



RESEARCH AND DEVELOPMENT

Takeda undertakes global research and development with the aim of creating new drugs that are both medically and socially meaningful.

Takeda has until now conducted research and development, from target discovery to drug creation, at research centers in Tsukuba and Osaka in Japan. In March 2005, however, Takeda secured its first research base outside Japan with the acquisition of a U.S. bioventure. Takeda is devoted to utilizing this global research network to deliver highly innovative pharmaceuticals as quickly as possible.

PROMOTING PATIENT-FOCUSED RESEARCH

Takeda is taking proactive steps to strengthen its pipeline. This involves accurately understanding patient needs and focusing management resources on the Company's four core therapeutic areas: lifestyle-related diseases, cancer and urological diseases, central nervous system (CNS) diseases, and life-cycle management of drugs for digestive system diseases. Takeda further facilitates drug discovery through a product strategy system named the MPDRAP strategy*.

* Enables rapid decision-making by sharing information across each of our marketing, production, development, research, alliance, and patent (MPDRAP) divisions.

CREATING TAKEDA'S NEXT INTERNATIONAL STRATEGIC PRODUCTS

The two most important keys to success as an R&D-driven pharmaceutical company are increasing the success ratio of drug discovery research, and efficiently generating a number of compounds that proceed to the development stage. To achieve that success and to launch the Company's next international strategic products, Takeda scientists are fully devoting themselves to research activities at the two research centers in Japan that created such global products as leuprolide acetate, lansoprazole, candesartan cilexetil, and pioglitazone, and also at Takeda's new overseas research base, which is equipped with a state-of-the-art technological infrastructure.

In addition to its in-house research, Takeda actively engages in joint research with research institutions and companies both in Japan and overseas. In July 2004, Takeda agreed to conduct joint research with the U.S. company Lexicon Genetics Incorporated to identify drug-discovery targets for hypertension treatments. In June 2005, Takeda agreed to conduct joint research with the U.K.'s Paradigm Therapeutics Ltd. in the area of CNS diseases.

TAKEDA SAN DIEGO, INC.: TAKEDA'S FIRST RESEARCH BASE OUTSIDE JAPAN

In March 2005, Takeda acquired Syrrx, Inc. (renamed Takeda San Diego, Inc. [TSD]), a U.S. bioventure with the world's best high-throughput X-ray crystallography technology for analyzing proteins, and an excellent, highly promising R&D pipeline.

The addition of TSD as a new research base to complement Takeda's two research bases in Japan will maximize the synergistic potential within the Company and enhance the efficiency of Takeda's target discovery, search and drug discovery process. This will translate into a strengthened R&D pipeline in terms of both quality and quantity.

IND ENGINE*: ENHANCING THE IDENTIFICATION OF CANDIDATE COMPOUNDS

By in-licensing genomic databases, Takeda is working to build up the foundation of its drug discovery research, in order to strengthen the search for drug discovery targets and the process for optimization of candidate compounds. The recent addition of TSD will enable the rapid clarification of key-keyhole structures between proteins and hit/lead compounds, which are drug discovery targets. It is also expected to enable efficient optimization research and TSD's technology is already being employed on a number of compounds.

*IND (Investigational New Drug application): Submission to the U.S. Food and Drug Administration (FDA) in order to conduct clinical trials on a new drug (candidate).

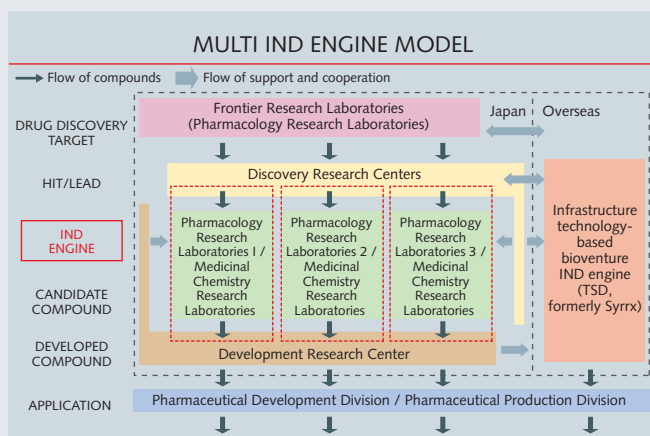
TSD'S PROMISING PIPELINE

In addition to possessing drug discovery research technology, TSD has also synthesized compounds in therapeutic areas such as diabetes and cancer. For diabetes treatment, TSD has synthesized a number of compounds targeting DPP-IV, which are now receiving attention in the industry. The most advanced project is currently in phase II clinical trials. For cancer treatment, TSD has a compound in the pre-clinical stages that targets aurora kinase, which is associated with the division of cancer cells.



