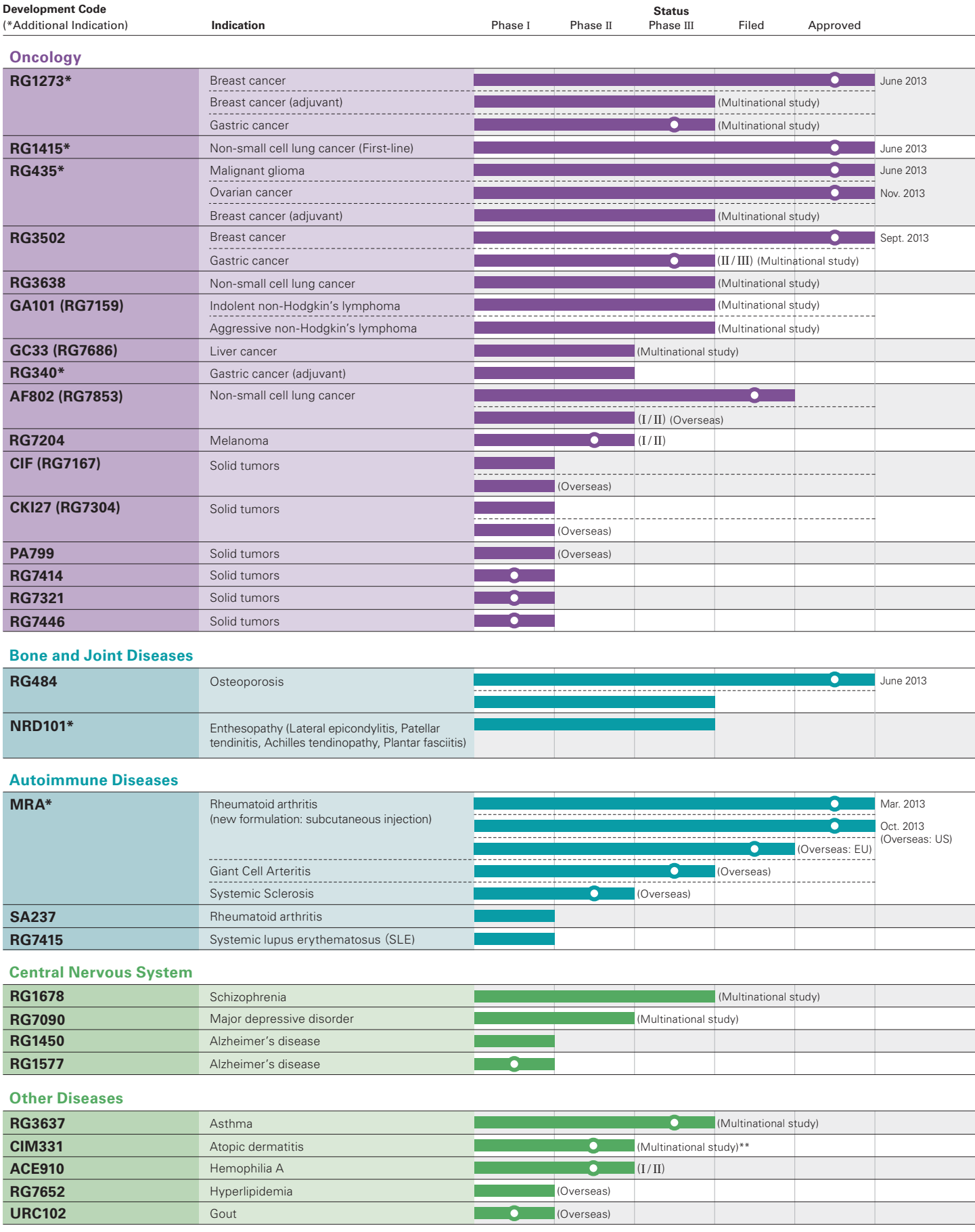
# Data Section

**This section is intended to give readers a deeper understanding of Chugai's innovations and the value we want to create. In addition to an overview of Chugai's development pipeline and basic information, this section includes general information on topics such as pharmaceutical industry and healthcare trends and the newest treatments.**

