

## State of New Product Development (as of May 8, 2009)

### 1. Pipeline in Japan

#### (1) New Molecular Entities

| Development code<br>(Generic name)    | Category<br>(Indications)   | Stage                    | Origin                      | Remarks   |
|---------------------------------------|---|--------------------------|-----------------------------|---|
| TA-8317 / ACREF<br>(Fentanyl citrate) | Narcotic analgesic<br>(Breakthrough cancer pain: oral transmucosal) | NDA filed<br>(Aug. 2008) | US:Cephalon                 |   |
| MCC-847<br>(Masilukast)               | Leukotriene D4 antagonist<br>(Asthma)<br>(Allergic rhinitis)        | Phase 3<br>Phase 2       | UK:<br>AstraZeneca          |   |
| MP-424<br>(Telaprevir)                | NS3-4A protease inhibitor<br>(Chronic hepatitis C)                  | Phase 3                  | US:Vertex                   |   |
| APTA-2217<br>(Roflumilast)            | PDE4 inhibitor<br>(Asthma)<br>(COPD)                                | Phase 2/3<br>Phase 2/3   | Switzerland:<br>Nycomed     | Co-development<br>-Nycomed                          |
| CNT0148<br>(Golimumab)                | Anti-TNF $\alpha$ monoclonal antibody<br>(Rheumatoid arthritis)     | Phase 2/3                | US:Centocor                 | Co-development<br>-Janssen Pharma                   |
| FTY720<br>(Fingolimod hydrochloride)  | Sphingosine-1-phosphate receptor modulator<br>(Multiple Sclerosis*) | Phase 2                  | In-house                    | Co-development<br>-Novartis Pharma<br>-Mitsui Sugar |
| MP-513<br>(Teneligliptin)             | DPP4 Inhibitor<br>(Type 2 Diabetes mellitus)                        | Phase 2                  | In-house                    |   |
| MP-214<br>(Cariprazine)               | D3/D2 antagonist<br>(Schizophrenia)                                 | Phase 2                  | Hungary: Gedeon-<br>Richter |   |
| MP-435                                | C5a antagonist<br>(Rheumatoid arthritis)                            | Phase 1                  | In-house                    |   |
| TA-6666                               | DPP4 inhibitor<br>(Type 2 Diabetes mellitus)                        | Phase 1                  | In-house                    |   |
| TA-7284                               | SGLT2 inhibitor<br>(Diabetes mellitus)                              | Phase 1                  | In-house                    |   |

\*: Orphan drug designated

(2) Additional Indications

| Product name<br>(Generic name)   | Category<br>(Indications)   | Stage                     | Origin                    | Remarks                            |
|--|---|---------------------------|---------------------------|------------------------------------|
| Venoglobulin-IH<br>(Polyethylene glycol treated human normal immunoglobulin) | Human immunoglobulin G<br>(IgG2 deficiency)   | sNDA filed<br>(Dec. 1997) | In-house                  |                                    |
|  | (Polymyositis, Dermatomyositis* )   | sNDA filed<br>(May 2003)  |                           |                                    |
|  | (Hypo and gammaglobulinemia: additional dose)   | sNDA filed<br>(Mar. 2008) |                           |                                    |
|  | (Systemic scleroderma)  | Phase 3                   |                           |                                    |
|  | (Myasthenia gravis)   | Phase 3                   |                           |                                    |
| Remicade<br>(Infliximab(recombinant))  | Anti-TNF $\alpha$ monoclonal antibody<br>(Rheumatoid arthritis: dose escalation)  | sNDA filed<br>(Sep. 2007) | US:Centocor               |                                    |
|  | (Psoriasis)   | sNDA filed<br>(Feb. 2008) |                           |                                    |
|  | (Ankylosing spondylitis*)   | sNDA filed<br>(Sep. 2008) |                           |                                    |
|  | (Ulcerative colitis)  | Phase 3                   |                           |                                    |
|  | (Crohn's disease: dose escalation)  | Phase 3                   |                           |                                    |
| Valixa<br>(Valganciclovir)   | Antiviral<br>(Post- transplantation cytomegalovirus infection )   | sNDA filed<br>(Jun. 2008) | Switzerland: Roche        |                                    |
| Ceredist<br>(Taltirelin hydrate)   | Spinocerebellar degeneration remedy<br>(Orally disintegrating tablet: additional formulation)                                 | sNDA filed<br>(Jul. 2008) | In-house                  |                                    |
| Modiodal<br>(Modafinil)  | Psychoneurotic agent<br>(Obstructive sleep apnea)   | Phase 3                   | US: Cephalon              | Co-development<br>-Alfresa Pharma  |
| Radicut<br>(Edaravone)   | Free radical scavenger<br>(Amyotrophic lateral sclerosis*)  | Phase 3                   | In-house                  |                                    |
| Maintate<br>(Bisoprolol)   | Selective $\beta$ 1 antagonist<br>(Chronic heart failure)   | Phase 3                   | Germany:<br>Merck KGaA    |                                    |
| Pazucross<br>(Pazufloxacin mesilate)   | Injectable quinolone synthetic antibacterial agent<br>(Severe or intractable case: additional dose)<br>(Sepsis, Pneumococcus) | Phase 3                   | Japan:<br>Toyama Chemical | Co-development<br>-Toyama Chemical |
| Cholebine<br>(Colestimide(JAN))  | New mode of action for diabetes treatment<br>(Type 2 Diabetes mellitus)   | Phase 2                   | In-house                  |                                    |
|  | Non-absorbed phosphate binder<br>(Hyperphosphatemia)  | Phase 1                   |                           |                                    |

