated that ESAs are currently used by approximately 80 percent of dialysis patients as well as by pre-dialysis renal disease patients with renal anemia. ESAs are thus an essential drug for the treatment of renal anemia.

Flat-Sum Reimbursement System for ESAs

Since the 2006 revisions of medical fees, ESAs have been included in medical fee points for dialysis. The integrated fee points are reviewed with each revision of medical fees.

Mircera

Long-acting erythropoiesis-stimulating agent
(Generic name: epoetin beta pegol)

Basic Information

Mircera is a drug that raises the stability of epoetin beta in the bloodstream through pegylation. It is a new type of renal anemia treatment with the longest serum half-life among ESAs, enabling stable and sustained control of hemoglobin. It stimulates erythropoiesis through a different interaction with the EPO receptor on burst-forming unit erythroid (BFU-E) cells in the bone marrow. Mircera was launched in Japan in July 2011 as a treatment for renal anemia. Outside Japan, Mircera obtained approval in Europe in 2007 and is currently sold in more than 100 countries, including the United States.

The serum half-life of Mircera is virtually the same for intravenous injection or subcutaneous administration, and the drug demonstrates efficacy in relieving the symptoms of anemia when administered at four-week intervals during the maintenance period. Consequently, it may reduce the burden of hospital visits on patients with pre-dialysis renal disease and is expected to contribute to better treatment adherence. Furthermore, as a dialysis-related treatment, Mircera is expected to reduce the burden on medical staff and improve medical safety by dramatically reducing administration frequency. The product thus has the potential to expand the range of options for the treatment of renal anemia.

Review of 2017 Performance

Sales of Mircera decreased ¥0.3 billion, or 1.2 percent, to ¥23.9 billion. The NHI drug price was reduced in the revisions in 2016 because it did not qualify for premium pricing. However, its use is steadily increasing in the renal anemia market, primarily for patients with pre-dialysis renal disease, in whom definite effects can be obtained with administration once every four weeks tailored to the frequency of their hospital visits.

Epogin

Recombinant human erythropoietin agent
(Generic name: epoetin beta)

Basic Information

Epogin is a human erythropoietin agent that uses epoetin beta, produced through Chugai's unique gene recombinant technology, as its main active ingredient. Erythropoietin is effective in improving renal anemia primarily caused by the decline in erythropoietin production due to CKD. It also contributes to the improvement of a wide range of complications arising from anemia. Since its launch in 1990, Epogin has been widely used in the clinical setting for its approved indications of renal anemia under dialysis and before dialysis, anemia of prematurity and autologous blood transfusion of patients scheduled for surgery.

Oxarol

Agent for secondary hyperparathyroidism
(Generic name: maxacalcitol)

Basic Information

Synthesized by Chugai, Oxarol is the first intravenous active vitamin D_3 derivative agent in Japan. It treats secondary hyperparathyroidism, a result of prolonged dialysis, by acting directly on the parathyroid gland with high concentration to control parathyroid hormone synthesis and secretion, and by acting to improve bone metabolism. With its short serum half-life, Oxarol is showing efficacy in patients who could not be treated adequately with oral vitamin D_3 derivatives due to the onset of hypercalcemia.

Review of 2017 Performance

Sales of Oxarol decreased ¥0.9 billion, or 9.9 percent, to ¥8.2 billion due to the impact of intensifying competition with the launch of a generic product and a substantial NHI drug price revision with the return of the premium for new drug creation in 2015.

EOS789

EOS789 is an oral drug created by Chugai with a molecular weight of over 500 g/mol. Following the completion of a phase I clinical trial as a potential treatment for hyperphosphatemia in Japan, a phase I clinical trial for the same indication started overseas in February 2017.

Neurology

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia. Pathologically, it is a progressive neurodegenerative disease that causes neuron death in the brain and brain atrophy. It leads to a general and progressive loss of memory and other cognitive functions, which can interfere with daily life. While existing AD treatments have some effect in slowing disease progression by several months, they are unable to stop the neuron death, and a treatment for the underlying cause does not yet exist. Consequently, unmet medical need is high, and there is strong demand for a more effective drug.