# Development Pipeline (As of January 30, 2014)




Designates change in status in 2013 and thereafter

** Multinational study managed by Chugai Pharmaceutical

| Generic Name / Product Name | Origin (Collaborator) | Mode of Action |
|---|---|---|
| pertuzumab / Perjeta<br>(Overseas name: Perjeta) | Roche | HER dimerization inhibitory<br>humanized monoclonal antibody (Injection) |
| erlotinib / Tarceva (Overseas name: Tarceva) | Roche / OSI | EGFR tyrosine kinase inhibitor (Oral) |
| bevacizumab / Avastin<br>(Overseas name: Avastin) | Roche | Anti-VEGF<br>(Vascular Endothelial Growth Factor)<br>humanized monoclonal antibody (Injection) |
| trastuzumab emtansine / Kadcyla<br>(Overseas name: Kadcyla) | Roche | Anti-HER2 antibody-drug conjugate (T-DM1) (Injection) |
| onartuzumab / Product name undetermined | Roche | Anti-MET humanized monoclonal antibody (MetMAb) (Injection) |
| obinutuzumab / Product name undetermined<br>(Overseas name: Gazyva) | Roche (Nippon Shinyaku) | Glycoengineered type II anti-CD20<br>monoclonal antibody (Injection) |
| — | In-house (Roche) | Anti-Glypican-3 humanized monoclonal antibody (Injection) |
| capecitabine / Xeloda (Overseas name: Xeloda) | Roche (Yakult Honsha) | Antimetabolite, 5-FU derivative (Oral) |
| alectinib / Product name undetermined | In-house (Roche) | ALK inhibitor (Oral) |
| vemurafenib / Product name undetermined (Overseas name: Zelboraf) | Roche | BRAF inhibitor (Oral) |
| — | In-house (Roche) | MEK inhibitor (Oral) |
| — | In-house (Roche) | Raf and MEK dual inhibitor (Oral) |
| — | In-house | PI3K class I inhibitor (Oral) |
| parsatuzumab / Product name undetermined | Roche | Anti-EGFL7 humanized monoclonal antibody (Injection) |
| pictilisib / Product name undetermined | Roche | PI3K inhibitor (Oral) |
| — | Roche | Engineered anti-PDL1 monoclonal antibody (Injection) |
| ibandronate sodium hydrate / Bonviva<br>(Overseas name: Boniva (US), Bonviva (EU)) | Roche (Taisho Pharmaceutical) | Bisphosphonate (Injection)<br>Bisphosphonate (Oral) |
| sodium hyaluronate / Suvenyl | In-house | Sodium hyaluronate (Injection) |
| tocilizumab / Actemra<br>(Overseas name: Actemra (US), RoActemra (EU)) | In-house (Roche) | Anti-human IL-6 receptor<br>humanized monoclonal antibody (Injection) |
| — | In-house | Anti-IL-6 receptor humanized monoclonal antibody (Injection) |
| rontalizumab / Product name undetermined | Roche | Anti-interferon alpha humanized monoclonal antibody (Injection) |
| bitopertin / Product name undetermined | Roche | Glycine reuptake inhibitor (Oral) |
| — | Roche | mGluR5 antagonist (Oral) |
| gantenerumab / Product name undetermined | Roche / MorphoSys | Anti-amyloid-beta human monoclonal antibody (Injection) |
| — | Roche | MAO-B inhibitor (Oral) |
| lebrikizumab / Product name undetermined | Roche | Anti-IL-13 humanized monoclonal antibody (Injection) |
| — | In-house | Anti-IL-31 receptor humanized monoclonal antibody (Injection) |
| — | In-house | Anti-factor IXa x anti-factor X humanized bispecific antibody (Injection) |
| — | Roche | Anti-PCSK9 human monoclonal antibody (Injection) |
| — | In-house / JW Pharmaceutical | URAT1 inhibitor (Oral) |

# 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 3 to 4 percent going forward. In the year ended March 2012, national medical expenses totaled ¥38,585.0 billion, a ¥1,164.8 billion or 3.1 percent increase from the previous year. The rapid aging of Japan's society presents the serious challenge of efficiently managing the increase in medical expenses for the elderly.

### Promotion of the Use of Generics

The Japanese government is promoting the use of generics[1] 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. The roadmap sets the goal of raising the volume market share of generics from 46.9 percent as of September 2013 to more than 60 percent by the end of March 2018.

1. Generic drugs, which are approved after the expiry of the patents for original drugs with the same active ingredients and efficacy

### 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 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 the year ended March 2014, drug reimbursement prices declined by 0.58 percent overall on a medical expense basis, or 2.65 percent on a reimbursement price basis.

**NHI Drug Price Revision Rate (%)**

| | 2008 | 2010 | 2012 | 2014* |
|---|---|---|---|---|
| Industry Average | (5.2) | (6.5) | (6.25) | (2.65) |
| Chugai | (7.2) | (6.8) | (6.0) | 0.8 |

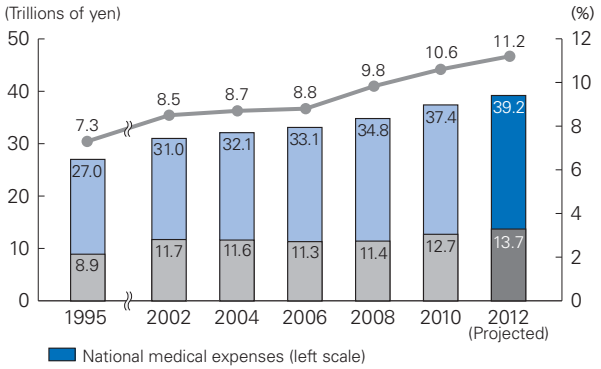
Source: Chugai data
* Includes provision for increase in consumption tax

### 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[2] problem. In this scheme, at the time of the NHI drug price revisions a premium equal to the weighted-average percentage price difference of all listed drugs minus 2 percent, multiplied by 0.8, is added to the price of 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.[3]

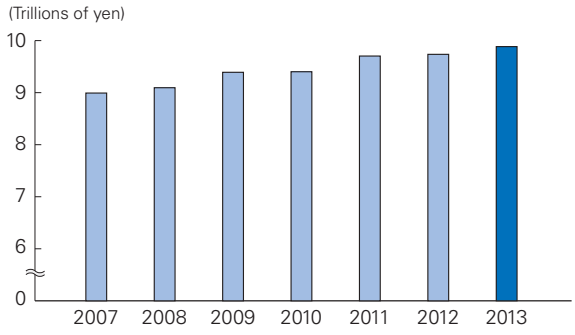
This premium pricing for new drugs was continued on a trial basis in the NHI drug pricing

**Trends in National and Elderly Medical Expenses**




Source: Overview of National Medical Expense by Ministry of Health, Labour and Welfare
Note: National income is based on the actual results of the System of National Accounts (announced in December 2012 by the Cabinet office).

**Prescription Drug Market**



system reforms of fiscal 2012 and fiscal 2014. The fiscal 2014 reforms, however, added the condition that only companies that 1) conduct research and development of unapproved or off-label drugs as requested by a panel of MHLW, or 2) conduct research and development of drugs that clearly contribute to improving treatment quality[4] will be eligible to receive premium pricing for their products. In the year ended March 2014, 397 compounds and 758 products received premium pricing.