\*: Orphan drug designated

## 2. Pipeline Overseas

### (1) New Molecular Entities

| Development code<br>(Generic name)                | Category<br>(Indications)                                      | Region | Stage   | Origin                | Region |
|---|--|--------|---------|-----------------------|--------|
| MCI-196<br>(Colestilan(INN))                      | Non-absorbed phosphate binder<br>(Hyperphosphatemia)           | US, EU | Phase 3 | In-house              |        |
| MP-146  | Uremic toxin adsorbent<br>(Chronic kidney disease)             | US, EU | Phase 3 | Japan:Kureha          |        |
| TA-6666   | DPP4 inhibitor<br>(Type 2 Diabetes mellitus)                   | US     | Phase 2 | In-house              |        |
| TA-5538   | NK-1 receptor antagonist<br>(Overactive bladder)               | EU     | Phase 2 | In-house              |        |
| MCC-135<br>(Caldaret)                             | Intracellular Ca handling modulator<br>(Myocardial infarction) | US, EU | Phase 2 | In-house              |        |
| MCC-257   | Neurotrophin enhancer<br>(Diabetic neuropathy)                 | US     | Phase 2 | In-house              |        |
| MT-2832   | Vitamin D analog<br>(Secondary hyperparathyroidism)            | Canada | Phase 2 | Canada:<br>Cytochroma |        |
| MCI-186<br>(Edaravone)                            | Free radical scavenger<br>(Acute cerebral infarction)          | EU     | Phase 1 | In-house              |        |
| TA-5493   | p38 inhibitor<br>(Rheumatoid arthritis, Psoriasis)             | EU     | Phase 1 | In-house              |        |
| MP-513<br>(Teneligliptin)                         | DPP4 inhibitor<br>(Type 2 Diabetes mellitus)                   | US, EU | Phase 1 | In-house              |        |
| GB-1057<br>(Human serum albumin<br>[recombinant]) | Recombinant human serum albumin<br>(Stabilizing agent)         | US     | Phase 1 | In-house              |        |
| TA-8995   | CETP inhibitor<br>(Dyslipidemia)                               | EU     | Phase 1 | In-house              |        |
| MP-124  | PARP inhibitor<br>(Acute Ischemic Stroke)                      | US     | Phase 1 | In-house              |        |
| MP-136  | PPAR alpha agonist<br>(Dyslipidemia)                           | EU     | Phase 1 | In-house              |        |

### (2) Additional Indications

| Development code<br>(Generic name) | Category<br>(Indications)  | Region | Stage                 | Origin   | Remarks |
|------------------------------------|--|--------|-----------------------|----------|---------|
| MCI-9038<br>(Argatroban)           | Thrombin inhibitor<br>(Heparin-induced thrombocytopenia (HIT))       | EU     | Preparing for<br>sNDA | In-house |         |
|                                    | (HIT Patients undergoing percutaneous coronary<br>intervention(PCI)) | EU     | sNDA<br>(Apr. 2009)   |          |         |

