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 2017 (the year ended March 2018), national medical expenses[1] totaled ¥42.2 trillion, a ¥0.9 trillion or 2.3 percent increase 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 2017) by Ministry of Health, Labour and Welfare

Promotion of the Use of Generics

The Japanese government is promoting the use of generics 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 72.6 percent[2] as of September 2018, 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. 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).

A special revision of NHI drug reimbursement prices will be implemented in conjunction with the increase in the consumption tax rate in October 2019. In its fiscal 2019 budget, the Japanese government has decided to reduce reimbursement prices by 0.51 percent on a government spending basis (+0.42 percent to reflect the consumption tax and a -0.93 percent revision based on actual market prices and other factors).

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

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 a 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.

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 a 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, including Avastin, were subject to the additional repricing rule. In fiscal 2018, two active ingredients and four products were subject to the rule. In the NHI drug pricing system fundamental reforms of fiscal 2018, it was decided to use the NHI listing of new drugs that takes place four times a year as an opportunity for repricing under this scheme.

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[3] 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 decision was made to revise the requirements for companies and products and list them 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

Response to Requests from the MHLW Review Committee on Unapproved Drugs and Indications with High Medical Needs
(As of February 1, 2019)

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 Q2W 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
	Avastin	Cerebral edema induced by radiation necrosis	Submitted company opinion and waiting for evaluation by committee
	Neutrogin	Combination therapy with chemotherapy including fludarabine for relapsed/refractory acute myeloid leukemia	Submitted company opinion and waiting for evaluation by committee

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 qualified for 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.

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

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 in fiscal 2017 was 11.8 months. For new drug applications filed in Japan during fiscal 2017, the median review time was 0.2 years longer than that of the United States, which was smaller than in the average year.

Annual Drug Price Survey and Annual NHI Drug Price Revision

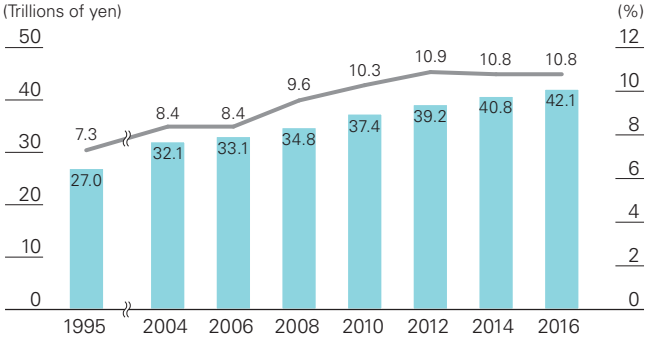
Due to the growing public financial burden of the current situation, in which drug prices are maintained for up to two years even if the market price declines, it was decided in the NHI drug pricing system fundamental reforms of fiscal 2018 that drug price surveys and drug price revisions will be carried 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 a price revision will be implemented 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.

Creation of a System for Cost-Effectiveness Assessments

A system of price adjustments based on cost-effectiveness assessments has been approved by Chuikyo, and will be implemented starting in April 2019. The system primarily applies to products that meet the requirements of the selection criteria at the time of their NHI price listing. Cost-effectiveness assessments will be conducted for a certain period after the listing, and the price will be adjusted according to the results. The extent of the price adjustment is the portion corresponding to the amount of the corrective premium for usefulness applied at the time of the drug's initial pricing (for products with a degree of disclosure under 50 percent, as calculated by the cost calculation method, the portion corresponding to operating profit is also subject to adjustment). Price adjustments will be made according to the incremental cost effectiveness ratio (ICER).[4] The corrective premium will be maintained if the ICER is less than ¥5 million (less than ¥7.5 million for anticancer agents), but will be reduced in stages by up to 90 percent if the ICER is ¥5 million or more. The price adjustment will be limited to 10-15 percent of the total drug price.

4. 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.

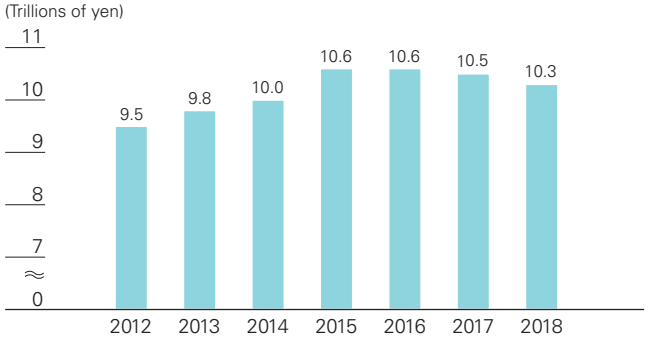
Trends of Medical Care Expenditure



Source: Overview of Estimates of National Medical Care Expenditure, FY2016 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 2017, 373,334 people[1] died of cancer, accounting for 27.9 percent[1] of all deaths in that year and the highest number since government surveys began in 1899.

