



 **serono**  
biotech & beyond

**living**  
annual review 2001



# another

I would like to welcome you to the Serono Annual Report.

This year we've made the report a little bit different, both to convey the spirit and uniqueness of Serono, as well as to inform you of the essential aspects of our performance and development.

During 2001 the performance of our businesses was excellent with double-digit underlying sales and earnings growth. We made the important decision to reinvest some of this profit immediately into our expanding multiple sclerosis franchise in order to prepare for the launch of Rebif® in the US.

The excellent efficacy of Rebif® three times a week is reflected in the fact that it has become the leading treatment for MS outside the US in 2001. The results of the EVIDENCE study, the head-to-head comparison of Rebif® (44 micrograms three times a week) and Avonex® (30 micrograms administered once a week) were outstanding. The primary and all secondary endpoints were in favor of Rebif® in a statistically meaningful manner at six months.



15% underlying growth in sales

Rebif® became the leading MS therapy outside the US

Approval of Rebif® in the US on March 7, 2002

Launches of Gonal-F® multidose, Ovidrel® and Luveris®

Seven molecules entered preclinical development

## great year

We submitted clinical data from the EVIDENCE study to the FDA during the third quarter of 2001 as part of our application for early marketing approval in the US. I'm delighted to report that on March 7, 2002, we received FDA approval, which is good news for people with multiple sclerosis in the US as well as an important milestone for Serono. Physicians are now free to prescribe Rebif® to patients in the US who have relapsing forms of MS.

Turning to reproductive health, Serono is the only company with a highly pure, totally recombinant portfolio, thus providing physicians with flexible, state-of-the-art treatments for infertility. In 2001 we launched a multidose form of Gonal-F® which better enables physicians to control and tailor the daily dose of recombinant FSH for their patients. With the introduction of the two new recombinant products Luveris® and Ovidrel®/Ovitrelle®, Serono became the only company to provide all three recombinant hormones involved in the treatment of infertility. All of these products have been well received by physicians and patients alike.

We continue as the world leader in infertility treatment. These launches, along with the new molecular entities we have in our pipeline, will consolidate that leadership over the next few years.

With the launches of the cool.click™ and one.click™ injection devices, which make life easier for children suffering from growth retardation, Saizen® had an excellent year.

The year also saw Serono receiving approval in Europe for the use of Saizen® in adult growth hormone deficiency. Serostim®, our HIV-associated wasting treatment, had a more complex time, due to the tightening of reimbursement guidelines in the US.

In clinical development, good progress has been made with interferon-beta and TNF binding protein, which are both in large Phase 2 clinical trials in inflammatory bowel diseases and rheumatoid arthritis. IL-18 binding protein recently entered Phase 1 development targeting rheumatoid arthritis and Crohn's disease. I look forward to seeing the results of some of these in 2002.

A development that particularly delighted me was our highly innovative and ground-breaking research in the detection of prions, as published in *Nature* in June 2001. Our early results raise the possibility of being able to detect the presence of abnormal disease-causing prions in human beings. Related research on the modification of protein configuration may offer potential treatments for illnesses such as Alzheimer's disease.

The team responsible for this research – our “pioneers” – is one of many working within Serono at the frontiers of science, to explore innovative therapies based on a profound understanding of disease biology and molecular approaches to therapy. Given these innovations I strongly feel we have much to look forward to in 2002 and the years ahead.

I hope you enjoy our Annual Report for 2001.

Ernesto Bertarelli  
Chief Executive Officer

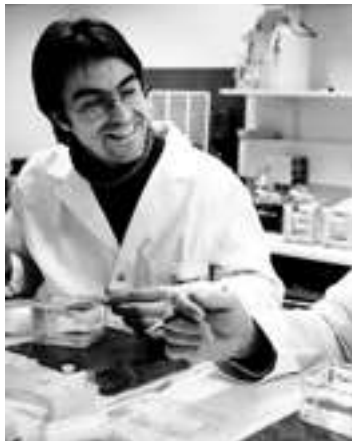
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## Rebif® special





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# the <sup>R</sup>pioneers

## Major scientific breakthroughs on prions

“A sense of urgency drives our research. We realize that what we are doing here could have enormous benefits for the patient.”