### 3. Licensing-out

| Development code<br>(Generic name)   | Category<br>(Indications)  | Region | Stage   | Licensee  |
|--------------------------------------|--|--------|---------|---|
| FTY720<br>(Fingolimod hydrochloride) | Sphingosine 1-phosphate receptor agonist<br>(Multiple sclerosis)                           | US, EU | Phase 3 | Switzerland:Novartis Pharma   |
| TA-1790<br>(Avanafil)                | PDE5 inhibitor<br>(Erectile dysfunction)   | US     | Phase 3 | US:Vivus  |
|                                      |  | Korea  | Phase 2 | Korea:Choongwae Pharma  |
| T-0047<br>(Fingolimod)               | Cell adhesion inhibitor [ $\alpha4\beta7/\alpha4\beta1$ inhibitor]<br>(Multiple sclerosis) | EU     | Phase 2 | UK:GlaxoSmithKline  |
| TA-7284                              | SGLT2 inhibitor<br>(Diabetes mellitus, Obesity)  | EU, US | Phase 2 | US: Johnson & Johnson<br>Pharmaceutical Research &<br>Development, L.L.C. |
| MKC-242                              | 5-HT1A receptor agonist<br>(Insomnia)  | US     | Phase 2 | US:MediciNova   |
| TA-2005<br>Carmoterol                | Long-acting $\beta2$ agonist<br>(Asthma, COPD)   | EU     | Phase 2 | Italy:Chiesi Farmaceutici   |
| MKC-231                              | Neurogenesis enhancer<br>(Depression/Anxiety)  | US     | Phase 2 | US:BrainCells   |
| Y-39983                              | ROCK (rho-kinase) inhibitor<br>(Glaucoma)  | Japan  | Phase 2 | Japan: Senju Pharmaceutical   |
| T-0128                               | DNA Topoisomerase I inhibitor [DDS drug<br>camptothecin derivative]<br>(Malignant tumor)   | EU     | Phase 1 | Italy:Menarini  |
| sTU-199<br>(Tenatoprazole)           | Proton pump inhibitor<br>(Gastroesophageal reflux disease)                                 | EU     | Phase 1 | France:Negma (Sidem)  |
| MP-412                               | Tyrosine kinase inhibitor<br>(Malignant tumor)   | US     | Phase 1 | US:AVEO Pharmaceuticals   |
| TT-138                               | $\beta3$ receptor agonist<br>(Pollakiuria, Anischuria)                                     | US     | Phase 1 | US:MediciNova   |

#### 4. Changes Since Previous Announcement on Jan. 29, 2009

| Product name<br>Development code<br>(Generic name) | Category<br>(Indications)  | As of Jan. 29, 2009 | As of May. 8, 2009        |
|--|--|---------------------|---------------------------|
| MCI-9038<br>(Argatroban)                           | Thrombin inhibitor<br>(HIT Patients undergoing percutaneous coronary intervention(PCI))                          | Phase 3 in EU       | sNDA filed<br>(Apr. 2009) |
| MP-136   | PPAR alpha agonist<br>(Dyslipidemia)   | None                | Phase 1 in E.U.           |
| Anplag<br>(Sarpogrelate hydrochloride)             | 5HT2 antagonist<br>(Prevention of recurrence of cerebral infarction)   | Phase 3 in Japan    | Deleted                   |
| MCI-225  | Norepinephrine reuptake inhibitor + 5-HT3 receptor antagonist<br>(Diarrhea-predominant irritable bowel syndrome) | Phase 2 in the USA  | Deleted                   |
| MKC-733  | 5-HT3 receptor agonist<br>(Constipation-predominant irritable bowel syndrome )                                   | Phase 2 in the USA  | Deleted                   |
|  | (Gastroesophageal reflux disease at nighttime)   | Phase 1 in the USA  |                           |

## 5. Additional Information for State of New Product Development (as of May 8, 2009)

### (1) Japan New Molecular Entities

|                                      |  |
|--------------------------------------|--|
| TA-8317/ACREF<br>(Fentanyl citrate)  | TA-8317 is an oral transmucosal fentanyl citrate product for the management of breakthrough pain in cancer patients, licensed from Cephalon (U.S.). This product is marketed in the United States and Europe. NDA was filed in August, 2008.   |
| MCC-847<br>(Masilukast)              | MCC-847 is a leukotriene D4 antagonist and an orally available product to treat respiratory diseases. Clinical stages in patients with asthma is Phase3, and allergic rhinitis is Phase 2.   |
| MP-424<br>(Telaprevir)               | MP-424 is an orally-available product for treatment of chronic liver diseases due to hepatitis C virus infection, licensed from Vertex (US). This compound inhibits protease NS3/4 in hepatitis C virus. Clinical stage in Japan is Phase 3.   |
| APTA-2217<br>(Roflumilast)           | APTA-2217 is a potent, highly selective and orally available product for the treatment of respiratory diseases, and licensed from Nycomed (Switzerland). An efficacy was obtained both in asthma and COPD. Phase 2/3 trials for asthma and COPD are underway in Japan.   |
| CNTO148<br>(Golimumab)               | CNTO148 is an anti-TNF $\alpha$ monoclonal antibody, licensed from Centocor. Clinical stage in Japan is Phase 2/3 for rheumatoid arthritis with subcutaneous injections as co-development with Janssen Pharma K.K.   |
| FTY720<br>(Fingolimod hydrochloride) | FTY720 is a sphingosine-1-phosphate receptor modulator. Overseas clinical trial in patients with multiple sclerosis is in Phase 3, and is being conducted by Novartis Pharma AG. In Japan, Phase 2 clinical trial in patients with multiple sclerosis is currently under co-development with Novartis Pharma K.K. and Mitsui Sugar Co., Ltd. |
| MP-513<br>(Teneligliptin)            | MP-513 is developed for the treatment of type-2 diabetes mellitus. It selectively inhibits dipeptidyl peptidase 4 (DPP4), thus accelerates the insulin secretion after meal intake. Clinical stage in Japan is Phase 2.  |
| MP-214<br>(Cariprazine)              | MP-214 is a dopamine D3/D2 antagonist, licensed from Gedeon-Richter (Hungary). Clinical stage in Japan is Phase 2 for schizophrenia.   |
| MP-435                               | MP-435 is a C5a (complement factor) receptor antagonist which modulates the immune system. Clinical stage in Japan is Phase 1 for oral antirheumatoid drug.  |
| TA-6666                              | TA-6666 is developed for the treatment of type-2 diabetes mellitus. It selectively inhibits dipeptidyl peptidase 4 (DPP4), thus accelerates the insulin secretion after meal intake. Clinical stage in Japan is Phase 1.   |
| TA-7284                              | As a selective SGLT2 inhibitor, TA-7284 decreases blood glucose levels by inhibiting reabsorption of glucose in the kidney. Clinical stage in Japan is Phase 1 for diabetes mellitus.  |