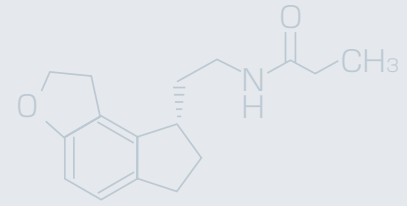
MESSAGE FROM TSD PRESIDENT STEPHEN KALDOR

Takeda San Diego will be a global center for excellence in structure-based drug discovery. We will be an efficient small molecule "IND engine" for Takeda, and will also use our structural biology platform to enable structure-based drug discovery at all Takeda research sites. TSD will support the growing Takeda presence in the United States. We will be a hub for enhancing Takeda's discovery research network, and will also participate in the evaluation of potential U.S.-based research alliance and in-licensing opportunities. TSD will work collaboratively with our colleagues at other Takeda sites to strengthen our collective drug hunting efficiency and enhance the strength of the Takeda pipeline. We will continue to attract world-class talent to TSD and will provide a highly motivating environment for employees to ensure the long term success of the site.



Takeda San Diego, Inc. (formerly Syrrx, Inc.)

ROZEREM: CREATED THROUGH IN-HOUSE R&D



TAKEDA SUPPLIES A TREATMENT WITH A NEW MECHANISM OF ACTION TO PATIENTS WITH INSOMNIA

In July 2005, Takeda received approval to market ROZEREM (generic name: ramelteon) in the United States. This is the first and only prescription insomnia medication which has not been designated as a controlled substance by the U.S. Drug Enforcement Administration. Different from existing insomnia medications, ROZEREM's mechanism of action is to bind MT₁/MT₂ receptors, which control the sleep-wake cycle. MT₁/MT₂ receptors, located in the suprachiasmatic nucleus in the brain, are known as the body's "master clock." ROZEREM triggers and maintains physiological sleep close to natural sleep by specifically acting on these receptors.

PROVEN EFFICACY AND SAFETY

Clinical studies have shown both objectively (using polysomnography) and subjectively (using patient assessments) that ROZEREM shortens sleep latency (the time before the onset of sleep).

Existing insomnia medications, which act on gamma-aminobutyric acid (GABA) receptors located throughout the brain, are known to induce adverse reactions such as dependence, memory and motor disorders. Moreover, other acknowledged problems include somnolence and dizziness the day after taking the medications, as well as even worse insomnia after stopping use (rebound insomnia). In contrast, as for safety, ROZEREM, which exhibits nearly no affinity for neurotransmitter receptors such as GABA or opioid receptors, has not been seen to cause the dependency or rebound insomnia often seen with existing sleeping drugs.

A HIGHLY ANTICIPATED NEW DRUG

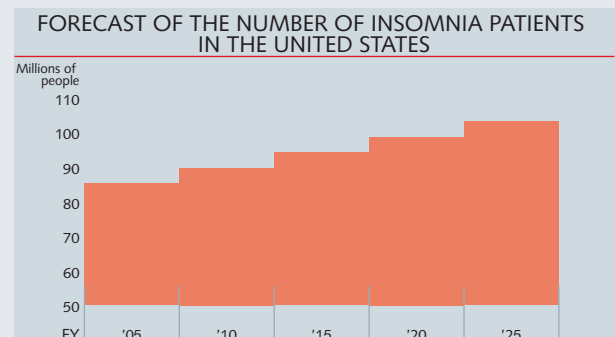
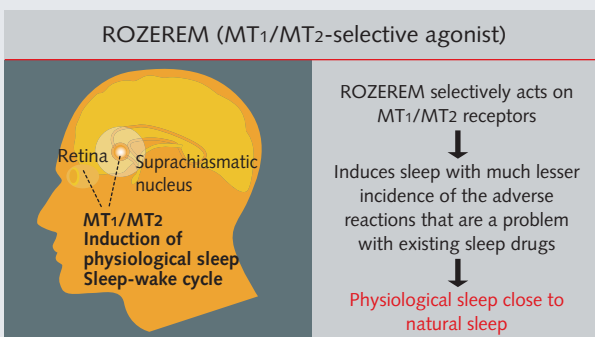
More than 60 million people in the United States suffer from insomnia*. These people complain of symptoms including impaired attention, memory, and