A team of researchers at the Serono Pharmaceutical Research Institute has discovered a revolutionary approach for the possible treatment and early detection of prion diseases. These include new variant Creutzfeldt-Jakob disease (vCJD) – the human equivalent of bovine spongiform encephalopathy (BSE) or “mad-cow” disease.

Using a laboratory-engineered peptide called a “beta-sheet breaker,” Serono’s researchers have been able to change the abnormal structure of prions back into the normal configuration of the protein. This procedure (described in *The Lancet*, January 2000) has significantly slowed the progression of prion disease in the laboratory. Pre-clinical trials are ongoing. Presently, there is no treatment for Creutzfeldt-Jakob disease. Once patients have symptoms, their life expectancy is between six months and two years.

### Detection methods complement therapeutic approach

Serono’s researchers have made another breakthrough in detecting prions.

Using a patented process known as “cyclic amplification” (described in *Nature*, June 2001), the team has succeeded in cultivating disease-causing prions *in vitro*. This procedure replicates prions in a “fast-forward” mode, condensing years of incubation time in, for example, cattle or humans into a few hours in the laboratory.

This breakthrough has far-reaching implications. Until now, detection methods for BSE or vCJD could only be performed on the brain tissue of deceased animals or humans. The work of Serono’s team will permit the development of more sensitive detection methods. The ultimate goal is to detect vCJD in humans and BSE in animals at a very early stage using blood or non-central-nervous-system tissue.

Preliminary tests on blood from prion-infected animals have been encouraging. Serono is in discussions with potential partners who specialize in developing and marketing diagnostic tests.

### Will an unidentified factor hold the key to some brain diseases?

Prions, a new class of infectious agent, are a modified form of a normal protein. The function of this normal protein is not yet known, however, it sometimes undergoes a change in its structure, and adopts an abnormal shape known as the beta sheet, which is infectious. A slow, but relentless, chain reaction ensues as more and more of the normal protein molecules are converted to the abnormal form – the prion. Serono’s researchers are developing a patented “beta-sheet breaker” peptide that reverses the process, causing the prion to revert back to a normal shape that is no longer infectious. This revolutionary new procedure has potential applications not only in prion diseases such as Creutzfeldt-Jakob, but also in Alzheimer’s and other diseases caused by abnormal protein conformations. Serono’s team and other scientists around the world are now racing to discover an unidentified factor in the brain that facilitates the infectious process caused by abnormal protein shapes and which could hold the key to unlocking the secrets of a number of diseases of the brain.

### Speaking as a doctor

One of the scientists responsible for prion research on Serono’s team is also a physician and knows what it meant to care for patients with devastating diseases such as Creutzfeldt-Jakob or Alzheimer’s. “Our team is conscious of the potential impact of our work on human lives,” she explained. “A sense of urgency drives our research. We realize that what we are doing here could have enormous benefits for the patient.”



# Alzheimer's disease affects some 25 million people worldwide



## Potential treatment for Alzheimer's disease

Serono's groundbreaking research on beta-sheet breakers extends to Alzheimer's disease, which affects some 25 million people worldwide. The Serono team has convincing evidence from animal studies to show how the abnormal amyloid protein that causes Alzheimer's is successfully changed back to its normal conformation. The data revealed a reduction of more than 50% of amyloid plaques in the brains of animals and a substantial decrease in neuronal death, which leads to the debilitation of Alzheimer's.