## (2) Japan Additional Indication

|  |   |
|--|---|
| <p>Venoglobulin-IH<br/>(Polyethylene glycol treated human normal immunoglobulin)</p> | <p>(IgG2 deficiency) sNDA has been filed.</p> <p>(Polymyositis and/or Dermatomyositis [orphan drug designated]) sNDA has been filed. Based on the instructions from the authorities, an additional clinical trial is in progress to confirm efficacy of Venoglobulin in patients with polymyositis or dermatomyositis who do not respond to steroid therapy.</p> <p>(Hypo and agammaglobulinemia: additional dose) sNDA was filed in March 2008.</p> <p>(Diffuse systemic scleroderma) Clinical research in Japan demonstrated IV-IG was effective in improvement of skin manifestation, a primary endpoint of systemic scleroderma. Efficacy of IV-IG was also reported in overseas studies. Clinical stage is Phase 3.</p> <p>(Myasthenia gravis) Clinical stage in Japan is Phase 3 in which is compared with blood purification therapy.</p>  |
| <p>Remicade<br/>(Infliximab [recombinant])</p>                                       | <p>(Rheumatoid arthritis, dose escalation) In order to verify the effectiveness of Remicade when administered in higher doses, Phase 3 trials have been conducted for patients showing an insufficient response to methotrexate. sNDA was filed in September 2007.</p> <p>(Psoriasis) Good effectivity and safety for plaque psoriasis and psoriatic arthritis were reported in validation trials and the indications were approved in the US and EU. sNDA was filed in February 2008.</p> <p>(Ankylosing spondylitis) Good efficacy and safety for ankylosing spondylitis were reported and the indication was approved in the US and EU. It was designated as an orphan drug in June 2008. sNDA was filed in September 2008.</p> <p>(Ulcerative colitis) Good effectivity and safety for ulcerative colitis was reported and the indication was approved in the US and EU. Clinical stage in Japan is Phase 3.</p> <p>(Crohn's disease) In order to verify the effectiveness of Remicade when administered in higher doses, Phase 3 trial is on going for patients showing an insufficient response to maintenance therapy.</p> |
| <p>Valixa<br/>(Valganciclovir)</p>   | <p>(Post- transplantation cytomegalovirus infection ) Valixa has been approved for cytomegalovirus retinitis in AIDS patients. sNDA was filed in June 2008.</p>   |
| <p>Ceredist<br/>(Taltirelin hydrate)</p>   | <p>(Orally disintegrating tablet: additional formulation) sNDA was filed in July 2008.</p>  |
| <p>Modiodal<br/>(Modafinil)</p>  | <p>(Obstructive sleep apnea) Modiodal has been approved for narcolepsy in Japan. It has been also approved in the U.S. and certain major European countries as an agent for the patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift-work sleep disorder. sNDA was filed by Alfresa Pharma Corp. in May 2008. As a result of the consultation with PMDA, additional data has been required. An additional clinical study for sNDA is under planning.</p>   |
| <p>Radicut<br/>(Edaravone)</p>   | <p>(Amyotrophic lateral sclerosis (Orphan drug designated)) Clinical stage is Phase 3.</p>  |
| <p>Maintate<br/>(Bisoprolol)</p>   | <p>(Chronic heart failure) In Europe, the result of the large-scale CIBIS-II trials demonstrated that bisoprolol significantly decreased mortality in patients with chronic heart failure (NYHA III-IV). In Japan, sNDA for an additional indication of chronic heart failure was submitted in April 2006. As a result of the consultation with PMDA, an additional clinical study (Phase 3) for sNDA is now under discussion.</p>  |
| <p>Pazucross<br/>(Pazufloxacin mesilate)</p>   | <p>(Severe and intractable case: additional dosage/Sepsis and Streptococcus pneumoniae: additional indication) New quinolone antibacterial agents for infection. Clinical stage is Phase 3.</p>   |
| <p>Cholebine<br/>(Colestimide (JAN))</p>   | <p>(Type 2 diabetes mellitus) Clinical stage is Phase 2.<br/>(Hyperphosphatemia) Clinical stage is Phase 1.</p>   |