concentration, emotional depression, irritability, and anxiety. As a result, insomnia has been shown to have an adverse impact on work, family, and school life. It is said that over half the U.S. population has experienced insomnia at least one time. The potential insomnia patient pool in the United States continues to grow every year, and therefore, a treatment that is both highly effective and safe is expected by the U.S. public.

From May through June 2005, clinical data demonstrating the efficacy and safety of ROZEREM were presented to the American Geriatrics Society, the American Psychiatric Association, and the Associated Professional Sleep Societies. ROZEREM is also currently undergoing phase III clinical trials on patients with insomnia in Japan and Europe. Takeda is advancing the development of ROZEREM with the aim of making it available as quickly as possible to patients in these regions suffering from insomnia.

*Insomnia: Insomnia is defined in terms of dissatisfaction with the amount and/or quality of sleep, including difficulty in initiating or maintaining sleep, or early awakening with the inability to fall asleep again, and is associated with adverse daytime consequences.

(American Psychiatric Association)



Source: Mattson Jack Group "Epi Database"

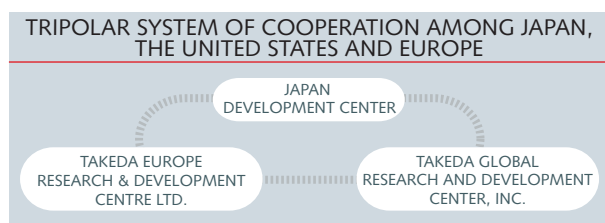
ACCELERATING CLINICAL DEVELOPMENT THROUGH A GLOBAL DEVELOPMENT SYSTEM

TAKEDA'S CLOSE-KNIT TRIPOLAR SYSTEM OF COOPERATION AMONG JAPAN, THE UNITED STATES AND EUROPE

In January 2004, Takeda established the Takeda Global Research and Development Center, Inc. (TGR&D), as a wholly owned subsidiary of Takeda Pharmaceuticals North America, Inc. (TPNA). With the aim of launching new products in the United States, the world's largest market, as top priority, TGR&D conducts integrated clinical trials in the United States and Europe, overseeing and managing the Takeda Europe Research & Development Centre Ltd. (EUR&D), and proceeds to the submission-approval process for new drug applications in the United States. At the same time, TGR&D designs and implements post-marketing surveillance clinical studies and develops strategies for maximizing added value for existing drugs. Takeda continues to coordinate and strengthen its global development system, including the Japan Development Center, and is working to continue achieving sustainable growth for the Company by accelerating the launch of new products.

AGGRESSIVE IN-LICENSING AND ALLIANCE ACTIVITIES: ENHANCING TAKEDA'S PIPELINE COMPANY-WIDE INITIATIVES TO STRENGTHEN TAKEDA'S PIPELINE

Takeda is moving aggressively to strengthen its pipeline in each of its core therapeutic areas. This effort is implemented through three fundamental strategies: (1) in-house research and development; (2) in-licensing and alliances; and (3) life-cycle management (LCM). Moreover, in April 2005 Takeda established a global Product Strategy Team (PST) that will rapidly plan and execute individual product strategies for main R&D projects. This PST complements Takeda's MPDRAP strategy as an execution team for each one of R&D projects.



IN-LICENSING AND ALLIANCE ACTIVITIES: GENERATING RESULTS

Takeda is focusing on in-licensing and alliance activities to complement in-house research as a means of strengthening its pipeline. R&D successes during fiscal 2004 include the following three products. Takeda is moving forward with the development of these products with the aim of launching them in the United States.

DIMESNA

Dimesna was created by BioNumerik Pharmaceuticals, Inc., based out of San Antonio, Texas in the United States. It alleviates the neurotoxicity (characterized by numbness in the extremities, pain, and sensory abnormalities) that develops in nearly half of the patients treated with taxane and platinum classes of chemotherapy drugs, which are standard drugs for some cancers.