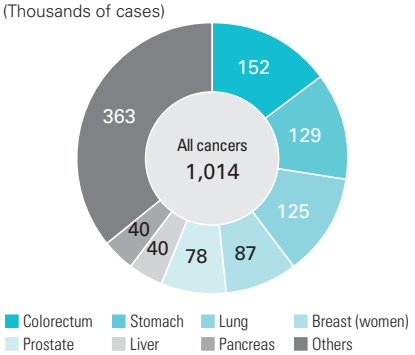
1. Source: Outline of Vital Statistics (2017) by Ministry of Health, Labour and Welfare

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

The Cancer Control Act was enacted in June 2006 to establish a system so that patients can receive appropriate treatment based on scientific knowledge regardless of the region in which they reside and with respect paid to their wishes, as well as to implement the Basic Plan to Promote Cancer Control Programs (the "Basic Plan"). Since the enactment of the Cancer Control Act, significant results have been obtained, including establishment of designated cancer hospitals and a reduction of the cancer mortality rate and improvement of the five-year survival rate owing to advances in cancer treatment. The goal of reducing the age-adjusted cancer mortality rate by 20 percent over the 10-year period from fiscal 2007 was judged difficult to achieve, and 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.

Projected Cancer Incidence (2018)

(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 (1975-2014 nationwide estimates) and cancer mortality figures from the Outline of Vital Statistics (1975-2016 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

In recent years, it has become apparent that new measures are necessary to fight rare cancers, difficult-to-treat cancers, childhood cancers, and cancers in adolescents and young adults (AYA); to promote new treatments such as genomic medicine; and to address societal problems including employment. The principles of the Cancer Control Act revised in 2016 require that the national and local governments make effective use of healthcare and welfare resources and implement cancer control measures from the viewpoint of serving the public in order to achieve the stated goal of creating a society in which cancer patients can live with peace of mind and dignity. In the 3rd Basic Plan to Promote Cancer Control Programs released in March 2018, measures are being implemented based on three pillars – cancer prevention, cancer medical care and research, and coexistence with cancer – to educate the public, including patients, about cancer and help them to overcome it.

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 who are likely to benefit 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 and gene panel testing using next-generation sequencing. Moreover, the MHLW and pharmaceutical industry organizations have been setting up a framework to promote the realization of genomic medicine, starting with the Council to Promote the Realization of Genomic Medicine, which was established by the Japanese government in January 2015. 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 rising for their high therapeutic efficacy 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.

Avastin (RG435)

Anti-VEGF humanized monoclonal antibody
(Generic name: bevacizumab)
Launch in Japan: June 2007

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 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 2018 Performance

Sales of Avastin increased ¥2.5 billion, or 2.7 percent, year on year to ¥95.6 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, the use of Avastin for other indications, including breast cancer, has increased steadily. Phase III multinational studies in combination with Tecentriq in renal cell carcinoma and hepatocellular carcinoma patients are under way.

Herceptin

Anti-HER2 humanized monoclonal antibody
(Generic name: trastuzumab)
Launch in Japan: June 2001

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 2018 Performance

Sales of Herceptin decreased ¥5.5 billion, or 16.4 percent, year on year to ¥28.1 billion. The decrease was mainly due to the substantial NHI drug price revision (-20.4 percent) that resulted from the return of the premium for new drug creation. Widely used in first-line treatment of HER2-positive advanced or recurrent breast cancer in combination with Perjeta, Herceptin is also 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)
Launch in Japan: September 2013

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. In 2018, Perjeta obtained approval for the additional indication of neoadjuvant and adjuvant therapy for HER2-positive breast cancer.

Review of 2018 Performance

Sales of Perjeta increased ¥2.5 billion, or 18.4 percent, year on year to ¥16.1 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 addition, a phase III multinational study is underway for RG6264 (subcutaneous injection), a fixed-dose combination of Herceptin and Perjeta, for the potential treatment of HER2-positive breast cancer.

Kadcyla (RG3502)

Anti-HER2 antibody-tubulin polymerization inhibitor conjugate
(Generic name: trastuzumab emtansine)
Launch in Japan: April 2014

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 2018 Performance

Sales of Kadcyla increased ¥0.5 billion, or 6.3 percent, year on year to ¥8.5 billion. Kadcyla is used as a second-line treatment in patients whose cancer worsened in first-line treatment with Herceptin and Perjeta plus a chemotherapeutic agent. In development, a phase III multinational study for the potential treatment of HER2-positive breast cancer (adjuvant) is under way.

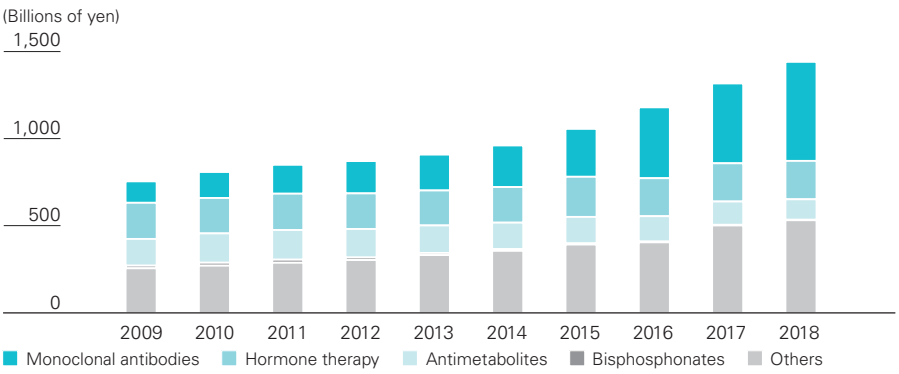
Rituxan

Anti-CD20 monoclonal antibody
(Generic name: rituximab)
Launch in Japan: September 2001