### (3) Overseas New Molecular Entities

|   |   |
|---|---|
| MCI-196<br>(Colestilan(INN))                      | MCI-196 is anion-exchange resin, and has been developed to obtain indication for the treatment of hyperphosphatemia in patients on dialysis in EU and the US. Clinical stage is Phase 3. It is marketed in Japan for the treatment of hypercholesterolemia, under the brand name of CHOLEBINE®.   |
| MP-146  | MP-146 is spherical carbon adsorbent, licensed from Kureha Corporation (Japan) in November, 2006. Clinical stage is Phase 3 for Chronic Kidney Disease patients in EU, North America and South America. It is marketed by other companies in Japan under the brand name, KREMEZIN®.   |
| TA-6666   | TA-6666 is developed for the treatment of type-2 diabetes mellitus. It selectively inhibits dipeptidyl peptidase 4 (DPP4), thus accelerates the insulin secretion after meal intake. Clinical stage is Phase 2 in the US.   |
| TA-5538   | TA-5538 selectively blocks binding of substance P to the receptor (NK-1 receptor), is under development for the treatment of overactive bladder. Clinical stage is Phase 2 for overactive bladder in Europe.  |
| MCC-135<br>(Caldaret)                             | MCC-135 improves cardiac function and clinical outcome in patients with acute myocardial infarction, by improving calcium mobilization in ischemic-reperfused myocardium. Clinical stage is Phase 2 in EU and the US.   |
| MCC-257   | MCC-257 is a product to treat diabetic neuropathy by facilitating secretion of neurotropic factors and potentiating their actions. Clinical stage is Phase 2 in the US.   |
| MT-2832   | MT-2832 was licensed from Cytochroma Inc. (Canada) in July 2008. Cytochroma development code is CTA018. MT-2832 is a strong activator of the vitamin D signaling pathway and a potent inhibitor of CYP24, intracellular enzyme responsible for catabolism of Vitamin D hormones. Clinical stage is Phase 2 for secondary hyperparathyroidism in patients with chronic kidney disease in Canada. |
| MCI-186<br>(Edaravone)                            | MCI-186 is the world's first cerebral neuroprotectant (free radical scavenger). Clinical stage in EU is Phase 1 for the acute cerebral infarction. It is marketed in Japan under the brand name, Raducut®.  |
| TA-5493   | TA-5493, a p38 MAP kinase inhibitor, suppresses the cytokine production including TNF $\alpha$ and consequently expresses anti-inflammatory effects. Clinical stage is Phase 1 for rheumatoid arthritis and psoriasis in Europe.  |
| MP-513<br>(Teneligliptin)                         | MP-513 is developed for the treatment of type-2 diabetes. It selectively inhibits dipeptidyl peptidase 4 (DPP4), thus accelerates the insulin secretion after meal intake. Clinical stages in the US and EU are Phase 1.  |
| GB-1057<br>(Human serum albumin<br>[recombinant]) | GB-1057 is a recombinant human serum albumin. Clinical stage is Phase 1 as a stabilizing agent in the US.   |
| TA-8995   | TA-8995 is a CETP inhibitor that has raising the HDL-C and lowering the LDL-C effects. Clinical stage is Phase 1 in Europe.   |
| MP-124  | MP-124 is a PARP inhibitor that has neuroprotective effect. Clinical stages in the US and Canada are phase 1 for the acute ischemic stroke.   |
| MP-136  | MP-136 is a PPAR alpha agonist. Clinical stage is Phase 1 in E.U. for the dyslipidemia.   |

### (4) Overseas Additional Indications

|                          |   |
|--------------------------|---|
| MCI-9038<br>(Argatroban) | (Heparin-induced thrombocytopenia (HIT)) Eight EU countries (Germany, Austria, Sweden, the Netherlands, Denmark, Norway, Iceland and Italy) have given the marketing authorization. We now consider the submission to other EU countries. |
|                          | (Percutaneous coronary intervention in patients with HIT) sNDA is filed in EU in April 2009.  |