RG1450

Anti-amyloid-beta human monoclonal antibody
(Generic name: gantenerumab)

RG1450 is an anti-amyloid-beta human monoclonal antibody in-licensed from Roche. The drug targets aggregate amyloid beta, with a high binding affinity to plaques in particular. It is expected to improve cognition by removing amyloid beta in the brain. A phase III multinational study of RG1450 as a potential treatment for AD is under way.

RG7412

Anti-amyloid-beta humanized monoclonal antibody
(Generic name: crenezumab)

RG7412 is an anti-amyloid-beta humanized monoclonal antibody in-licensed from Roche. The drug targets all types of amyloid beta, with a high binding affinity to oligomers. It is expected to improve cognition by removing amyloid beta in the brain. A phase III multinational study of RG7412 as a potential treatment for AD began in March 2017.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a lower motor neuron disease characterized by amyotrophy and progressive muscle weakness caused by degeneration of anterior horn cells in the spinal cord. The estimated number of patients in Japan is reported to be around 1,000. The disease is caused by a defect in the *SMN1* gene, and onset usually occurs in childhood. In severe cases it is fatal.

RG7916

SMN2 splicing modifier

RG7916 is an SMN2 splicing modifier that increases generation of a protein derived from the *SMN2* gene. This protein is nearly identical to the protein made from the *SMN1* gene, which is not functional in SMA patients. RG7916 shows promise in improving neural and muscular function. A phase I clinical trial of RG7916 began in March 2017, and a phase II multinational study began in November 2017.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a fatal hereditary disease primarily characterized by degeneration, necrosis and regeneration of the skeletal muscles, with progressive muscle weakness as the clinical symptom. It is caused by a mutation of the dystrophin gene located on the X chromosome. In Japan, such mutations have been reported to be the cause in approximately 40 percent of patients. It affects one in 3,000 to 4,000 males at birth, and the estimated number of patients in Japan is between 4,000 and 5,000. At present, steroid therapy is the only approved treatment available in Japan, but it has been recognized that life expectancy and quality of life have improved due to progress in breathing control methods such as non-invasive positive-pressure ventilation.

RG6206

Anti-myostatin-inhibiting adnectin fusion protein

RG6206 is a recombinant protein with two anti-myostatin adnectin molecules binding to the human IgG1 Fc fragment. Myostatin is a cell growth inhibitor that negatively regulates skeletal muscle mass. By lowering the level of active, free serum myostatin, RG6206 is expected to have therapeutic effects including maintenance of muscular strength associated with an increase in skeletal muscle mass. A phase II/III multinational clinical study started in November 2017.

Other Diseases

Influenza

Influenza is an acute infectious disease characterized by the rapid onset of high fever (38 degrees centigrade or more) and severe systemic symptoms. It is highly infectious, and epidemics can develop quickly. In some cases, secondary infections can lead to very serious illness and death. Influenza is classified into types A, B and C based on differences in the antigenicity of the underlying virus. Types A and B can infect humans and cause major outbreaks.

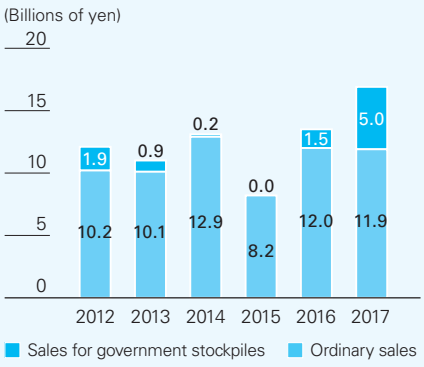
Tamiflu

Anti-influenza agent
(Generic name: oseltamivir phosphate)