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,

Anticancer Agent Market in Japan



Source: JPM 2009-2018
Reprinted with permission.
The scope of the market is defined by Chugai.

the usefulness of Rituxan has been recognized in treating CD20-positive, B-cell lymphoma in immunosuppressed patients, granulomatosis with polyangiitis (GPA) (formerly known as Wegener's granulomatosis) and microscopic polyangiitis (MPA), refractory nephrotic syndrome with frequent relapses or steroid dependence, suppression of antibody-mediated 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 2018 Performance

Sales of Rituxan decreased ¥12.1 billion, or 36.2 percent, year on year to ¥21.3 billion. The decrease was due to more intense competition resulting from the launch of a generic product and the substantial NHI drug price revision (-26.2 percent) with the return of the premium for new drug creation.

Alecensa (AF802/RG7853)

ALK inhibitor
(Generic name: alectinib)
Launch in Japan: September 2014

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 contributing to the treatment of patients around the world. Outside Japan, after obtaining approval in the United States in December 2015 and in Europe in February 2017 for the indication of ALK-positive metastatic (advanced) NSCLC in patients whose disease has progressed or who are intolerant to crizotinib, Alecensa obtained approval as a first-line treatment in the United States in November 2017 and Europe in December 2017.

Review of 2018 Performance

Market penetration proceeded further with the announcement of positive results that led to the early stopping for benefit of a study comparing the efficacy and safety of Alecensa and a competing product on patients in Japan (J-ALEX study). Sales of Alecensa in Japan increased ¥3.9 billion, or 23.4 percent, year on year to ¥20.6 billion, due to a high rate of continuation of treatment. Overseas sales of Alecensa (including exports to Roche) increased ¥15.6 billion, or 112.2 percent, year on year to ¥29.5 billion. In development, a phase III multinational study for the potential treatment of ALK-positive NSCLC (adjuvant) is under way.

Xeloda

Antimetabolite, 5-FU derivative
(Generic name: capecitabine)
Launch in Japan: June 2003

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 2018 Performance

Sales of Xeloda increased ¥0.3 billion, or 2.5 percent, year on year to ¥12.5 billion. Backed by Chugai's initiatives to promote adverse drug reaction management, Xeloda has established a top position in adjuvant therapy performed to inhibit recurrence after surgery for colon cancer. In gastric cancer, prescriptions have increased for adjuvant therapy, for which Xeloda obtained approval in November 2015.

Tarceva

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor
(Generic name: erlotinib)
Launch in Japan: December 2007

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 15 percent of NSCLC patients in Europe and about 40 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 2018 Performance

Sales of Tarceva decreased ¥2.2 billion, or 21.0 percent, year on year to ¥8.3 billion. In NSCLC, sales decreased compared with the previous year due to competition from other products.

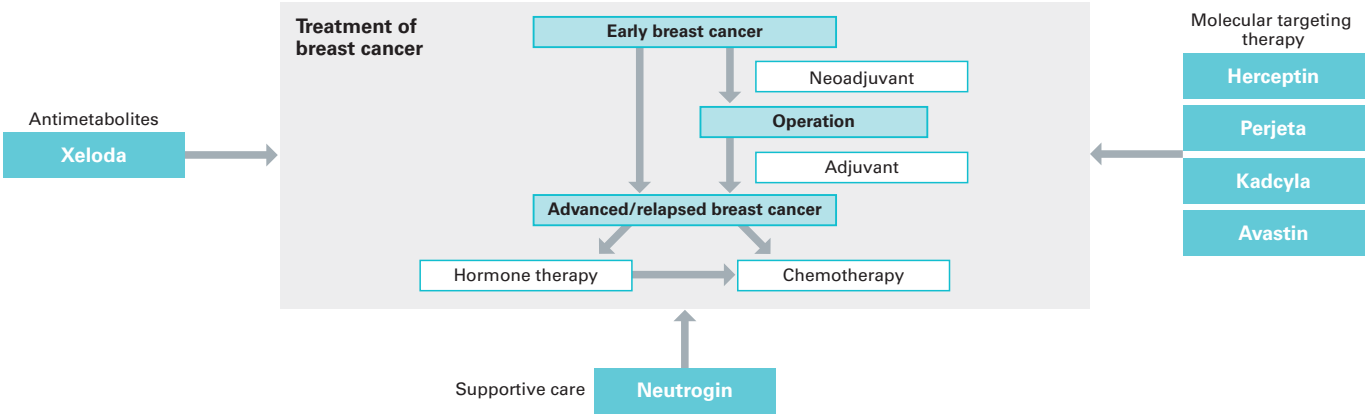
Neutrogin

Recombinant human granulocyte colony-stimulating factor (G-CSF)
(Generic name: lenograstim; overseas product name: Granocyte)
Launch in Japan: December 1991

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

Extensive Contribution to Cancer Treatment (Breast Cancer)



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 2018 Performance

Sales of Neutrogin decreased ¥1.2 billion, or 9.8 percent, year on year to ¥11.1 billion due to intensified competition.