## (5) Licensing-Out

|                                      |   |
|--------------------------------------|---|
| FTY720<br>(Fingolimod hydrochloride) | FTY720 prevents regression of lymphocytes from the lymphoid tissues by acting on sphingosine-1-phosphate receptors. Novartis Pharma A.G. is conducting a Phase 3 clinical trials in patients with multiple sclerosis, primarily in the US and EU.   |
| TA-1790<br>Avanafil                  | TA-1790 is developed for the treatment of erectile dysfunction by Mitsubishi Tanabe Pharma, which is expected to have a quick onset and fewer side effects. Clinical trial stage is Phase 3 in the US and Phase 2 in Korea.   |
| T-0047<br>(Firategrast)              | T-0047 inhibits the cell adhesion and cell migration processes of white blood cells in inflammatory region. Although US Food and Drug Administration has taken the precautionary measure of placing a clinical hold on investigational new drugs in the $\alpha 4$ integrin antagonist class being tested on human subjects, including this product. The reason for the clinical hold as cited by the FDA is the uncertainty surrounding the cause of the reports of progressive multifocal leukoencephalopathy (PML) in patients who had been taking Tysabri (natalizumab), a multiple sclerosis biological agent marketed by Biogen Idec and Elan Pharmaceuticals. FDA has approved to relaunch Tysabri in 2006. The resuming clinical Phase 2 trial is conducted by GSK in Europe, Canada, Australia, and New Zealand. |
| TA-7284                              | As a selective SGLT2 inhibitor, TA-7284 decreases blood glucose levels by inhibiting reabsorption of glucose in the kidney. Phase 2 clinical trials in patients with diabetes and obesity in EU and the US are underway.  |
| MKC-242                              | MKC-242 is a serotonin 5-HT1A receptor agonist, used to treat psychiatric disorders such as anxiety and depression. This compound is expected to reveal rapid onset with low possibility of dependency. Medici Nova Inc.(US) is conducting Phase 2 clinical trials in patients with generalized anxiety disorder or insomnia.   |
| TA-2005<br>(Carmoterol)              | TA-2005 is a selective, potent and long acting $\beta 2$ agonist for the treatment of asthma and COPD. Clinical trial stage is Phase 2 in Europe.   |
| MKC-231                              | MKC-231 is a neurogenesis enhancer. Phase 2 study in major depression is underway by BrainCells Inc.(US).   |
| Y-39983                              | Y-39983 is a ROCK (Rho-kinase) inhibitor, which relaxes vascular smooth muscle. Clinical trial stage in Japan is Phase 2 by Senju Pharmaceutical Co. Ltd.   |
| T-0128                               | T-0128 is a prodrug with its drug-delivery system, which is composed of a novel camptothecin analog covalently linked to a macromolecular carrier via a short peptide chain, and reaches the tumor tissue effectively. Clinical trial stage is Phase 1 in Europe.   |
| sTU-199<br>(Tenatoprazole)           | sTU-199 is an isomer of TU-199, developed in Japan, and licensed to Negma (France). Pharmacokinetic/pharmacodynamic results from phase 1 clinical trials in EU and the US demonstrated that sTU-199 controlled gastric acid secretion at nighttime in patients receiving this compound once-daily, with the long terminal half-life. It is expected that this compound will reveal rapid improvement for non-erosive reflux disease. Sidem Pharma, a subsidiary of Negma, is conducting phase 1 trial for gastroesophageal reflux disease in EU.  |
| MP-412                               | MP-412 is expected to have superior efficacy for solid tumors to other anticancer agents that belong to the same class. Phase 1 study is conducted by AVEO Pharmaceuticals Inc. in the US.  |
| TT-138                               | TT-138 is a $\beta 3$ receptor agonist used to treat pollakiuria and anischoria. Phase 1 study is conducted by Medici Nova Inc. in the US.  |