### Adding years to a patient's life

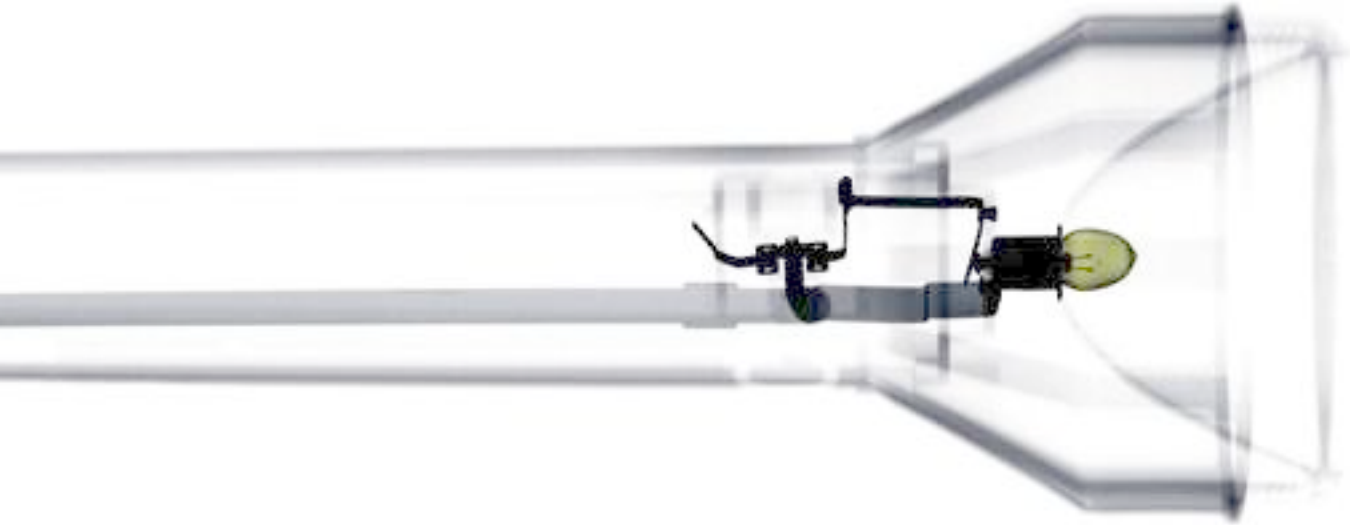
Preclinical trials in a model of Alzheimer's disease are ongoing and if these substantiate the initial positive findings, Phase 1 trials with human volunteers could begin in 2002. While this approach will probably not offer a cure for the disease, it may significantly delay its onset – slowing debilitation and perhaps adding years to a patient's life. That's why early detection and treatment are so critical, before too many neurons have been damaged. If Serono's patented cyclic amplification technique proves successful in detecting prion diseases at an early stage (see facing page), a comparable diagnostic test may also become possible for Alzheimer's disease.

### Lead optimization

Building on the discovery of a beta-sheet breaker for the Alzheimer-causing amyloid protein, a team at Serono Pharmaceutical Research Institute has optimized its efficacy and stability by making small adjustments to its molecular structure.

The resulting compound is relatively stable in the body and penetrates the blood brain barrier at an unusually high rate, important since Alzheimer's therapies are targeted at the brain. Because beta-sheet breakers are small molecules, an oral form of therapy may even become possible with additional optimization; however, for the time being, the most likely therapeutic form will be a subcutaneous injection.

Serono is a world leader in biotechnology innovation. We are building a world class and leading edge discovery capability, focused upon using the best technology to find proteins and other molecules with potential as significant treatments.



# leading the way



## Functional genomics

The driving force of genomics has been the ability to sequence entire genomes using automated DNA sequencing that culminated in 2001 with the publication of the first draft of the human genome. Serono's functional genomics program will identify some of the pharmaceutically valuable proteins encoded in the human genome. To have the entire genetic content in a computer file is only the start of a new epoch in biology that is called the post-genomic era. Our challenge is to identify the function of the therapeutically important proteins through a highly parallel processing of the genome using high throughput bioinformatics, protein expression and cellular biological assays.



## High throughput screening

Serono's high throughput screening is used in our effort to find new medicines. It begins with data analyses that are conducted using a proprietary, substructure-identification process termed "discrete sub-structural analysis". When used to direct high throughput screening efforts, the end result is a revolutionary discovery process that is 20 to 100-fold more effective than random screening – and is unique to Serono. These sophisticated techniques, allow the members of the design technologies teams to play an important role in the Serono drug discovery process.



## In silico pharmacology/ structure-based design

Drug discovery research is a highly integrated, multidisciplinary process. Serono has improved the process by integrating a group of scientists working in design technologies who apply knowledge-based *in silico* techniques for small molecule discovery and in the design of protein drug candidates with improved properties (metabolic stability, reduced immunogenicity, modified biological activity, etc.). The structure-based design of potential drug candidates (proteins or small molecules) is based on state-of-the-art X-ray crystallography.



## Pharmacology

Drug discovery begins with a basic understanding of disease. Pharmacology research in Serono revolves around the development and deployment of state-of-the-art models of human disease. The pharmacology research units are integrally involved in multidisciplinary teams focusing on drug target identification and target validation and in the downstream processes of drug candidate optimization, through testing in proof of concept studies in relevant disease models.

# DISCOVERY

THE SEARCH FOR TREATMENT TO HELP MS SUFFERERS

AT SERONO HQ...