Tecentriq (RG7446)

Engineered anti-PD-L1 monoclonal antibody
(Generic name: atezolizumab)
Launch in Japan: April 2018

Basic Information

Tecentriq is an engineered anti-PD-L1 monoclonal antibody in-licensed from Roche. One way that tumor cells evade the immune system is by expressing a protein called programmed death-ligand (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 obtained approval in January 2018 for the treatment of unresectable advanced or recurrent NSCLC, and obtained approval in December 2018 for the treatment of previously untreated unresectable advanced or recurrent non-squamous NSCLC in combination with Avastin and chemotherapy. In December 2018, Chugai also filed applications for approval of Tecentriq as a treatment for breast cancer and small cell lung cancer (SCLC). In addition, Chugai is participating in phase III multinational studies for the potential treatment of NSCLC (adjuvant), urothelial carcinoma, muscle invasive urothelial carcinoma (adjuvant), renal cell carcinoma, renal cell carcinoma (adjuvant), early breast cancer, ovarian cancer, prostate cancer, hepatocellular carcinoma, and head and neck carcinoma (adjuvant).

Review of 2018 Performance

Sales of Tecentriq were ¥9.1 billion, substantially higher than expected. Uptake was strong because in its position in second-line treatment and later for NSCLC, it can be prescribed regardless of PD-L1 expression.

Gazyva (GA101/RG7159)

Glycoengineered type II anti-CD20 monoclonal antibody
(Generic name: obinutuzumab)
Launch in Japan: August 2018

Basic Information

Gazyva is a glycoengineered type II monoclonal antibody in-licensed from Roche that, like Rituxan, targets CD20. A study that directly compared its efficacy and safety with Rituxan, currently the most widely used monoclonal antibody, in patients in Japan and overseas (the GALLIUM study) was stopped early for benefit after positive results were reported. Gazyva obtained approval for the treatment of CD20-positive B-cell follicular lymphoma in July 2018, and was launched in August 2018. In November 2012, Chugai entered into an agreement with Nippon Shinyaku Co., Ltd. to co-develop and co-market this agent in Japan.

Review of 2018 Performance

Sales of Gazyva after its launch in August 2018 were ¥0.6 billion.

GC33 (RG7686) Development project

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. 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 has been under way since August 2016, and the study results were presented at the European Society of Medical Oncology (ESMO) 2018 Congress.

ERY974 Development project

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.

RG7596 Development project

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. To demonstrate a cytostatic effect on tumor cells, a phase III multinational study for the treatment of previously untreated diffuse large B-cell lymphoma (DLBCL) started in November 2017, and a phase II clinical study for the treatment of relapsed or refractory DLBCL started in Japan in October 2018.

RG7440 Development project

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 Development project

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. Multiple investigator-initiated clinical studies (as monotherapy and in combination therapy) are ongoing in the United Kingdom and the United States, and study results were announced at the 2017 Annual Meeting of the American Society of Clinical Oncology (ASCO). A presentation of summary results is planned at the International Congress on Targeted Anticancer Therapies (TAT) in 2019.

RG7421 Development project

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) Development project

Anti-CEA/CD3 bispecific antibody
(Generic name: cibisatamab)

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 started a phase I clinical study of CEA-TCB for the treatment of solid tumors in Japan in January 2018.

CD20-TDB (RG7828) Development project

Anti-CD20/CD3 bispecific antibody
(Generic name: mosunetuzumab)

CD20-TDB is a bispecific antibody in-licensed from Roche. Similar to CEA-TCB, it is expected to activate T cells and attack tumor cells by cross-linking CD3 on T cells to CD20 on B cells. Chugai started a phase I clinical study for the treatment of hematologic tumors in Japan in March 2018.

RG6268 Development project

ROS1/TRK inhibitor
(Generic name: entrectinib)

RG6268, in-licensed from Roche, is an orally bioavailable CNS-active tyrosine kinase inhibitor that potently and selectively inhibits the ROS1 and TRK family, and also acts on brain metastases. Targeting *NTRK* fusion gene-positive solid tumors, RG6268 has been granted breakthrough therapy designation in the United States, PRIorityMEdicines (PRIME) designation in the EU, and Sakigake designation in Japan. Chugai filed an application for approval for the treatment of *NTRK* fusion gene-positive solid tumors in December 2018.

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 bedridden and can also increase mortality risk. About 13 million people in Japan suffer from osteoporosis. However, the treatment rate stands at around only 20 percent of the estimated number of sufferers because there are usually no 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.