<Ref.> Major Ethical Drugs 1

| Product Name                   | Launch  | Category  | Notes                  |
|--------------------------------|---|---|------------------------|
| <b>Product Profile</b>         |   |   |                        |
| Remicade<br>(Infliximab)       | May 2002  | Anti-TNF $\alpha$ monoclonal antibody (Treatment of rheumatoid rthritis (RA), active Crohn's disease and Behcet's disease with refractory uveoretinitis ) | Origin: Centocor, Inc. |
|                                | Remicade is an anti-TNF $\alpha$ antibody, which targets TNF $\alpha$ , an important inflammatory cytokine. It is very fast-acting and its efficacy is sustained for two months with a single administration. Remicade has been shown to inhibit joint destruction in rheumatoid arthritis. It was approved in Japan for the treatment of Behcet's disease with refractory uveoretinitis in January 2007 and for the maintenance treatment of Crohn's disease in November 2007.   |   |                        |
| Radicut<br>(Edaravone)         | Jun. 2001   | Cerebral neuroprotectant<br>(Free radical scavenger)  |                        |
|                                | Radicut developed in Japan is the world's first brain protecting agent (free radical scavemger) shown to improve neurological symptoms, interference with activities of daily living, and disability (at hospital discharge) in patients at acute stage of cerebral infarction. Specific indications include the treatment of various types of infarction (cerebral lacunar, atherothrombotic and cardiogenic infarction). It is initiated administration within 24 hours after onset, and its dosing period is within 14 days.                       |   |                        |
| Anplag<br>(Sargogrelate)       | Oct. 1993   | Anti-platelet (5-HT2 blocker)   |                        |
|                                | Anplag, an oral anti-platelet, is used to patients with arteriosclerosis obliterans (ASO) to improve ischemic symptoms like as ulcer, pain and coldness of limbs associated with chronic arterial occlusion. Anplag especially improves the bloodstream of collateral circulation and inhibits platelet aggregation, vascular contraction and growth of vascular smooth muscle cell by antagonistic action to serotonin receptor in platelets and vessels. The downsized tablet which is convenient for elderly patients was approved in August 2007. |   |                        |
| Urso<br>(Ursodeoxycholic Acid) | Jul. 1962   | Agent for improving hepatic, biliary and digestive functions  |                        |
|                                | Ursodeoxycholic acid (UDCA), principal ingredient of Urso, had been extracted from blackbear's gallbladder in the past and has been used in the treatment of various digestive diseases. It is one of the bile acids existing in human body. Urso has effects of hapatic protection and indications of improvement of liver function in chronic liver diseases and hepatitis C, and dissolution of gallstones.  |   |                        |
| Ceredist<br>(Taltirelin)       | Sep. 2000   | Agent for treating spinocerebellar degeneration   |                        |
|                                | Thyrotropin releasing hormone (TRH) was known to be effective against ataxia caused by spinocerebellar degeneration, but it was previously administered only through injection. Ceredist, developed by Tanabe, is the world's first oral TRH derivative drug.   |   |                        |
| Tanatril<br>(Imidapril)        | Dec. 1993   | ACE inhibitor (Treatment of hypertension)   |                        |
|                                | Tanatril shows excellent blood pressure control with effective organ protection as well as minimal incidence of dry cough, a common side effect of ACE inhibitors. With the approval of an additional indication in 2002, it became the first drug in Japan approved for diabetic nephropathy with type I diabetes.   |   |                        |
| Herbesser<br>(Diltiazem)       | Feb. 1974   | Calcium antagonist (Treatment of angina pectoris and hypertension)  |                        |
|                                | Herbesser is a representative calcium antagonist that is used in more than 110 countries around the world. In addition to a blood pressure lowering effect, it has a cardioprotective action in patients with hypertension or angina pectoris by reducing the cardiac load through a heart rate lowering effect and by increasing the oxygen supply through a coronary vasodilating effect.   |   |                        |
| Depas<br>(Etizolam)            | Mar. 1984   | Antianxiety agent   |                        |
|                                | Depas is the most widely used anxiolytic agent in Japan. Due to its broad pharmacological properties, Depas shows reasonable effectiveness for psychosomatic disease, neurosis, low back pain, neck pain and muscle-contraction headache, depression and sleep disorder.  |   |                        |

<Ref.> Major Ethical Drugs 2

| Product Name   | Launch    | Category  | Notes  |
|--|-----------|---|--|
| <b>Product Profile</b>   |           |   |  |
| Venoglobulin-IH<br>(Human immunoglobulin)  | Jan. 1992 | Plasma derivatives  |  |
| Venoglobulin-IH is intravenous human immunoglobulin derived from donated plasma in Japan. It shows high efficacy on serious infectious diseases in combined administration with anti-bacterial agent due to its opsonic, immuno-bacteriolytic and antibody-dependent cytotoxic effects and neutralizing effects on toxics and viruses.   |           |   |  |
| Talion<br>(Bepotastine)  | Oct. 2000 | Agent for treatment of allergic disorders (Treatment for allergic rhinitis and urticaria)   | Origin: Ube Industries, Ltd.<br>Co-development       |
| Talion has rapid onset of anti-histamine(H1) effects and has been demonstrated to be effective for allergic rhinitis, urticaria, and pruritus accompanying dermatitis. It has minimal incidence of sedation. In March 2007, approval was received for an additional formulation, orally disintegrating tablets, and it was launched in July.   |           |   |  |
| Maintate<br>(Bisoprolol)   | Nov. 1990 | Selective $\beta_1$ antagonist (Treatment of angina pectoris hypertension, and arrhythmias) | Origin: Merck KGaA                                   |
| Maintate is a representative $\beta$ -blocker used in more than 85 countries around the world. It exhibits high selectivity for $\beta_1$ receptor and excellent pharmacokinetics profiles. It has high efficacy and safety, and there is evidence for its cardioprotective action. An application has been filed in Japan for an additional indication for chronic heart failure.   |           |   |  |
| Liple<br>(ArprostadiI)   | Nov. 1988 | Chronic arterial occlusion / Circulatory disturbance (PG E1)                                | Co-developed with<br>Taisho Pharmaceutical Co., Ltd. |
| Liple, the world's first DDS (Drug Delivery System) agent of intravenous PGE1, improves the peripheral circulatory disturbance and skin ulcer in chronic arterial occlusive disease and diabetes by its direct vasodilating effects. DDS maximizes the therapeutic effects and simultaneously minimizes the adverse effects of PGE1.   |           |   |  |
| Sermion<br>(Nicergoline)   | June 1988 | Cerebral circulation and metabolism ameliorator   | Origin: Pfizer Inc.                                  |
| Sermion ameliorates blood flow and metabolism in the brain. It is used to treat sequela of cerebral infarction. In 1998, in a reevaluation by the Ministry of Health and Welfare in Japan, its effectiveness was confirmed. In "the treatment guidelines for strokes in 2004," Sermion was recommended as a treatment drug for chronic cerebral infarction.  |           |   |  |
| Omeprazon<br>(Omeprazole)  | Apr. 1991 | Antiulcerogenic agent (Proton pump inhibitor)   | Origin: AstraZeneca<br>Co-developed with AstraZeneca |
| Omeprazon is the world's first proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H <sup>+</sup> /K <sup>+</sup> -ATPase enzyme in the gastric parietal cell. It strongly and sustainably blocks the final step in gastric acid production results in reducing gastric acidity. Omeprazon has excellent efficacy for gastric ulcer, duodenal ulcer and reflux esophagitis. Additional indications for non-erosive reflux disease (NERD) and secondary eradication of Helicobacter pylori were approved in May and August 2007, respectively. |           |   |  |
| Neuart<br>(Anti-thrombin III)  | Jun. 1987 | Plasma derivatives (Anticoagulant agent)  |  |
| Neuart is highly purified human anti-thrombin III derived from donated plasma in Japan. It shows strong anticoagulant effects in the treatment of DIC patients by inhibiting various kinds of activated serine proteases including thrombine.  |           |   |  |