2. The inability of Japanese patients to gain access to global standard or most advanced treatments because the drugs are not developed in Japan
3. The percentage price difference between the current market price and the reimbursement price of the original drug must not exceed the weighted-average percentage price difference of all listed drugs.
4. Drugs for pediatric use, orphan drugs and drugs for diseases for which no currently available treatments are adequate (e.g., drugs for intractable diseases or unmet medical need)

### 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. MHLW has also reinforced several functions of the Pharmaceutical and Medical Devices Agency, an independent administrative institution responsible for reviewing drugs and medical devices for approval. Measures have included increasing the number of staff involved in the reviewing process, introducing a project management system using a dedicated staff, providing guidelines on multinational clinical studies, clarifying reviewing criteria and offering an improved consultancy function. As a result, the median total review time for new drugs in the year ended March 2013 was 10.3 months.

**Response to Requests from the MHLW Review Committee on Unapproved Drugs and Indications with High Medical Needs** (As of January 30, 2014)

| Development request | Product | Indication | Development status |
|---|---|---|---|
| First development request | Xeloda | Advanced or recurrent gastric cancer | Approved in Feb. 2011 |
| | Tarceva | Advanced or recurrent pancreatic cancer | Approved in Jul. 2011 |
| | Avastin | Advanced or recurrent breast cancer | Approved in Sep. 2011 |
| | Herceptin | Q3W dosage metastatic breast cancer overexpressing HER2 | Approved in Nov. 2011 |
| | | Neoadjuvant breast cancer overexpressing HER2 | |
| | CellCept | Pediatric renal transplant | Approved in Sep. 2011 |
| | Kytril | Gastrointestinal symptoms associated with radiotherapy | Approved in Dec. 2011 |
| | Avastin | Ovarian cancer | Approved in Nov. 2013 |
| | Pulmozyme | Improvement of pulmonary function in patients with cystic fibrosis | Approved in Mar. 2012 |
| | Bactramin | Treatment and prevention of pneumocystis pneumonia | Approved in Aug. 2012 |
| Second development request | Avastin | Recurrent glioblastoma | Approved in Jun. 2013 (Malignant glioma) |
| | Herceptin | Q1W dosage postoperative adjuvant breast cancer overexpressing HER2 | Approved in Jun. 2013 |

# Oncology

## Overview of Diseases and Treatment Methods

### Leading Cause of Death in Japan

Cancer has been the single most common cause of death in Japan since 1981. In 2012, 360,963 people died of cancer, accounting for 28.7 percent of all deaths in that year and the highest figure recorded since government surveys began in 1899.

### 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

optimal treatment in accordance with their wishes ("the availability of optimal treatment" 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.

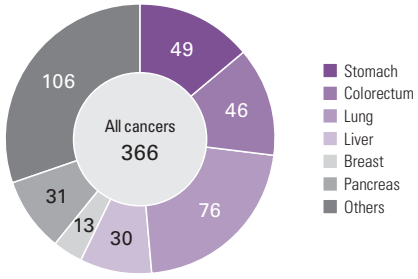
## Changes in Treatment Methods

Cancer treatment is increasingly being based on a multimodal approach that combines surgery, radiation therapy and anticancer agents. In particular, the field of anticancer agents is evolving, and highly innovative medications such as molecular targeted drugs have been introduced. This has brought about a dramatic improvement in treatment outcomes in colorectal, lung and breast cancer, hematological malignancy and other forms of cancer.

It is recognized that the safety profiles of these drugs differ from those of conventional anticancer agents. Consequently, there is a need for cancer drug therapy specialists with a thorough knowledge of drug modes of action, pharmacokinetics and drug interactions. Furthermore, whereas many earlier drug therapies were administered in an inpatient setting, there has been an increase in drug therapies that can be administered on an outpatient basis, which allows patients to maintain normal lifestyles as much as possible during treatment. To ensure the medical safety of drug therapy for these patients, various medical staff in addition to oncologists must contribute their respective expertise. As a result, multidisciplinary team care is becoming increasingly important.

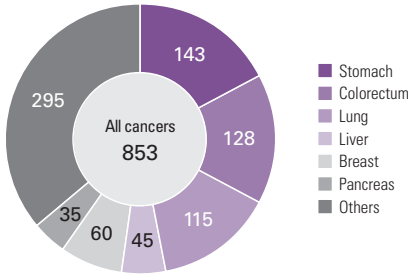
**Cancer Mortality** (Estimates for 2015)

(Thousands of cases)




**Cancer Incidence** (Estimates for 2015)

(Thousands of cases)

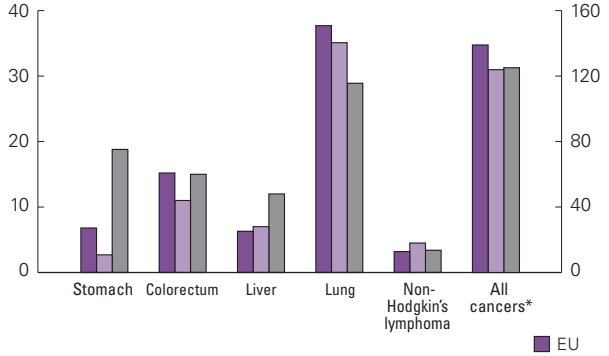



Source: Cancer White Paper-Incidence/Death/Prognosis-2012 (Shinoharashinsha Publishers Inc.)

**International Comparison of Cancer Mortality Rates** (2012)

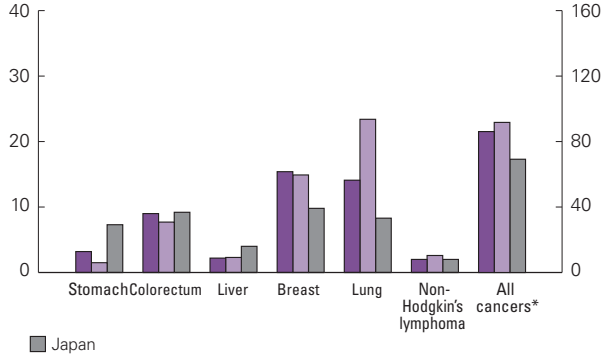
**Male**

Age-standardized rate per 100,000 population (persons)
(By cancer type) (All cancers)




**Female**

Age-standardized rate per 100,000 population (persons)
(By cancer type) (All cancers)





* 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 28/02/2014.