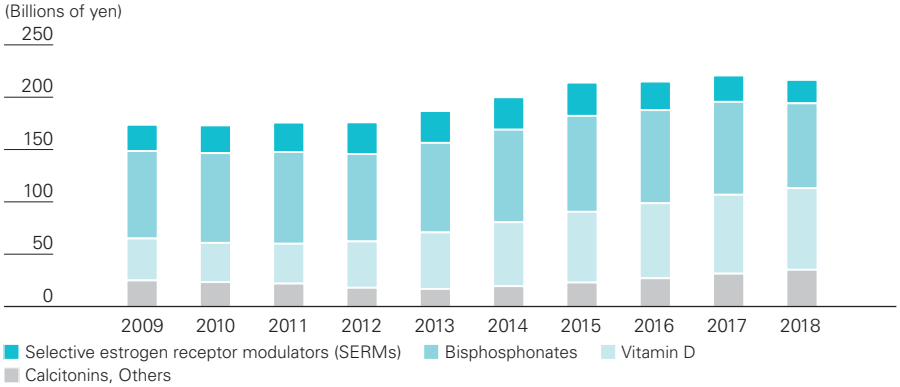
Treatment Methods

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

Regulatory Trends

National prevention and treatment guidelines for osteoporosis 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 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 2009-2018
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The scope of the market is defined by Chugai.

Recently, an osteoporosis liaison service (OLS) initiated by the Japan Osteoporosis Society was introduced for the purpose of preventing osteoporosis and inhibiting bone fractures by coordinating the efforts of various healthcare professionals, including doctors, nurses, pharmacists and physical therapists. Medical staff involved in liaison and possessing extensive knowledge related to osteoporosis are called osteoporosis managers. This education program has been ongoing since 2012, and more than 2,400 osteoporosis managers were active as of April 2018.

Edirol

Active vitamin D_3 derivative
(Generic name: eldecalcitol)
Launch in Japan: April 2011

Basic Information

Edirol, a vitamin D_3 preparation born out of Chugai's many years of research in vitamin D, is an agent that improves bone metabolism in addition to calcium metabolism. Chugai started sales of Edirol in April 2011 as the successor drug to Alfarol for the indication of osteoporosis. 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 2018 Performance

Sales of Edirol increased ¥3.3 billion, or 11.1 percent, to ¥32.9 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 broadened. As a result, its use in combination with other drugs is expanding, 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)
Launch in Japan: August 2013

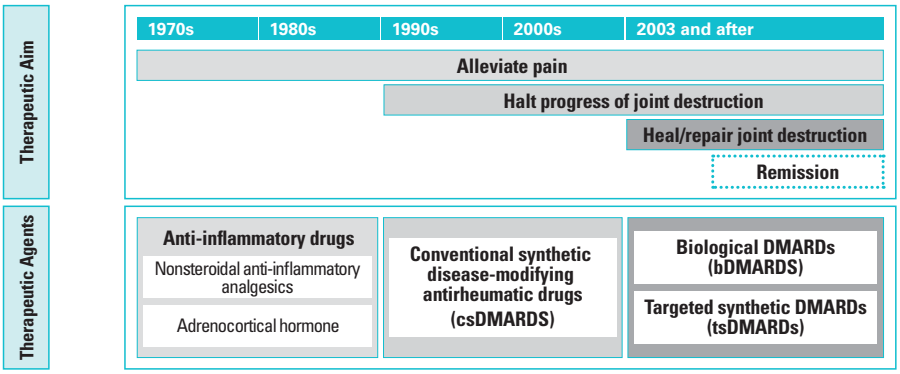
Basic Information

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. Bonviva IV Injection can be given as a rapid intravenous injection once a month, and thus may significantly reduce the burden on patients. It is also expected to benefit patients who have difficulty taking oral formulations or who tend to forget to take their medication. In addition, Bonviva Tablet, a once–monthly oral formulation, demonstrated non-inferiority to Bonviva IV Injection in a phase III clinical trial, and Chugai 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 2018 Performance

Sales of Bonviva increased ¥0.7 billion, or 8.0 percent, to ¥9.4 billion. The intravenous injection and oral formulations have the same high level of efficacy, and the ability to select the formulation according to the patient's condition has helped to differentiate Bonviva from other bisphosphonates.

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

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. There are currently an estimated 700,000 to 800,000 patients in Japan suffering from RA, of whom some 330,000 are currently receiving drug treatment. The aging of the patient population has also become a problem in recent years. On the other hand, there are only about 8,000 patients in Japan with juvenile idiopathic arthritis (JIA), a form of RA suffered by children under 16 years of age.

Treatment Methods and Market Conditions

In drug therapy for RA, the introduction of biologics has made high remission rates a realistic treatment goal. 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 $56.7 billion* by 2024. The market continues to change, and the range of treatment options for RA is expanding. In 2013, biological DMARDs, a new class of oral drugs, were launched in the United States and Japan, and in 2014, a biosimilar was launched in Japan after previously being launched in Europe.