Basic Information

Tamiflu is an oral anti-influenza agent that is effective against both type A and type B infections. It inhibits viral replication by blocking the action of neuraminidase, an enzyme essential for the multiplication of the influenza virus. Launched in capsule form in February 2001 and dry syrup form in July 2002, dosages are available for patients one year of age and older. Since March 2007, restrictions on the use of Tamiflu in teenage patients with seasonal influenza have been in force in Japan. The measure was introduced as a safety precaution following several reports of abnormal behavior in influenza patients who had taken Tamiflu. The report of an epidemiological survey with 10,000 flu patients conducted by a working group of MHLW suggested that there are no findings to date that point to a causal association between Tamiflu and the abnormal behavior of patients taking the drug. MHLW has concluded that it is appropriate to continue to take precautions and other measures, and is thus continuing the restriction on the use of Tamiflu. New research investigating the relationship between abnormal behavior and the use of Tamiflu began in 2016. The shelf life of Tamiflu capsules was extended to 10 years from seven years for capsules manufactured after July 2013, and the shelf life of dry syrup was extended to 10 years starting with the portion shipped in 2015.

Tamiflu Sales



Review of 2017 Performance

Sales of Tamiflu increased ¥3.4 billion, or 25.2 percent, to ¥16.9 billion. Ordinary sales were ¥11.9 billion, while sales for government stockpiles were ¥5.0 billion. Chugai continued to highlight the drug's efficacy and the benefits of its unique dry syrup formulation. In March 2017, Chugai obtained approval for additional dosage and administration of Tamiflu Dry Syrup 3% for neonates and infants younger than 12 months.

CellCept

Immunosuppressant
(Generic name: mycophenolate mofetil)

Sales of CellCept, an immunosuppressant, increased ¥1.0 billion, or 12.7 percent, to ¥8.9 billion. CellCept is used to treat refractory rejection after kidney transplants and to prevent rejection after kidney, heart, liver, lung and pancreas transplants. The need for transplantation medication has been rising in Japan, driven by advances in transplantation therapy. In May 2016, CellCept received approval for the indication of lupus nephritis, a refractory disease associated with the autoimmune disease systemic lupus erythematosus.

Hemophilia

Hemophilia is a disease that leads to bleeding in the joints, muscles and other areas in the body due to a congenital deficiency or abnormal function of blood coagulation factors. A low level or absence of blood coagulation factor VIII is known as hemophilia A, while a low level or absence of blood coagulation factor IX is referred to as hemophilia B. Treatment is centered on replacement therapy to supplement factor VIII or IX. However, since it involves intravenous injections two to three times a week, treatment is a significant burden, particularly on children. Moreover, patients must be monitored for the development of autoantibodies, called inhibitors, to the supplemented factor. Patients with inhibitors are treated by means such as bypass therapy or immune tolerance therapy, but these therapies are limited in terms of convenience and the stability of their effects. A more useful treatment method is therefore needed.

Hemlibra (ACE910/RG6013)

Anti-factor IXa/X bispecific antibody
(Generic name: emicizumab)

Hemlibra is an anti-factor IXa/X bispecific antibody that employs Chugai's innovative antibody engineering technologies. Like factor VIII, Hemlibra simultaneously binds to factor IXa and factor X, stimulating the activation of factor X by activated factor IX and promoting normal blood coagulation. Unaffected by inhibitors, Hemlibra is expected to prevent bleeding with once weekly (or less-frequent) subcutaneous injections.