TO CREATE NEW TREATMENTS FOR MS WE HAVE TO GET INSIDE BAD CELLS AND REWIRE THEM

BUT THERE ARE SO MANY TARGETS... WHERE DO WE START?



DR X WILL HAVE SOME IDEAS. LET'S PAY HIM A VISIT

AT DR X'S PLACE...

THE LATEST RESULTS FROM OUR LABS SHOW THAT Z-KINASE CONTROLS THE LIFE OF NERVE CELLS IN MS. IF ONLY WE COULD BLOCK IT...



...THERE ARE INFINITE POSSIBILITIES. BUT WE KNOW THE STRUCTURE OF Z-KINASE. NOW WE MUST SEARCH OUR MOLECULE LIBRARIES TO FIND THE RIGHT INHIBITOR

LATER IN THE ROBOT LAB...

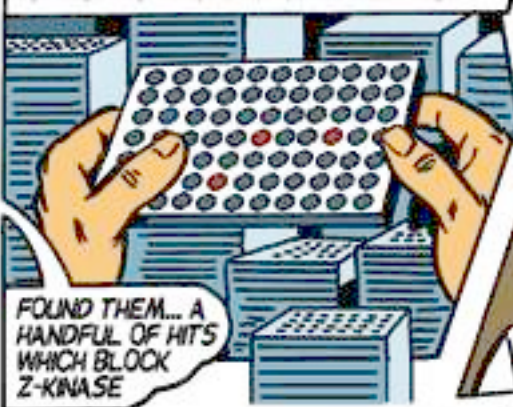


WE SCREEN THOUSANDS AND THOUSANDS OF HAND PICKED MOLECULES ON REAL CELLS.

THE SEARCH CONTINUES...



AT LAST AFTER MONTHS OF TESTING...



FOUND THEM... A HANDFUL OF HITS WHICH BLOCK Z-KINASE

THE CHEMISTS KNOW WHAT THEY MUST DO...



WE NEED TO REFINE THESE COMPOUNDS...

THEY HAVE TO BE EXACTLY THE RIGHT SIZE...

HAVE THE RIGHT ELECTRIC CHARGE AND SOLUBILITY...

ARGH!! NO HOLIDAYS FOR THE NEXT SIX MONTHS

PUTTING ON THEIR 3D GLASSES THE CHEMISTS PERFECT THE MOLECULES



FINALLY, A LEAD COMPOUND



YES!

THIS IS WHAT IT'S ALL ABOUT! ...NOW WE HAND IT OVER TO THE DEVELOPMENT GUYS!

TO BE CONTINUED...

EARLY IN 2001 AFTER 3 YEARS OF WORK, A LEAD COMPOUND WHICH BLOCKS THE ENZYME JUN-KINASE AND WHICH COULD PREVENT THE INFLAMMATORY PROCESS TYPICAL OF MS, WAS PUT INTO PRE-CLINICAL DEVELOPMENT...

# our pipeline

Serono's approach to R&D ensures that we have a strong pipeline with wave after wave of products in development. In addition to the six recombinant products which are currently marketed (see pages 12-13), Serono has fifteen molecules in its development pipeline. Of these, eight are recombinant proteins, the rest being small molecules. As well as our current three therapeutic areas where we already have marketed products, we are also developing products in other areas as diverse as ulcerative colitis, psoriasis and rheumatoid arthritis.

Therapeutic area	Pre-clinical phase
<b>Reproductive health</b>	<b>oxytocin receptor antagonist</b> pre-term labor
<b>Neurology</b>	<b>breaker peptide</b> Alzheimer's disease <b>chemokine inhibitor</b> multiple sclerosis <b>IKK-2 inhibitor</b> multiple sclerosis <b>JNK inhibitor</b> central nervous system disorders
<b>Growth and metabolism</b>	<b>PEG GHRF</b> growth retardation
<b>Gastroenterology</b>	
<b>Inflammatory and autoimmune diseases</b>	<b>IKK-2 inhibitor</b> rheumatoid arthritis <b>JNK inhibitor</b> ischemic and inflammatory conditions <b>TACI</b> autoimmune conditions <b>BCMA</b> autoimmune conditions
<b>Oncology</b>	<b>itrelax nanospheres (GnRH antagonist)</b> prostate cancer
<b>Cardiology</b>	