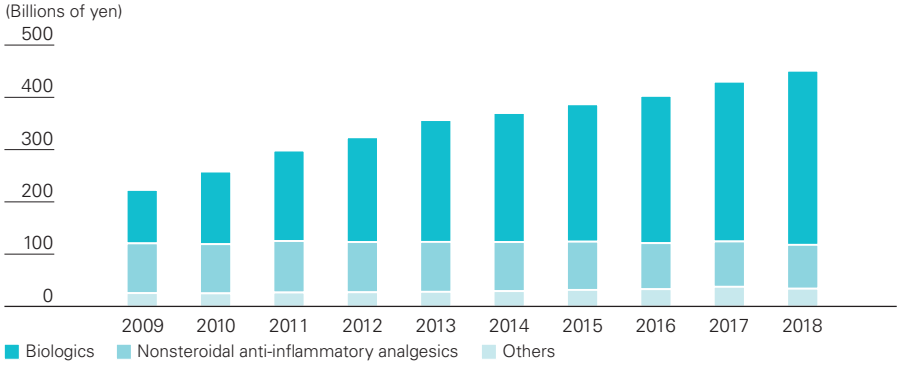
Systemic juvenile idiopathic arthritis (sJIA) accounts for 30 to 40 percent of all JIA cases, but steroids, the main treatment for sJIA, can cause growth impairment and other adverse reactions. Consequently, the approval and launch of Actemra in April 2008 provided a significant advance in therapy.

* Source: Evaluate Pharma®

Regulatory Trends

In November 2018, MHLW released an update of the Report of the Rheumatism and Allergy Countermeasure Committee, which was previously issued in 2005 and 2011. To maximize long-term quality of life of RA patients through appropriate treatment that controls disease activity, and to provide comprehensive support in daily life at workplaces and schools, and for life events such as pregnancy and childbirth, the report calls for (1) enhancement of medical service systems; (2) improvement of the patient environment, including consultation opportunities and access to information, and (3) promotion of research and development and other activities. 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

Rheumatoid Arthritis Market in Japan



Source: JPM 2009-2018
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The scope of the market is defined by Chugai.

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.

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 are reduced head and cerebral blood flow-related conditions, primarily 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)
Launch in Japan: June 2005

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 2016 as a treatment for giant cell arteritis. In Japan, it became possible in June 2017 to reduce the dose interval of Actemra from two weeks to one week in patients with an inadequate response to use of the subcutaneous formulation for RA. Actemra obtained approval in Japan for the additional indications of Takayasu arteritis and giant cell arteritis in August 2017.

Review of 2018 Performance

Sales of Actemra in Japan increased ¥5.1 billion, or 15.4 percent, to ¥38.2 billion. The increase continued to be driven by the strong growth of the subcutaneous formulation after Chugai obtained approval for an additional dosage and administration with a shorter dose interval of the subcutaneous formulation for RA, and for the additional indications of Takayasu arteritis and giant cell arteritis. Sales of the subcutaneous formulation accounted for more than 50 percent of the total.

Sales of Actemra outside Japan (including exports to Roche) increased ¥19.3 billion, or 32.5 percent, to ¥78.7 billion. Roche's global sales increased 12.0 percent year on year with steady market penetration, including solid uptake of the subcutaneous formulation in all regions.

In development, Actemra obtained approval for the additional indication of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome in Europe in August 2018. In the United States, an autoinjector obtained approval as an additional formulation for the treatment of RA, giant cell arteritis, and sJIA and pJIA in November 2018.

RG7845 Development project

BTK Inhibitor
(Generic name: fenebrutinib)

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.

Osteoarthritis

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. The prevalence of this disease increases with age. Knee osteoarthritis is particularly common among women, and is reported to affect an estimated 30 percent of women in their fifties, 57 percent in their sixties, and 80 percent at 80 years of age or older.

Academic societies 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.

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.

Suvenyl

Agent for joint function improvement
(Generic name: sodium hyaluronate)
Launch in Japan: August 2000

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 2018 Performance

Sales of Suvenyl decreased ¥1.0 billion, or 11.4 percent, to ¥7.8 billion, due to the impact from NHI drug price revisions and from competing products. In China, phase III clinical studies are under way for the potential treatment of knee osteoarthritis and shoulder periarthritis.

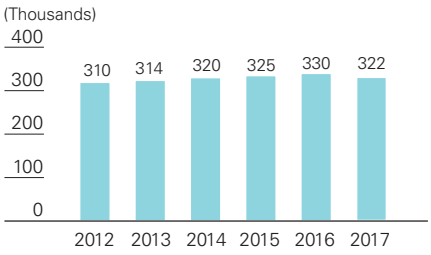
Renal Diseases

Renal Anemia

Complications of Renal Dysfunction

In dialysis patients and end-stage chronic kidney disease (CKD) patients, a key issue is treating the various complications of advanced renal dysfunction, such as renal anemia, secondary hyperparathyroidism, and abnormal calcium and phosphorus metabolism. 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 CKD patients. Renal anemia is associated with reduced quality of life, and is also a factor in the progress of organ damage, including decreased cardiac function.

Number of Dialysis Patients in Japan



Source: Overview of Regular Dialysis Treatment in Japan (as of December 31, 2017) by Statistical Survey Committee, The Japanese Society for Dialysis Therapy

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 (2018) issued by the Japanese Society of Nephrology.