Dimesna is currently undergoing phase III trials. Once it is approved and launched on the market, dimesna is expected to help improve patients' quality of life (QOL) by alleviating the neurotoxicity induced by chemotherapy agents. It is also expected to contribute significantly to the continued administration and maintenance of dosage levels in patients in whom chemotherapy would otherwise be unavoidably stopped or dosages reduced due to neurotoxicity.

LUBIPROSTONE

Lubiprostone, a treatment for chronic idiopathic constipation and constipation-predominant Irritable Bowel Syndrome (c-IBS), was created by Sucampo Pharmaceuticals, Inc., based out of Bethesda, Maryland in the United States. In March 2005, Sucampo filed a new drug application in the United States for lubiprostone, with an indication of chronic idiopathic constipation. In parallel to the NDA, Phase III trials in patients are currently ongoing.

Lubiprostone has the potential to become a new treatment for irritable bowel syndrome, a disorder with a large market in the United States, where it is estimated that over 30 million people suffer from this condition.

R851

R851 was created by 3M, based out of St. Paul, Minnesota in the United States. It is a treatment for cervical high-risk human papillomavirus (HPV) infection accompanying cervical dysplasia, which is strongly related to cervical cancer.

It has been reported in the United States that over half of the women who show abnormality on uterine cancer screenings also have a high-risk HPV infection. It is expected that an understanding of the importance of HPV infection treatment will increase the value of R851.

MAXIMIZING ADDED VALUE THROUGH LIFE-CYCLE MANAGEMENT OF DRUGS ALREADY ON THE MARKET

Takeda is aggressively implementing life-cycle management to maximize the added value of drugs already on the market by expanding indications and adding new formulations, all with the aim of improving convenience for medical professionals and patients.

CANDESARTAN (BLOPRESS, AMIAS, KENZEN)

In August 2004, 14 European countries approved a 32-mg high-dose formulation of candesartan. Based on the results of the outcome study CHARM*¹, an additional indication of chronic heart failure was approved in Europe and the United States in November 2004 and February 2005, respectively. Candesartan is the first angiotensin II receptor antagonist to prove its efficacy in reducing mortality in patients suffering from chronic heart failure. Moreover, the outcome study DIRECT is currently being conducted to examine the potential of candesartan to prevent and treat diabetic retinopathy.

*¹ *Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity: An outcome study that examines mortality in patients due to chronic heart failure and the number of hospitalizations due to deterioration of heart failure symptoms.*

ACTOS

In October 2004 and February 2005, respectively, Takeda submitted applications to market a fixed combination product of *Actos*-metformin combination in the United States and Europe. Also, Takeda submitted an application to market a fixed combination drug with *Actos* and glimepiride, a sulfonylurea, both in the United States and Europe in June and July 2005, respectively. In Europe, the outcome study PROactive*² is now being conducted to study the efficacy of *Actos* on macrovascular events in patients with type 2 diabetes. In the United States, Takeda is conducting two post-marketing clinical trials on *Actos*: the CHICAGO study, which studies *Actos*' efficacy for controlling the progress of atherosclerosis, and the PERISCOPE study, which studies *Actos*' efficacy on coronary artery disease.

*² PROspective pioglitAzone Clinical Trial In macro Vascular Events

OUR PIPELINES

Development Code	Generic Name	Brand Name (Country/Region)
LIFESTYLE-RELATED DISEASES		
TCV-116	Candesartan cilexetil	<i>Blopress</i> (Japan, Europe, Asia) <i>Amias, Kenzen</i> , etc. (Europe)
AD-4833	Pioglitazone hydrochloride	<i>Actos</i> (Japan, U.S.A., Europe, Asia)
AO-128	Voglibose	<i>Basen</i> (Japan, Asia)
TAK-475	Not decided	
TAK-428	Not decided	
TAK-654	Not decided	
TAK-536	Not decided	
LY333531	Ruboxistaurin	
TAK-128	Not decided	
SYR-322	Not decided	
ONCOLOGY AND UROLOGIC DISEASES		
TAP-144-SR	Leuprorelin acetate	<i>Leuplin</i> (Japan) <i>Lupron Depot</i> (U.S.A.) <i>Enantone</i> , etc. (Europe, Asia)
TAK-453-SR	Morphine hydrochloride	
MH-15E	Morphine hydrochloride	
CENTRAL NERVOUS SYSTEM DISEASES, BONE/JOINT DISEASES		
TAK-375	Ramelteon	
NE-58095	Risedronate	
TAK-715	Not decided	
GASTROENTEROLOGY DISEASES PRODUCT LIFE-CYCLE MANAGEMENT		
AG-1749	Lansoprazole	<i>Takepron</i> (Japan, Asia) <i>Prevacid</i> (U.S.A., Asia) <i>Ogast, Agopton, Lansox</i> , etc. (Europe)
TAK-242	Not decided	
TMR	Double combination vaccine against measles and rubella	