## Overview of Products and Development Projects

### Avastin

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 microenvironment in the cancer cells. Its primary modes of action are thought to be regression of tumor vessels, inhibition of tumor angiogenesis and improvement of VEGF-induced vascular permeability. In Japan, Avastin was launched in 2007 for the treatment of unresectable, advanced or recurrent colon and rectal cancer. Chugai obtained regulatory approval for the additional indications of advanced or recurrent non-squamous non-small cell lung cancer in 2009, and inoperable or recurrent breast cancer in 2011. Chugai also obtained approval for the additional indications of malignant glioma and ovarian cancer in June and November 2013, respectively.

### Rituxan

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. Outside Japan, Rituxan is sold under the brand name MabThera/Rituxan by the Roche Group.

### Herceptin

Herceptin is a humanized monoclonal antibody that targets human epidermal growth factor receptor type 2 (HER2), which contributes to tumor cell growth. Overexpression of HER2 is found in about 20 percent of breast cancers, which are diagnosed as HER2-positive. HER2-positive breast cancer progresses rapidly, and has historically been associated with a poor prognosis. However, treatment outcomes have improved significantly with the emergence of Herceptin and other medicines targeting HER2. In 2011, Herceptin obtained regulatory 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.

### Perjeta

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 obtained regulatory approval of Perjeta for the additional indication of HER2-positive inoperable or recurrent breast cancer in June 2013, and launched it in September 2013. Phase III multinational studies began in April 2012 for the indication of postoperative adjuvant chemotherapy in HER2-positive breast cancer and in July 2013 for the indication of HER2-positive gastric cancer.

### Kadcyla

Kadcyla is an antibody-drug conjugate combining the anti-HER2 humanized monoclonal antibody trastuzumab (active ingredient of Herceptin) with the potent chemotherapeutic agent DM1. Chugai filed an application for regulatory approval for the treatment of HER2-positive inoperable or recurrent breast cancer in January 2013 and obtained approval in September 2013 after priority review. In addition, a phase II/III multinational study for this drug as a potential treatment for HER2-positive metastatic gastric cancer started in September 2012.

### Xeloda

Xeloda is a 5-fluorouracil (5-FU) anticancer agent developed at the Kamakura Research Laboratories of the former Nippon Roche. Orally administered Xeloda is absorbed by the body, then gradually metabolized by certain highly active enzymes in the liver and tumor cells, and is eventually converted into active 5-FU within tumor tissue.

In Japan, Xeloda is currently used to treat inoperable or recurrent breast cancer and as a postoperative adjuvant chemotherapy for colon cancer. In addition, Xeloda has obtained regulatory approval for treating patients with advanced or recurrent colorectal cancer and for advanced or recurrent gastric cancer not amenable to curative resection. Phase II clinical trials started in Japan in July 2012 for the additional indication of postoperative adjuvant chemotherapy for gastric cancer (co-development with Yakult Honsha Co., Ltd.).

### Tarceva

Tarceva is an oral targeted small-molecule drug that inhibits the activation of human 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 non-small cell lung cancer 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 non-small cell lung cancer patients in Europe and about 30 percent in Asia test positive for EGFR mutations. In July 2011, Tarceva obtained regulatory approval for the additional indication of pancreatic cancer not amenable to curative resection.

### Neutrogin

Neutrogin is a recombinant human granulocyte colony-stimulating factor (G-CSF) developed 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, which allows the use of more potent chemotherapy, thus helping to improve outcomes. Neutrogin is also essential in hematopoietic cell transplantation, which is performed for illnesses that affect production of normal blood cells, such as leukemia. Overseas, Neutrogin is sold under the name Granocyte.

### RG3638

RG3638 (onartuzumab), a humanized antibody in-licensed from Roche, targets MET, a hepatocyte growth factor (HGF) receptor. A phase III multinational study of RG3638 as a potential treatment for inoperable advanced or recurrent non-small cell lung cancer with high MET expression started in November 2012. Roche announced in March 2014 that an independent data monitoring committee has recommended that this phase III study be stopped due to a lack of clinically meaningful efficacy.

### GA101 (RG7159) (overseas product name: Gazyva)

GA101 (obinutuzumab) is a type II glycoengineered humanized monoclonal antibody in-licensed from Roche. Like Rituxan, GA101 targets CD20. Phase III multinational studies as a potential treatment for aggressive non-Hodgkin's lymphoma and indolent non-Hodgkin's lymphoma are currently under way. In November 2012, Chugai entered into an agreement with Nippon Shinyaku Co., Ltd. to co-develop and co-market this compound in Japan.

### GC33 (RG7686)

GC33, a humanized antibody from Chugai, targets glypican-3, which is specifically expressed in liver cancer. The project involves joint research between Chugai and Tokyo University, as well as clinical proteomics work by PharmaLogicals Research Pte. Ltd., a former subsidiary of Chugai. A phase II multinational study started in March 2012.

### AF802

AF802 (alectinib) is an oral targeted molecular therapy created by Chugai that is being developed for the treatment of anaplastic lymphoma kinase (ALK)-positive unresectable, recurrent/advanced non-small cell lung cancer. It inhibits the activity of EML4-ALK, a recombinant kinase expressed in about 2-5 percent of non-small cell lung cancers. AF802 was designated as an orphan drug in September 2013, and Chugai filed an application for regulatory approval in Japan in October 2013 based on the results of a phase I/II clinical trial in Japan, before phase III clinical trial results were available. Chugai has out-licensed the rights to this compound to Roche in Europe, North America and other markets outside Japan, and is co-developing it with Roche. Phase I/II clinical trials are under way overseas. In June 2013, AF802 was designated as a breakthrough therapy by the U.S. Food and Drug Administration (FDA).