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. ESAs are currently used by approximately 80 percent of dialysis patients as well as by some pre-dialysis CKD 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 hemodialysis (artificial kidney). The integrated fee points are reviewed with each revision of medical fees, and were reduced in 2018, which has led to intensified price competition for ESAs in the dialysis market.

Mircera

Long-acting erythropoiesis-stimulating agent
(Generic name: epoetin beta pegol)
Launch in Japan: July 2011

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 is expected to reduce the burden of hospital visits on patients with pre-dialysis CKD and 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 2018 Performance

Sales of Mircera decreased ¥0.8 billion, or 3.3 percent, to ¥23.1 billion. While the use of Mircera in pre-dialysis CKD patients expanded, sales decreased because of an NHI drug price revision as well as intensified price competition in the dialysis market after integrated fee points for artificial kidney (hemodialysis) were reduced due to the revision of medical fees.

Others

Oxarol

Agent for secondary hyperparathyroidism
(Generic name: maxacalcitol)
Launch in Japan: September 2000

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 conditions such as impaired vitamin D activation associated with renal dysfunction, by acting directly with high concentration on the parathyroid gland to control parathyroid hormone synthesis and secretion, and by acting to improve bone metabolism. With its short serum half-life, Oxarol shows efficacy and enables treatment in patients who previously could not be treated adequately with oral vitamin D_3 derivatives due to the onset of hypercalcemia.

Review of 2018 Performance

Sales of Oxarol decreased ¥0.9 billion, or 11.1 percent, to ¥7.3 billion due to the impact of the NHI drug price revision, despite slower uptake of a generic product.

EOS789 Development project

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 Development project

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 reduce cognitive deterioration by removing amyloid beta in the brain. Phase III multinational studies of RG1450 as a potential treatment for AD began in June and July 2018.

RG7412 Development project

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 reduce cognitive deterioration by removing amyloid beta in the brain. A phase III multinational study of RG7412 as a potential treatment for AD is under way.

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMOSD) 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 (in some cases progressing to blindness) and impairment of motor function and sensation. In some cases, the disease results in death. However, as there are no approved treatments available, NMOSD 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. Formerly, the diagnostic criteria of neuromyelitis optica (NMO) accompanied by optic neuritis and myelitis, and NMOSD accompanied by either optic neuritis or myelitis were proposed. Recently, however, it was proposed to reorganize and unify the definitions of both disorders under the term NMOSD. This term is now widely used to refer to a broader spectrum of disease.

SA237 Development project

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 with a longer duration of action. Chugai created SA237 by applying its novel antibody technology (Recycling Antibody technology) that enables a single antibody molecule to block the target antigen repeatedly. As a result, a prolonged serum half-life has been demonstrated in clinical trials, and it is expected that a lower dosing frequency will be possible. Because IL-6 promotes the production of the anti-AQP4 antibodies that cause NMOSD, this drug is expected to improve (reduce recurrence of) the symptoms of these diseases as it inhibits the production of those antibodies by blocking the IL-6 signal. Two Chugai-sponsored phase III multinational studies in NMO and NMOSD patients achieved their primary endpoints. 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. SA237 was granted breakthrough therapy designation by the FDA in December 2018 for the treatment of NMO and NMOSD.

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. 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. Currently, steroids are 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 noninvasive positive-pressure ventilation.

RG6206 Development project

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 study is under way.

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 Development project

SMN2 splicing modifier
(Generic name: risdiplam)

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 II/III multinational study is under way. RG7916 was granted PRIME designation by the European Medicines Agency (EMA) in December 2018.

Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disease characterized by aggregation of α-synuclein in the central nervous system and peripheral nervous system. A wide range of motor symptoms (tremor, muscle rigidity, akinesia, impairment of postural reflexes, etc.) and non-motor symptoms (sleep disorders, autonomic dysfunction, cognitive and mental disorders, etc.) occur. The estimated number of patients in Japan is 150,000. A progressive disease seen mainly in people age 50 or older, it can lead to becoming bedridden as the condition worsens.

RG7935 Development project

Anti-α-synuclein monoclonal antibody
(Generic name: prasinezumab)

RG7935 inhibits the spread of synuclein and the expansion of nerve cell death by removing neurotoxic α-synuclein aggregations with an antibody, and is expected to reduce and delay progression of the disease. A phase I clinical trial began in February 2018.

Others

GYM329/RG6237 Development project

GYM329, created by Chugai, is a next-generation antibody that applies Chugai's proprietary antibody technologies, including its recycling antibody and sweeping antibody technologies. A phase I clinical trial of GYM329 for the potential treatment of neuromuscular disease began in October 2018. Chugai out-licensed GYM329 to Roche at an early stage before the start of clinical testing in order to accelerate global development by taking advantage of Roche's experience and expertise.

RG7906 Development project

RG7906 is a small molecule drug in development for the potential treatment of psychiatric disorders. A phase I clinical trial began in January 2019.