Hemlibra was granted orphan drug designation for the potential treatment of hemophilia A with inhibitors in the United States in January 2014. Chugai concluded an out-licensing agreement with Roche in July 2014 and in May 2017 entered into a license agreement with JW Pharmaceutical Corporation for the exclusive marketing rights in South Korea. The drug received breakthrough therapy designation from the U.S. FDA in September 2015 for its potential to prevent bleeding in hemophilia patients with inhibitors. In a phase III multinational study on adult and adolescents with inhibitors that began in November 2015, a statistically significant reduction in the number of bleeds was confirmed in patients who received Hemlibra prophylaxis. Phase III multinational studies also began on pediatric patients with inhibitors in July 2016, and showed a clinically significant reduction in the bleeding rate. Based on the results of these two studies, applications for approval for the treatment of hemophilia A (with inhibitors) were filed in the United States and Europe in June 2017 and in Japan in July 2017. In the United States, Hemlibra received priority review designation in August 2017, and in November 2017 obtained approval for routine prophylaxis with once-weekly subcutaneous administration in adult and pediatric patients with hemophilia A with factor VIII inhibitors. Hemlibra was also granted accelerated assessment in Europe, and received regulatory approval from the European Commission in February 2018 for routine prophylaxis of bleeding episodes in patients with hemophilia A with factor VIII inhibitors. In Japan, Hemlibra is being reviewed under orphan drug designation (as of February 28, 2017). At the same time, the results of a phase III multinational study that began in September 2016 on patients without inhibitors confirmed a statistically significant reduction in the bleeding rate in patients who received Hemlibra prophylaxis (November 2017). In addition, the results of an interim analysis of a phase III multinational study to evaluate a dosing schedule of once every four weeks for people with and without inhibitors, which began in January 2017, showed a positive reduction of the bleeding rate with Hemlibra prophylaxis dosed once every four weeks (December 2017). Presentation of the results of these latter two phase III studies is planned at major scientific conferences in 2018. In addition, filings of applications for approval of additional indications and effects, and additional dosages and administration based on the results of these studies are planned in Japan, the United States, Europe and elsewhere in 2018.

Hemlibra has the potential to change the existing therapeutic system. Another key feature of this drug is that Chugai's proprietary ART-Ig technology can be applied to enable commercial-scale production of bispecific antibodies.

Atopic Dermatitis

A type of allergic disorder, atopic dermatitis is a chronic skin disease characterized by an itchy rash that alternately improves and worsens. Scratching the affected area exacerbates the skin symptoms and makes the itching worse, leading to an itch-scratch cycle. The basic treatment is drug therapy using topical steroid preparations and/or topical immunosuppressants to control the inflammation and a skin care regimen to prevent the inflammation from recurring.

Pruritus in Dialysis Patients

Pruritus is a complication found in more than 40 percent of dialysis patients. Various factors are thought to play complex roles in development of the condition, including skin dryness, accumulation of uremic toxins, secondary hyperparathyroidism, complement activation by dialysis membranes, the effect of heparin, and itch mediators. It is systemic and refractory, and the degree, site and timing of itching vary by patient. The itching not only reduces quality of life due to discomfort and sleeplessness, but is also reported to be involved in life expectancy.

CIM331

Anti-IL-31 receptor A humanized monoclonal antibody
(Generic name: nemolizumab)

Nemolizumab (CIM331) is an anti-IL-31 receptor A humanized monoclonal antibody originating from Chugai. The drug is expected to suppress itching in atopic dermatitis and reduce skin inflammation by blocking IL-31, a proinflammatory cytokine, from binding to its receptor. Chugai conducted a phase II multinational study in Japan, the United States and Europe. In March 2017, it was announced in the *New England Journal of Medicine* that efficacy and tolerability at 12 weeks of treatment had been observed.

A phase II clinical study of CIM331 as a potential treatment for pruritus in dialysis patients has been completed.

In July 2016, Chugai entered into a global license agreement granting Galderma S.A. of Switzerland exclusive rights for the development and marketing of nemolizumab worldwide, with the exception of Japan and Taiwan. In September 2016, Chugai entered into a license agreement granting Maruho Co., Ltd. the rights for the development and marketing of nemolizumab in the skin disease area for the Japanese market. Clinical trials by both companies are currently under way.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a disorder that leads to complications such as thrombosis and CKD, in addition to anemia and dark brown urine caused by hemolysis as well as infections and bleeding tendency associated with a decrease in white blood cells and platelets. An acquired genetic mutation affecting hematopoietic stem cells causes the creation of red blood cells that have no complement resistance, and hemolysis occurs when complements are activated in vivo. While there are only an estimated 430 patients suffering from PNH in Japan, it is a progressive disease with a high risk of mortality. The drug approved in Japan to suppress hemolysis in patients who need blood transfusions must be administered once every two weeks, requiring regular hospital visits due to the seriousness of the disease.