### RG7204 (overseas product name: Zelboraf)

RG7204 (vemurafenib), in-licensed from Roche, is a BRAF inhibitor for the treatment of metastatic melanoma. It is an oral small-molecule drug that selectively inhibits a mutated form of the BRAF protein that is present in about half of melanoma patients. Phase I/II clinical trials started in Japan in September 2012.

### CIF (RG7167)

CIF is a MEK inhibitor from Chugai. Chugai has out-licensed CIF to Roche overseas, and the two companies are co-developing it. Phase I clinical trials are currently under way in Japan and overseas for the potential treatment of solid tumors.

### CKI27 (RG7304)

CKI27 is a Raf and MEK dual inhibitor from Chugai. Chugai has out-licensed CKI27 to Roche overseas, and the two companies are co-developing it. Phase I clinical trials are currently under way in Japan and overseas for the treatment of solid tumors.

### PA799

PA799, a PI3K class I inhibitor, is an oral agent from Chugai. Overseas phase I clinical trials are currently under way for the potential treatment of solid tumors.

### RG7414

RG7414 (parsatuzumab) is an injectable anti-EGFL7 humanized monoclonal antibody in-licensed from Roche. Phase I clinical trials started in Japan in March 2013 for the potential treatment of solid tumors, but Roche discontinued development in October 2013. Development in Japan is currently under consideration.

### RG7321

RG732 (pictilisib) is an oral PI3K inhibitor in-licensed from Roche. Phase I clinical trials started in Japan in June 2013 for the potential treatment of solid tumors.

### RG7446

RG7446 is an engineered anti-PDL1 monoclonal antibody in-licensed from Roche, and is expected to become a treatment for various cancers. 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. RG7446 maintains the immune response of T cells by binding to PD-L1, and is expected to demonstrate efficacy against cancer. Phase I clinical trials started in Japan in September 2013 for the potential treatment of solid tumors.

# 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 everyday 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 risks. It is estimated that over 12 million people suffer from osteoporosis in Japan, including one in every two women age 65 and older. However, the treatment rate stands at around only 30 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

Bone resorption inhibitors, bone formation stimulants and active vitamin $D_3$ derivatives are mainly used in the treatment of osteoporosis. Conventionally, bisphosphonates, calcitonin preparations and selective estrogen receptor modulators (SERMs), which are bone resorption inhibitors, and active vitamin D3 derivatives, which improve bone metabolism, have been the primary drug treatments used. More recently, treatments such as human parathyroid hormone (PTH) therapy and a humanized anti-RANKL antibody have also been approved and are being used.

### Regulatory Trends

National guidelines for osteoporosis treatment were revised in October 2006. Subsequently, notable 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 addition, Edirol and other medicines are now covered by insurance. Revised guidelines issued in December 2011 added preventative and diagnostic items from the standpoint of the importance of early treatment to broaden the overall scope of osteoporosis treatment. Since then, Bonviva and other medicines have been launched and covered by insurance, and updates to the guidelines are under discussion. Revision of management and treatment guidelines for steroid-induced osteoporosis is also under way.

### Overview of Products and Development Projects

#### Alfarol

Alfarol, an active vitamin $D_3$ derivative that stimulates calcium/bone metabolism, is positioned as the base drug for osteoporosis treatment. Alfarol inhibits the decline of bone mass by adjusting calcium and bone metabolism, and therefore is effective in preventing vertebral fractures. The latest treatment guidelines also indicate the drug's effect on prevention of falls, focusing attention on this feature that other osteoporosis treatments do not have.

### Edirol

Edirol (eldecalcitol) is a new 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. 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 the existing $D_3$ derivatives with a statistically significant greater effect in preventing fractures. Edirol received a grade A recommendation in the osteoporosis prevention and treatment guidelines in December 2011, the first for an active vitamin $D_3$ preparation.

### Bonviva

Bonviva is a bisphosphonate in-licensed from Roche that was launched in August 2013. Under the agreement signed in September 2006, Bonviva is being co-developed and co-marketed with Taisho Pharmaceutical Co., Ltd. Bisphosphonates in Japan until then had been drip infusions, but Bonviva is given in a single intravenous injection, as slowly as possible, once a month, which is expected to significantly reduce the burden on patients at the time of administration. Phase III clinical trials for the oral formulation started in Japan in October 2012.

## 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, juvenile idiopathic arthritis (JIA), the form of RA suffered by children below 16 years of age, is associated with growth disorders, and is considered even more difficult to treat than adult forms of the disease, as few treatment options are available.

The most common joint disease is osteoarthritis. Degeneration of the cartilage in the joints and surrounding areas causes joint pain and reduced mobility in daily life. The prevalence of this disease increases with age, and it is thought to occur in 80 percent or more of people 60 years of age or older.

### Treatment Methods and Market Conditions

Conventional RA treatment has been mainly symptomatic, using antirheumatic drugs, anti-inflammatory analgesics and steroids, but biologics (anti-tumor necrosis factor (TNF) agents) targeting proteins involved in the process of inflammation have recently entered the market and expanded the range of treatment choices. 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 reached US$2.78 billion* in 2012, and continues to grow. 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 addition to drip infusions, which were the only formulations previously available, subcutaneous formulations have also been added, and formulations that improve convenience, such as a dosage form that can be injected simply by pushing a button, are increasing. The intravenous and subcutaneous markets each comprise about half of their respective total markets in Japan, while in Europe and the United States, the subcutaneous market is estimated to be larger by a 7:3 ratio.

JIA is a serious and potentially fatal disease. While it is rare in Japan, with only a few hundred patients, effective treatments were limited. Steroid drugs, which had been the only treatment available, can cause growth impairment and other adverse reactions. Accordingly, the approval and launch of Actemra in April 2008 provided a significant step forward in therapy.