## Glossary

**Pre-clinical** Investigate safety of a product candidate in a controlled laboratory environment

**Phase 1** Clinical trials in healthy volunteers to determine safety, dosages and the best route for delivery of the medicine

**Phase 2** Clinical trials in patients to further determine dose, safety and efficacy

**Phase 3** Large clinical trials to determine definitive safety and efficacy in patients

Phase 1	Phase 2	Phase 3	Filed
<b>microencapsulated r-FSH</b> to reduce the frequency of administration of r-FSH  <b>r-LIF</b> embryo implantation failure  <b>type 1 5-alpha reductase inhibitor</b> hirsutism associated with polycystic ovarian syndrome	<b>r-LH (high dose)</b> ovulation trigger in female infertility (OI)  <b>r-TBP-1</b> endometriosis (planned)	<b>r-LH (high dose)</b> ovulation trigger in female infertility (ART)	<b>Luveris®</b> hypogonadotropic hypogonadism in women – US  <b>Gonal-F®</b> fill by mass – US, EU
<b>IFNAR-2</b> to increase the half life of IFNβ-1a  <b>PEG r-IFNβ-1a</b> to increase the half life of IFNβ-1a	<b>r-IFNβ-1a</b> Guillain-Barré syndrome		<b>Rebif®</b> relapsing forms of multiple sclerosis – US*   <small>*Approved by FDA on March 7, 2002</small>
	<b>r-GH</b> HARS/lipodystrophy		<b>Serostim®</b> AIDS wasting – EU
<b>r-IL-18 bp</b> Crohn's disease	<b>r-IFNβ-1a</b> Crohn's disease  <b>r-IFNβ-1a</b> ulcerative colitis  <b>r-TBP-1</b> Crohn's disease  <b>r-IFNβ-1a</b> chronic hepatitis C – a genotypic subgroup of patients	<b>r-GH</b> short bowel syndrome	
<b>r-IL-18 bp</b> rheumatoid arthritis	<b>r-IFNβ-1a</b> rheumatoid arthritis  <b>r-TBP-1</b> rheumatoid arthritis  <b>r-TBP-1</b> psoriasis and psoriatic arthritis		
<b>type 1 5-alpha reductase inhibitor</b> prostate disease	<b>r-hCG</b> breast cancer		
	<b>r-TBP-1</b> cardiac reperfusion injury		

**Filed** File under review by regulatory authorities  
**AIDS** Acquired immune deficiency syndrome  
**ART** Assisted reproductive technologies  
**BCMA** B cell maturation antigen  
**EU** 15 European Union member countries  
**GnRH** Gonadotropin releasing hormone  
**GHRF** Growth hormone releasing factor  
**HARS** HIV-associated adipose redistribution syndrome  
**OI** Ovulation induction

**PEG** Pegylated – the addition of polyethylene glycol molecules to a potential drug candidate in order to modify some of its properties such as solubility, stability, pharmacokinetic half-life or immunogenicity profile  
**r-hCG** Recombinant human chorionic gonadotropin  
**r-FSH** Recombinant follicle stimulating hormone  
**r-GH** Recombinant growth hormone  
**r-IFNβ-1a** Recombinant interferon beta-1a  
**r-IL-18 bp** Recombinant interleukin-18 binding protein

**r-LH** Recombinant luteinizing hormone  
**r-LIF** Recombinant leukemia inhibitory factor  
**r-TBP-1** Recombinant tumor necrosis factor binding protein 1  
**TAC1** Transmembrane activator and CAML-interactor

# our products

We are proud of our six recombinant products. They will make a significant contribution to the future of both medical practice and the company.



## Gonal-F®



Name: follitropin alfa  
Strength: 37.5IU, 75IU, 150IU, 1200IU multidose

## Ovidrel®/ Ovitrelle®



Name: choriogonadotropin alfa  
Strength: 250mcg

Gonal-F® is a preparation of recombinant FSH which was first registered in 1995. It is registered in 81 countries worldwide for the treatment of female infertility and in 44 countries worldwide for the treatment of male infertility. Following regulatory approvals in the EU and USA, a multidose formulation was launched in 2001. It is now registered in 24 countries.

Ovidrel®, the first and only available preparation of recombinant hCG was launched in 2001 following regulatory approval in the USA and EU. It is registered in 19 countries for ovulation induction in women undergoing treatment for infertility. It has been launched in the USA as well as three European countries in 2001 and roll out is continuing in 2002.