Drug Class	Indication (Formulation)	Country/Region	Stage of Development					
			Phase1	Phase2	Phase3	NDA submission	NDA approval	
Angiotensin II receptor antagonist	Chronic heart failure	Japan	█	█	█	'01 Dec.		
		U.S.A.	█	█	█		'05 Feb.	
		Europe	█	█	█		'04 Nov.	
	Diabetic nephropathy	Japan	█	█	█			
		Fixed combination with diuretic	Japan	█	█	█	'02 Dec.	
		High dose	Japan	█	█	█		
Insulin resistance-improving drug	Outcome study, DIRECT (Diabetic REtinopathy Candesartan Trial)	Europe	█	█	█			
	Outcome study, PROactive (PROspective PioglitAZone Clinical Trial In MacroVascular Events)	Europe	█	█	█			
Insulin resistance-improving drug	Delay in progression of atherosclerosis	U.S.A.	█	█	█			
		U.S.A.	█	█	█	'04 Oct.		
	Combination drug of Actos/Metformin	Europe	█	█	█	'05 Feb.		
		U.S.A.	█	█	█	'05 Jun.		
Combination drug of Actos/SU	U.S.A.	█	█	█	'05 Jul.			
	Europe	█	█	█				
α-glucosidase inhibitor	Impaired glucose tolerance (IGT)	Japan	█	█	█			
Squalene synthase inhibitor	Hyperlipemia	Japan	█	█	█			
		U.S.A.	█	█	█			
		Europe	█	█	█			
Neurotrophic factor production accelerator	Diabetic neuropathy	U.S.A.	█	█	█			
Insulin resistance-improving drug	Diabetes mellitus	Europe	█	█	█			
		Japan	█	█	█			
Angiotensin II receptor antagonist	Hypertension	U.S.A.	█	█	█			
		Europe	█	█	█			
PKCβ inhibitor	Diabetic maculopathy	Japan	█	█	█			
Myelin formation accelerator	Diabetic neuropathy	U.S.A.	█	█	█			
DPP-IV inhibitor	Diabetes	U.S.A.	█	█	█			
LH-RH agonist	3-month depot/premenopausal breast cancer	Japan	█	█	█	'04 Feb.		
		U.S.A.	█	█	█			
	6-month depot/prostate cancer	Germany	█	█	█	'05 Jun.		
Morphine hydrochloride sustained-release capsules	Cancerous pain	Japan	█	█	█	'03 Nov.		
Morphine hydrochloride injection	Cancerous pain	Japan	█	█	█		'04 Dec.	
MT ₁ /MT ₂ receptor agonist	Insomnia	Japan	█	█	█			
		U.S.A.	█	█	█		'05 Jul.	
		Europe	█	█	█			
Bone resorption inhibitor	Once-a-week formulation	U.S.A.	█	█	█			
		Japan	█	█	█	'04 Dec.		
p38 MAPkinase inhibitor	Rheumatoid arthritis	Japan	█	█	█			
		U.S.A.	█	█	█			
		Europe	█	█	█			
Proton pump inhibitor	Symptomatic-GERD	Japan	█	█	█	'04 Sep.		
		Injectable formulation	Japan	█	█	█	'04 Feb.	
TLR4 Signal transmission inhibitor (STI)	Severe sepsis	Japan	█	█	█			
		U.S.A.	█	█	█			
		Europe	█	█	█			
Double combination vaccine against measles and rubella	Prevention of measles and rubella	Japan	█	█	█	'04 Jun.		