## <Ref.> Major Ethical Drugs 3

| Product Name   | Launch     | Category   | Notes                                  |
|--|------------|--|--|
| Product Profile  |            |  |  |
| Theodur<br>(Theophylline)  | Apr. 1984  | Bronchodilator (Xanthine-bronchodilator)           |  |
| Theodur, an oral bronchodilator, is widely prescribed to treat symptoms of asthma and COPD. The active ingredient, theophylline, has pleiotropic effects including bronchodilating and antiinflammatory activities relevant to asthma. Theophylline is recommended to use for asthma in the management guidelines in Japan. Compared with other anti-asthma medications, the treatment by Theodur is also highly evaluated from a cost-effective viewpoint.  |            |  |  |
| Gastrom<br>(Ecabet)  | Dec. 1993  | Agent for treatment of gastritis and gastric ulcer |  |
| Gastrom is hardly absorbed from but covers the gastrointestinal tract after administration. It protects the gastric mucosa and has no serious side effects or drug interactions. In single-agent treatment of gastritis, it has efficacy of equivalent to H2 blockers. Evidence that the concomitant use of Gastrom with an H2 blocker significantly improves the cure rate in gastric ulcer was included in gastric ulcer treatment guidelines in April 2007, and it has been recommended for concomitant use with an H2 blocker.   |            |  |  |
| Fulcaliq   | Jan. 2003  | High-calorie infusion with vitamins                | Co-development with Terumo Corporation |
| Fulcaliq is the world's first high-calorie infusion with triple chambers which makes it possible to add multivitamins to sugars, amino acids and electrolytes. Fulcaliq significantly improves customers' safety and convenience.  |            |  |  |
| Novastan<br>(Argatroban)   | June. 1990 | Selective antithrombin agents                      | Co-developed with Daiichi-Sankyo       |
| Novastan is a fully synthesized, selective thrombin inhibitor. In Japan, it was launched in June, 1990 and has been approved for the treatment of limb ulcers, rest pain and a sensation of cold in chronic arterial occlusive disease, the acute treatment of neurological symptoms and activities of daily living for patients with acute-phase cerebral thrombosis, and the prevention of blood clotting in the circuit during hemodialysis in the patients with congenitally decreased antithrombin III levels. In July 2008, it was also approved for the prophylaxis of thrombosis in the patients with type 2 heparin-induced thrombocytopenia (HIT). In overseas market, it was approved by the FDA in 2000 for the prophylaxis or treatment of thrombosis in patient with HIT and has since been approved in nine countries for the same indications. |            |  |  |
| Mearubik<br>(Measels and Rubella Vaccine Live Attenuated)  | Dec. 2005  | Measels and rubella immunization                   | Manufacturer: *BIKEN                   |
| Mearubik is the combination vaccine for Measels and Rubella, and children are able to receive both Measels and Rubella shot at a time with Mearubik. It is expected to contribute enhancement of immunization rate for Measels and Rubella in Japan.   |            |  |  |

\*BIKEN:The Research Foundation for Microbial Diseases of Osaka University