The main drug therapies for osteoarthritis include non-steroidal anti-inflammatory analgesics, steroids and hyaluronic acid preparations. However, as the joint fluid in osteoarthritis patients is known to have reduced hyaluronic acid content (density and molecular weight), intraarticular administration of hyaluronic acid preparations is used as a treatment in the early and middle-stages.



### 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 rheumatism 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 the European Union, revised treatment recommendations in 2013 added Actemra and Orencia to the biologic drugs recommended in first-line therapy, which was previously limited to anti-TNF agents.

The 2000-2010 period was designated as the Global Bone and Joint Decade, and academic societies and other players have been aggressively promoting research, diagnosis and treatment of osteoarthritis. In 2010, it was decided to extend these activities for ten more years through 2020.

### Overview of Products and Development Projects

#### Actemra

Actemra, the first therapeutic antibody created in Japan, blocks the activity of interleukin-6 (IL-6), a type of cytokine. It was first launched in Japan in 2005 as a treatment for Castleman's disease. In April 2008, we obtained regulatory approval in Japan for the additional indications of RA, polyarticular-course juvenile idiopathic arthritis (pJIA) and systemic-onset juvenile idiopathic arthritis (sJIA). The requirement for post-marketing all-case registration surveillance as a condition of Actemra's approval in Japan was lifted in August 2010 for RA and pJIA, making Actemra an important option in treatment as a biological product. In May 2013, Chugai launched a new subcutaneous formulation that is expected to improve 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 the European Union, where it is known as RoActemra, sales of the drug started for the treatment of RA in 2009. Chugai's marketing subsidiary co-promotes RoActemra with Roche in the UK, France and Germany. In the United States, Actemra obtained regulatory approval in January 2010 for the treatment of adult patients with moderately to severely 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 was launched in the United States in November 2013 and is scheduled for approval and launch in the European Union in 2014.

Actemra obtained approval for the additional indication of treatment of sJIA in the United States in April 2011 and the European Union in August 2011.

#### Suvenyl

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. Because its physical and chemical properties are close to that of hyaluronic acid found in the body, the superior performance of Suvenyl over low molecular weight hyaluronic acid has been recognized. Phase III clinical trials are currently under way in Japan for the additional indication of enthesopathy.

#### SA237

SA237, a compound from 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. This sustained efficacy is expected to lead to greater convenience for patients by allowing them to take smaller, less frequent doses. A phase I clinical trial is under way in Japan.

## Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder in which the immune system attacks its own body due to an immune abnormality, causing various types of inflammation throughout the body. In Japan, 60,122 people had received certificates issued for specific disease treatment as of 2012. The actual number of patients is estimated to be even higher, with a 9:1 female-to-male ratio. Generalized symptoms include fever and fatigue, as well as skin and joint conditions and organ dysfunction. Steroids and immunosuppressants are used in current therapies.

### Overview of Development Project

#### RG7415

RG7415 (rontalizumab) is an anti-interferon alpha humanized monoclonal antibody in-licensed from Roche. It binds to and neutralizes the 12 human interferon alpha subtypes, and thus is expected to inhibit the processes that cause chronic inflammation. Phase I clinical trials of RG7415 as a potential treatment for SLE started in July 2012.

# Renal Diseases

## Renal Anemia

### Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as the continuation for three months or more of "manifestations showing the existence of renal disease, such as positive proteinuria" or "presence of kidney damage (a glomerular filtration rate of less than 60ml/min)." Recently, reports containing ample evidence of the major risk posed by chronic kidney disease in end-stage renal failure and cardiovascular disease have prompted efforts to address this disease around the world. In Japan, too, measures are fully under way to deal with the problem. For example, the Japanese Society of Nephrology issued the CKD Clinical Practice Guidebook in 2007 and the Evidence-based Practice Guidelines for the Treatment of CKD in 2009, which were revised in 2012 and 2013, respectively. MHLW has started strategic research through The Kidney Foundation Japan with the objective of achieving a 15 percent reduction in five years of the number of dialysis patients compared with current forecasts.

### Chronic Renal Failure and Renal Anemia

Chronic renal failure is a disease in which renal function is significantly reduced due to a variety of causes, including diabetes-related renal disease, chronic glomerulonephritis, nephrosclerosis and polycystic kidney disease. In recent years, the rise in the number of diabetes patients has led to a corresponding increase in chronic renal failure in patients with underlying diabetes-related renal disease; this has become the primary reason for dialysis use.

For dialysis patients and end-stage renal failure patients, the treatment of serious 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 dialysis patients but also in pre-dialysis patients. Renal anemia, in turn, is thought to be responsible for a wide range of further complications suffered by renal failure patients, including deterioration in heart, brain and hemostatic functions. 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 (2008) and the Clinical Practice Guidelines for the Management of CKD-MBD (2012) issued by the Japan Society for Dialysis Therapy and in the Evidence-based Practice Guidelines for the Treatment of CKD (2013) issued by the Japanese Society of Nephrology.

### Erythropoietin

Erythropoietin (EPO) is a hemopoietic factor produced mainly in the kidneys. It speeds up erythrocyte production by acting on normoblastic progenitor cells found in bone marrow. EPO preparations are effective in treating renal anemia caused primarily by the decline in erythropoietin production due to chronic renal failure. In addition, by correcting and controlling anemia, the drug is also thought to help improve the secondary complications listed above. Large-scale studies have shown that correction of anemia with EPO preparations helps reduce the length of hospital stays and improves both quality of life and life expectancy. It is estimated that EPO preparations are currently used by approximately 80 percent of dialysis patients and the majority of pre-dialysis renal failure patients with serum creatinine levels of 2mg/dl or more. Chugai's Epogin is thus an essential drug for the treatment of renal anemia.