## Luveris®

## Rebif®

## Serostim®

## Saizen®



Name: lutropin alfa  
Strength: 75IU

Name: interferon-beta 1a  
Strength: 22mcg, 44mcg

Name: somatotropin  
Strength: 4mg, 5mg, 6mg

Name: somatotropin  
Strength: 1.33mg, 3.3mg, 5mg, 8mg

Luveris®, the first and only available preparation of recombinant LH was launched in 2001. It is registered in 26 countries for the treatment of infertility in women with hypogonadotropic hypogonadism who are unable to produce adequate amounts of LH and FSH in their pituitary glands. It has been launched in 9 countries and filed in a further 14 countries.

Rebif® is a preparation of recombinant IFNβ-1a which was first registered in 1997. It is now available in 76 countries worldwide for the treatment of patients with relapsing remitting multiple sclerosis. In 2001 the European Commission approved expansion of the label to include all forms of relapsing multiple sclerosis. Serono offers the highest available registered dose of IFNβ-1a (44mcg 3x week) and this dose has been approved as first line Rebif® therapy in the EU countries.

Serostim® is a preparation of recombinant hGH which was first registered in 1996 for the treatment of HIV-associated wasting. It is registered in the USA and 11 additional countries. A needle-free injection device Serojet™ was launched in February 2002, following approval from the US Food and Drug Administration.

Saizen® is a preparation of recombinant hGH which was first registered in 1989. It is registered in 81 countries for the treatment of growth retardation due to a variety of causes. Following its approval in Europe for growth hormone deficiency in adults in 2001, it has already been launched in the first two countries for this indication. Saizen® can be conveniently injected using either the needle-free injection device cool.click™ in North America or the state-of-the-art autoinjector one.click™ in Europe.

**STOP PRESS**

MARCH 7 2002

**APPROVED  
LAUNCH IN THE US**

# Rebif®

## The world's fastest growing MS therapy

Only four years after launch, Rebif® has become the leading treatment for multiple sclerosis outside the United States and Serono's biggest selling drug. Why? Excellent efficacy. Rebif® 44 micrograms three times per week (44mcgx3) is the highest dose treatment of recombinant interferon-beta 1a available. Provided as a liquid in a pre-filled syringe, it is also practical to use. That's why physicians and patients have made Rebif® the fastest growing MS therapy outside of the US. As of March 7, 2002, Rebif® is now available to patients in the United States.



# Living life...



**Giving MS patients new hope**  
Multiple sclerosis is a disease that typically strikes young adults in the prime of their lives, afflicting women twice as often as men. Until recently physicians could only treat the symptoms of multiple sclerosis as the disease inexorably took its toll. In the 1990s, interferon-beta, a natural human protein, showed positive results in treating MS in the first clinical trials. While interferon-beta did not offer a cure, it delayed the progression of disability in MS and reduced its severity. Serono, a pioneer in discovering and developing human proteins for therapeutic purposes, launched a pure, recombinant form of interferon-beta in 1998 in Europe.

What makes Rebif® so remarkable is its efficacy: 44 micrograms administered three times a week has achieved excellent results in treating relapsing forms of multiple sclerosis. By significantly reducing the frequency and severity of relapses and slowing the progression of disability, Rebif® helps patients better manage the disease and lead more active, normal lives. Available in a convenient, pre-filled syringe, Rebif® may be used with an autoinjector, the Rebiject®, which makes administration quick and easy. It's more than a compelling story of efficacy and convenience. It's a new sense of hope. That's why so many MS patients are asking their doctors specifically for Rebif®.



### What is multiple sclerosis?

Multiple sclerosis is an autoimmune disease that targets the central nervous system – the brain and spinal cord. While the cause of MS is still unknown, the disease mechanism is better understood. The body's own immune system attacks the myelin sheaths that contain sensitive nerve bundles. Once this protective layer is stripped away, scar tissue forms that interrupts the neural impulses, triggering sensory distortion, loss of movement and irregular bodily functions that gradually become more severe. The disease takes its name from this scar tissue, which becomes hard or "sclerotic," and may form at multiple sites in the central nervous system.