Other Diseases

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 of hemophilia A is centered on replacement therapy to supplement factor VIII. 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)
Launch in Japan: May 2018

Hemlibra is an anti-factor IXa/X bispecific antibody that employs Chugai's innovative antibody engineering technologies. Like factor VIII, which is low or missing in hemophilia A, Hemlibra simultaneously binds to factor IXa and factor X, stimulating the activation of factor X by activated factor IX and promoting normal blood coagulation for hemostasis. Unaffected by inhibitors, Hemlibra can prevent

bleeding with once weekly (or less-frequent) subcutaneous injections, and is promising as a drug that can potentially change the existing system of treatment. Another key feature is that Chugai's proprietary technology ART-Ig can be applied to Hemlibra, enabling industrial production of bispecific antibodies.

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, and in April 2018 for its potential to prevent bleeding in patients without inhibitors. 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. In Japan, it obtained approval in March 2018 and was launched in May 2018. It also obtained approval in Taiwan in December 2018.

Applications were filed in the United States, Europe and Japan in April 2018, and in Taiwan in January 2019, for routine prophylaxis of bleeding episodes, as well as for additional dosage and administration as a biweekly or four-weekly treatment, for people with hemophilia A without inhibitors. In the United States, Hemlibra was granted priority review status in June 2018, and in October 2018, it obtained approval for prophylactic treatment by subcutaneous administration once weekly, every two weeks, or every four weeks in adults or children with hemophilia A without inhibitors, as well as additional dosing options of every two weeks or every four weeks in adults and children with hemophilia A with inhibitors. Hemlibra also obtained approval in Japan in December 2018, and received an approval recommendation from the EU Committee for Medicinal Products for Human Use (CHMP) in February 2019.

Review of 2018 Performance

Hemlibra was launched in Japan for treatment of patients with inhibitors in May 2018, and sales were ¥3.0 billion. With more cases than expected in which people struggled to control bleeding, the launch was smooth as switches to Hemlibra took place early on, mainly in pediatric patients.

Influenza

Influenza is an acute infectious disease characterized by the rapid onset of high fever (38 degrees centigrade or higher) 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.

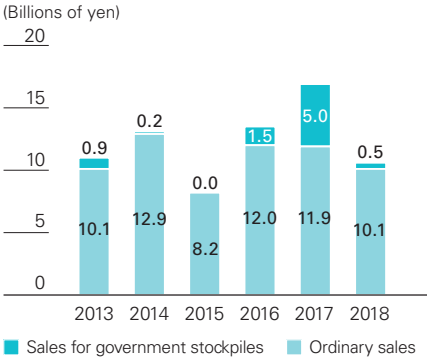
Tamiflu

Anti-influenza agent
(Generic name: oseltamivir phosphate)
Launch in Japan: February 2001

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. From March 2007, restrictions on the use of Tamiflu in teenage patients with seasonal influenza were 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. In May 2018, the Subcommittee on Drug Safety of the Ministry of Health, Labour and Welfare confirmed that abnormal behavior occurs regardless of whether anti-influenza drugs have been given, and in July 2018, the same subcommittee decided that the restrictions should be removed. Accordingly, the package insert was revised and restrictions on the use of Tamiflu in teenage patients were removed in August 2018. 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. In March 2017, Chugai obtained approval for additional dosage and administration of Tamiflu Dry Syrup for neonates and infants younger than 12 months.

Tamiflu Sales



Review of 2018 Performance

Sales of Tamiflu decreased ¥6.2 billion, or 36.7 percent, to ¥10.7 billion. Ordinary sales were ¥10.1 billion, while sales for government stockpiles were ¥0.5 billion. Chugai continued to highlight the drug's efficacy and the benefits of its unique dry syrup formulation.

Others

CellCept

Immunosuppressant
(Generic name: mycophenolate mofetil)
Launch in Japan: November 1999

Sales of CellCept increased ¥0.1 billion, or 1.1 percent, to ¥9.0 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.

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 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 Development project

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 and skin inflammation in atopic dermatitis by blocking IL-31, a proinflammatory cytokine, from binding to its receptor.

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

Paroxysmal nocturnal hemoglobinuria (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. It is a progressive and life-threatening disease in which 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. An estimated 430 patients suffer from PNH in Japan, and the disease reportedly affects approximately 5,000 people globally. Although this number is small, PNH 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/RG6107 Development project

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.

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 Development project

Anti-VEGF/Ang-2 bispecific antibody
(Generic name: faricimab)

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 2017, and a phase III multinational study for the potential treatment of DME began in September 2018.

Endometriosis

Affecting one out of 10 women in their twenties to forties, endometriosis is the repeated proliferation and shedding of endometrial tissue outside the uterus, accompanied by dysmenorrhea and chronic lower abdominal pain, and is a cause of infertility. The disease can interfere with daily life, including absences from work or school, as sufferers find it difficult to do more than lie still when symptoms are severe. The only existing medications are hormonal agents. Moreover, if the pain cannot be controlled by drugs, the only treatment is surgical removal, and many patients experience a recurrence years after surgery, making this a disease with a high level of unmet medical need.

AMY109 Development project

AMY109 is the third therapeutic antibody to apply the recycling antibody technology created by Chugai. Its approach differs from hormone therapy, which is the standard treatment for endometriosis, and its anti-inflammatory action is expected to provide new value to patients. A phase I clinical study started in February 2018.