### A Flat-Sum Reimbursement System for Erythropoietin Preparations

The number of patients receiving dialysis treatment in Japan has increased by about 2 to 3 percent annually, reaching approximately 310,000 people as of December 2012, partly due to increased use of dialysis in patients with diabetes-related renal disease. Expenses for EPO preparations, essential for dialysis treatment, accounted for 8.8 percent of all dialysis-related expenses in 2005. Consequently, the government decided in its 2006 revisions of medical fees that the administration of erythropoietin in dialysis treatment would be comprehensively incorporated as a flat-sum reimbursement within the medical fee points* for "artificial kidney" (dialysis treatment). The government changed the previous mechanism under which the number of fee points awarded depended on the amount of erythropoietin used. The new mechanism provides an integrated fee structure by adding the average amount of

erythropoietin used per dialysis session to the medical fee points for one session.

* Formerly, the average amount of erythropoietin used per patient was approximately 4,500 international units per week, on the basis of three dialysis sessions per week. The new system adds points equivalent to 1,500 international units to the artificial kidney medical fee points and provides an integrated fee structure. The integrated fee points were set for review in 2008, 2010, 2012 and 2014.

## Overview of Products and Development Projects

### Mircera

Mircera is a new anemia treatment with a very long plasma half-life, enabling stable and sustained control of hemoglobin. It stimulates erythropoiesis by a different interaction with the erythropoietin receptor on progenitor cells in the bone marrow. Mircera was launched in Japan in July 2011 as a treatment for anemia. Outside Japan, Mircera obtained regulatory approval in the European Union in 2007 and is currently sold in more than 100 countries.

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

### Epogin

Epogin is a human erythropoietin formulation 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 chronic renal failure. 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, and anemia of prematurity. In June 2010, Epogin Subcutaneous Injection Syringe 24000 obtained regulatory approval for autologous blood transfusion of 800ml or more for a patient's scheduled surgery with a blood collection period of more than one week.

### Oxarol

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 osteitis fibrosa and excess remodeling. With its short serum half-life, Oxarol is proving to be effective in cases that could not be treated sufficiently with oral vitamin $D_3$ derivatives due to the onset of hypercalcemia.

# Central Nervous System Diseases

## Schizophrenia

Schizophrenia is a severe mental disorder that affects approximately 26 million people worldwide and is a leading cause of disability. Typically diagnosed between the ages of 16 and 25, schizophrenia is broadly characterized by three types of symptoms: positive symptoms including hallucination and delusions, negative symptoms including lack of motivation and social withdrawal, and cognitive deficits including difficulty concentrating and disordered thinking.

### Overview of Development Project

**RG1678**

RG1678 (bitopertin), a glycine reuptake inhibitor in-licensed from Roche, is an oral small-molecule compound that is expected to be effective in treating schizophrenia. Chugai joined Roche's phase III multinational study in 2011.

## 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 thus do not treat the underlying cause. Consequently, the level of satisfaction with these treatments is low, and there is strong demand for a more effective drug.

### Overview of Development Projects

**RG1450**

RG1450 (gantenerumab) is an anti-amyloid-beta human monoclonal antibody in-licensed from Roche. Phase I clinical trials investigating RG1450 as a potential treatment for AD are currently under way.

**RG1577**

RG1577, a monoamine-oxidase-B (MAO-B) inhibitor in-licensed from Roche, is an oral small-molecule compound that is expected to be effective in treating Alzheimer's disease. Phase I clinical trials started in Japan in May 2013.

## Depression

Depression is a condition associated with brain dysfunction. It is classified by type, including exogenous, psychogenic, endogenous, reactive or situational, depending on the cause. Depression characterized by the presence of specific symptoms is called major depressive disorder. For treatment of depression, if the cause of the depressive state is clear, removal of the cause may be considered. However, if the cause is undetermined, or the depressive state is severe, drug therapy with an antidepressant is carried out. The number of patients in Japan with mood disorders including depression was estimated at 1.04 million in 2008, and has been trending upward year by year.

### Overview of Development Project

**RG7090**

RG7090 is an oral metabotropic glutamate receptor subtype 5 (mGluR5) antagonist in-licensed from Roche. Since September 2012, Chugai has been participating in Roche's phase II multinational study for the treatment of major depressive disorder.

# Other Diseases

## Chronic Hepatitis C

Chronic hepatitis C is a liver disease caused by persistent infection by the hepatitis C virus (HCV). In Japan, this disease has been designated a "21st century national health issue," as there are an estimated 2 million HCV carriers. Early detection and treatment of HCV is particularly important because approximately 70 percent of those infected develop chronic hepatitis, which gradually progresses to liver cirrhosis and then liver cancer.

### Treatment Methods and Market Conditions

There are two methods of treating chronic hepatitis C: antiviral therapy to eradicate HCV from the body, and liver-support therapy to improve liver function and prevent the hepatitis from worsening.

Interferon therapy is the main antiviral treatment. However, its efficacy was limited until about 2000, which led to an increase in the use of liver-support therapy in Japan. Since 2001, the introduction of interferon-ribavirin combination therapy and of peginterferon[1] has increased the treatment options available for patients with hepatitis C. Moreover, the approval in 2012 of a protease inhibitor that suppresses the growth of HCV now makes triple combination therapy with peginterferon and ribavirin possible.

1. Interferon conjugated with polyethylene glycol, which makes the medication longer-acting

### Regulatory Trends

In January 2010, a new law went into effect to promote comprehensive measures against hepatitis. This law establishes a new Hepatitis Countermeasures Promotion Council in MHLW to formulate basic policies for promoting measures against hepatitis, including prevention and medical treatment. The law also includes necessary provisions for the national and local governments to ease the financial burden on hepatitis patients to ensure that they can get appropriate treatment when necessary. In April 2011, pegylated interferon monotherapy for hepatitis B and three-drug combination therapy for hepatitis C were among the treatments that became eligible for medical expense subsidies.