The first signs of MS are often numbness or tingling sensations, problems with balance or partial loss of vision. The disease itself is rarely fatal, but may lead to extreme disability and even paralysis. Almost 50% of MS patients suffer from a relapsing-remitting form of the disease, which means that periodic surges of debilitation are followed by a lessening of symptoms. The course of multiple sclerosis varies in every individual.

Total commitment to the field of MS Nurses spend more time with MS patients than physicians. They are often the patient's most important point of medical care. To raise professional standards and share best practices, Serono has supported MS nurses' associations in a number of

countries. Continuing education courses focus on both treatment and alleviating the physical symptoms of MS, as well as on the psychological and emotional aspects of the disease.

Serono Symposia has recently launched a program called MS Academia. In intensive courses, top opinion leaders in the field pass on their knowledge to young neurologists who want to specialize in MS.

Serono's extensive clinical studies on multiple sclerosis have not only documented the efficacy and safety of Rebif®, but also helped the medical community understand more about the disease itself. These insights are being applied to our research and discovery efforts as we look for even better therapies and perhaps, one day, find a cure.

# ...to the fullest





# Strong evidence of efficacy

EVIDENCE<sup>1</sup> was the largest comparative study of two disease modifying therapies in MS, involving 677 patients with relapsing-remitting multiple sclerosis at 56 sites in North America and Europe. The study provided a direct, head-to-head comparison of Rebif® (44 micrograms administered three times per week) and Avonex® (30 micrograms once a week) – the standard doses of both products.

Results showed statistically significant benefits on all primary and secondary outcomes measured over 24 weeks. The primary endpoint of the study was based on a comparison of the proportion of patients who did not experience a relapse during this period. The secondary endpoints included a number of other clinical and brain scan parameters.

As expected, and consistent with the high dose of interferon-beta therapy, side effects were more common with Rebif® but had little impact on the ability of patients to continue on treatment.

Serono submitted clinical data from the EVIDENCE study to the FDA during the third quarter of 2001 as part of its application for marketing approval in the US.

<sup>1</sup>Evidence for Interferon Dose-response: European-North American Comparative Efficacy.

## Talking shop Solid science based on clinical results

Rebif® has solid scientific foundations, with over 3,000 MS patients around the world having participated in Serono's clinical studies and the accumulation of over 7,000 "patient years" of data. These studies have helped us – and neurologists around the world – to better understand multiple sclerosis and the best ways to treat it. The findings from some of the most important studies in our program were published during 2001 in top peer-reviewed medical journals.

One of these publications concerned the four-year data from the PRISMS study. This study, which was first published in *The Lancet* in 1998, demonstrated the efficacy and safety of Rebif® and was the basis for the initial registration in many countries around the world. The recently released long-term data, published in *Neurology* in June 2001, was accompanied by a strong statement from the editors describing the four-year data from PRISMS as: "the most convincing evidence yet that patients with relapsing-remitting MS treated with interferon-beta will develop less permanent disability."

The EVIDENCE study, the largest-ever comparative trial of interferon therapies, demonstrated a significant statistical difference between Rebif® and Avonex® in preventing relapses and reducing the number of active brain lesions during the first six months of therapy. The data from this study was first presented at the World Congress of Neurology in London in June 2001. Shortly afterwards it was filed with the FDA.

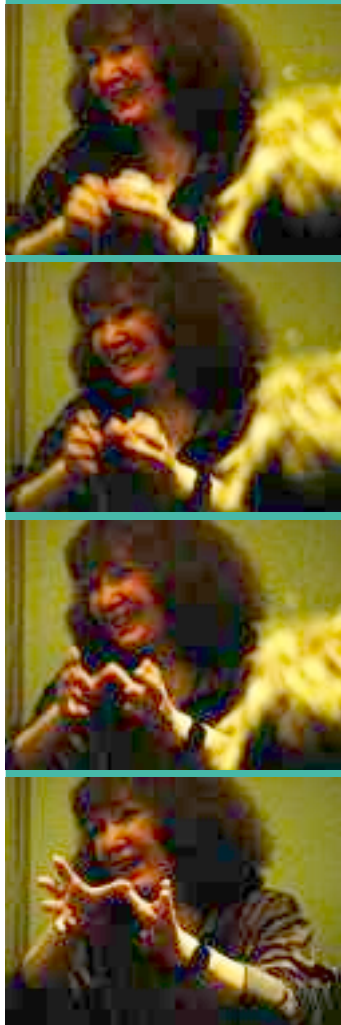
Data from two other important studies in our program, one in patients with an early stage of the disease (ETOMS), and the other in the secondary progressive phase of the disease (SPECTRIMS), were also published during the year in *The Lancet* (May 2001) and *Neurology* (June 2001), respectively. In the fourth quarter of 2001, the European Commission approved expanding the Rebif® label to cover treatment of patients with early secondary progressive disease who are still suffering from relapses.