SKY59

Anti-C5 recycling antibody

SKY59 is a recycling antibody discovered by Chugai that inhibits the C5 complement component. By blocking cleavage of C5 to C5a and C5b, it is expected to inhibit complement activation, which is the cause of a number of diseases. In PNH, SKY59 may have a suppressive effect on hemolysis by preventing the destruction of red blood cells. Application of multiple Chugai proprietary antibody engineering technologies resulted in a prolonged half-life (in preclinical trials), and the antibody is being developed as a subcutaneous self-injection. Chugai is co-developing SKY59 with Roche, and a phase I/II multinational study began in November 2016. In September 2017, SKY59 received orphan drug designation in the United States as a potential treatment for PNH.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease of unknown cause and poor prognosis in which extensive fibrosis results in irreversible honeycomb lung. It is a fatal disease, with a five-year survival rate of around 50 percent. The goal of treatment is to slow the progression of the disease. Currently, only two drugs, pirfenidone and nintedanib, are approved for the treatment of this disease, but considering their side effects and efficacy, IPF remains a disease with high unmet medical need.

RG3637

Anti-IL-13 humanized monoclonal antibody (Generic name: lebrikizumab)

RG3637 is an anti-IL-13 humanized monoclonal antibody in-licensed from Roche. A phase II multinational study as a potential treatment for IPF is under way.

Gout

Gout occurs when uric acid crystals are deposited in the joints due to prolonged high levels of serum uric acid (hyperuricemia), causing inflammation. The peak age of onset is becoming younger, and has shifted from the 50s to the 30s. The number of patients with hyperuricemia, the underlying cause of gout, has been increasing annually, and as many as 5 million people are estimated to be at risk for gout in Japan.

URC102

URAT1 inhibitor

URC102 is a URAT1 inhibitor discovered at C&C Research Laboratories, a joint venture between Chugai and JW Pharmaceutical Corporation of South Korea. It is an oral small molecule uricosuric agent expected to be effective against gout. This compound is expected to reduce the level of serum uric acid by promoting its excretion through inhibition of URAT1. URC102 is being co-developed with JW Pharmaceutical, and a phase II clinical trial has been completed.

wAMD/DME

Wet age-related macular degeneration (wAMD) is a disease in which abnormal blood vessel growth (choroidal neovascularization) caused by age-related accumulation of waste products extends into the space under the retinal pigment epithelium (RPE) or between the retina and the RPE, leading to retinal tissue injury. If the choroidal neovascularization and the associated effusion progress into the fovea centralis, which governs vision, it may lead to deterioration of visual acuity along with the symptoms of image distortion, vision loss and central scotoma. Left untreated, wAMD may lead to irreversible visual impairment.

Diabetic macular edema (DME) is a retinal disease associated with diabetic retinopathy. In diabetes, consistently high blood sugar causes blockage of retinal capillaries, ischemic change, and edema induced by vascular hyperpermeability. Blurred vision occurs when swelling extends to the central part of the macula, which governs vision. Left untreated, DME may lead to irreversible visual impairment.

RG7716

Anti-VEGF/Ang-2 bispecific antibody

RG7716, which Chugai in-licensed from Roche, is the first bispecific antibody for ophthalmology diseases. It selectively binds to vascular endothelial growth factor (VEGF-A), a key mediator of angiogenesis and vascular permeability, and angiopoietin-2 (Ang-2, an antagonist of Ang-1, which contributes to the stability of mature vessels), a destabilizer of chorioretinal vessels and inducer of vascular permeability. By simultaneously neutralizing intraocular VEGF-A and Ang-2 in wAMD and DME patients, RG7716 is expected to demonstrate better treatment outcomes and a more sustained effect than the anti-VEGF drugs that are the current standard of care. A phase I clinical trial began in September 2017.