### Overview of Products and Development Projects

#### Pegasys/Copegus

Pegasys is a pegylated interferon-based drug that was improved to achieve a sustained antiviral effect with once-weekly[2] administration. The guidelines for chronic hepatitis C treatment published by the MHLW recommend Pegasys as monotherapy for patients with a low viral load or those who cannot use ribavirin. In 2011, Pegasys obtained approval for the additional indications of compensated liver cirrhosis caused by hepatitis C (in combination with Copegus) in July and chronic active hepatitis B (as a monotherapy) in September.

Copegus is a chronic hepatitis C treatment that synergistically strengthens the antiviral effect when used in combination with interferon. Chugai obtained regulatory approval for Copegus in January 2007 and launched it in March in combination with Pegasys for the treatment of patients with chronic hepatitis C serogroup 1 infection[3] and high viral load, or those who have either not responded to, or have relapsed following, interferon monotherapy.

2. Conventional interferon must be injected three or more times per week.
3. Genotypes I (1a) and II (1b), with which more than 70 percent of HCV patients in Japan are infected

## 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. 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.

### Overview of Product

#### Tamiflu

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 interim report of an epidemiological survey published 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.

## Angina Pectoris

Hardening of the coronary artery or coronary spasms can cause constriction of the artery and lead to ischemia, a condition in which the heart does not receive sufficient blood flow. Clinical symptoms of angina pectoris include chest pain and pressure that accompany temporary ischemia. Nitric acid is used to treat angina pectoris, enlarging the coronary artery and increasing blood flow to the ischemia-affected areas. In addition, beta blocker agents are used to treat exertional angina pectoris, a symptom that appears during physical activity such as climbing stairs, and calcium blockers are used for coronary spasm-related angina pectoris.

### Overview of Product

**Sigmart**

Anti-anginal agent Sigmart is a drug that overcomes the flaws of nitric acid compounds such as nitroglycerin and is effective in treating various types of angina pectoris. Both oral and injectable forms are approved. Approval of the injectable formulation for acute heart failure was obtained in October 2007.

## 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 interleukin-6 (IL-6), one of the proteins that causes inflammation. Castleman's disease is very rare, affecting approximately 1,500 people in Japan.

### Overview of Product

**Actemra**

Actemra, an anti-human IL-6 receptor humanized monoclonal antibody produced using genetic recombination technology, is the first therapeutic antibody created in Japan. With a mode of action that inhibits the receptor for IL-6, a type of cytokine, the drug improves Castleman's disease symptoms. An estimated 160 patients in Japan are eligible for Actemra treatment because they cannot be treated by surgery due to the presence of multiple enlarged lymph nodes and show resistance to traditional therapies.

## Asthma

Asthma is a disease in which airways that have become sensitive due to inflammation narrow when exposed to irritants such as allergens, chemical substances or stress, causing attacks of breathing difficulty. It is accompanied by symptoms such as coughing, mucus production, wheezing and shortness of breath. In Japan, asthma affects an estimated 4 million people, and about 10 percent of patients have symptoms that are not adequately controlled with existing treatments.

### Overview of Development Project

**RG3637**

In-licensed from Roche, RG3637 (lebrikizumab) is an anti-IL-13 humanized monoclonal antibody under development for the treatment of asthma. It is expected to improve symptoms and prevent attacks in patients with moderate to severe asthma who are unable to adequately control their symptoms with existing treatments. This agent has demonstrated particular efficacy in patients with high serum periostin[4] levels. Chugai joined Roche's phase III multinational study in July 2013.

4. An extracellular matrix protein induced by IL-13, periostin is thought to be involved in fibrosis of the airways of asthma patients.

## Atopic Dermatitis

A type of allergic disorder, atopic dermatitis is a skin disease characterized by a chronic itchy rash. Scratching the affected area exacerbates the skin symptoms and makes the itching worse, leading to an itch-scratch cycle. The basic treatment method 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.

### Overview of Development Project

**CIM331**

CIM331 is an anti-IL-31 receptor humanized monoclonal antibody originating from Chugai that is being developed as a potential treatment for atopic dermatitis. It is expected to suppress itching and improve skin inflammation. A phase II multinational study led by Chugai started in December 2013.

## 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, patients must be watched for the development of autoantibodies, called inhibitors, to the supplemented factor. Patients with inhibitors are treated by other means, such as bypass therapy or immune tolerance therapy.

### Overview of Development Project

**ACE910**

ACE910 is a bispecific antibody to factor IXa and factor X that employs Chugai's innovative antibody engineering technologies. Factor VIII simultaneously binds to factor IXa and factor X, stimulating the activation of factor X by active factor IX and promoting the blood coagulation that occurs as a result. The bispecific antibody generated by Chugai mimics the function of factor VIII by simultaneously binding to factor IXa and factor X, and thus can stimulate blood clotting even in patients lacking factor VIII. Unaffected by inhibitors, ACE910 is expected to prevent bleeding with once-weekly subcutaneous injections. Phase I/II clinical trials started in Japan in August 2013.

## Dyslipidemia

Dyslipidemia (Hyperlipidemia) is a type of lifestyle disease characterized by abnormally high levels of lipids (fat) such as cholesterol and triglycerides in the blood. Increased blood lipids can cause atherosclerosis, and can also lead to myocardial infarction and cerebral infarction. Although hyperlipidemia has no subjective symptoms, it is estimated that there are 22 million potential patients in Japan.

### Overview of Development Project

**RG7652**

RG7652 is an anti-PCSK9 human monoclonal antibody in-licensed from Roche. It lowers LDL cholesterol by inhibiting the action of PCSK9, which promotes LDL receptor degradation. Phase I clinical trials for the treatment of hyperlipidemia started overseas in October 2012.

## 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. 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.

### Overview of Development Project

**URC102**

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 agent expected to be effective against gout. This compound is being co-developed with JW Pharmaceutical, and phase I clinical trials started in South Korea in June 2013.