All of the above studies were identified as class 1 in terms of quality in a recently published review of the literature pertaining to multiple sclerosis therapy by Goodin and his colleagues on behalf of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines (*Neurology*, January 2002).

## Spotlight on Rebif® at the World Congress of Neurology

The main plenary forum of the World Congress of Neurology in London was packed on June 22, 2001 as Dr. Patricia Coyle, Professor of Neurology at the School of Medicine, State University of New York at Stony Brook, explained the design of the study and presented the findings of EVIDENCE, the first head-to-head trial between Avonex® and Rebif®.

Later that day, Dr. Coyle was asked for her personal opinion on the impact of EVIDENCE for physicians and patients: "This is a well-designed, cutting-edge clinical trial with a clear outcome. The results need to penetrate the neurological community so that we can do the right thing for the patient. This will clearly impact our therapeutic practice."





# It's **cool** to click!

Nobody likes needles – especially children. But for an estimated 10,000 - 15,000 children in the US who suffer from pediatric growth hormone deficiency (GHD), daily needle injections can be a normal part of their treatment regimen. However, some of them now have a different way to take their medication. Cool.click™ is the first needle-free drug delivery system in the US and Canada for growth hormone. It was introduced there in 2000 exclusively for use with Saizen® and will be launched in other parts of the world in 2002.

**Children who use cool.click™ think of it as a fun way to make them grow. For their parents, Serono provides a treatment and needle-free delivery device that offers convenience and peace of mind. Cool.click™ helps to improve the lives of patients by offering them an alternative, as Saizen® is dispersed through the skin in a fine stream in less than a second. Patients prefer cool.click™ over conventional needles and syringes.**

#### **What is Pediatric Growth Hormone Deficiency?**

Many factors are involved in the growth of an infant to an adult. Growth is a complex process involving a number of genes and hormones, as well as nutrition, diet, exercise and rest. Growth hormone is central to growth and development, and is the principal hormone governing height in an individual. Some children grow abnormally slowly due to a deficiency of growth hormone or other problems (Turner's syndrome or kidney failure, for example). In most cases GHD is caused by a problem with the pituitary gland or hypothalamus, either while the fetus is in the womb (congenital) or as a result of damage or disease (acquired).

In some cases there is no apparent cause (idiopathic). Pediatric GHD is a result of the body's inability to naturally produce or release an adequate amount of growth hormone to stimulate normal growth. Children may be growth hormone deficient if they experience a growth rate of less than two inches (five centimeters) per year between the age of two and puberty, or if they are extremely small for their age. Once diagnosed, GHD is treated with growth hormone to stimulate or replace the growth factors the body normally produces, and treatment is usually continued for several years until the child reaches

puberty or maximum growth potential is reached. Because treatment typically includes daily injections, many parents and children are understandably anxious to find a therapy solution that does not require the use of needles.

Ease of use increases patient acceptance so the introduction in mid-2001 of one.click™, the world's only true autoinjector, and click.easy™, a simplified reconstitution system, was another advance for Saizen® users. This next-generation delivery device offers pain-free administration of Saizen® in one simple step and will be launched in additional markets during 2002.





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Your questions answered by  
Silvano Fumero, who heads  
Serono's activities in Research and  
Pharmaceutical Development

**What are the unique strengths of research and development at Serono?**

Serono is a world leader in developing innovative therapies based on human proteins. Some of these are multifunctional cytokines, which means they have broad activities with potential in many therapeutic areas. In discovery, we have established disease models in-house that allow us to better predict which human diseases might be treated by our protein therapeutics.

In recent years, our R&D efforts have expanded to small molecules with the potential to be administered orally – a big step forward in patient convenience. Our researchers have created highly focused screens for the right molecules against the right targets. Based on a good understanding of the biology, the disease, and the molecular nature of the target, we have identified a number of compounds that are now in development. Serono's small multidisciplinary teams are very efficient in bringing potential new drugs quickly to the stage of clinical evaluation.

**How can you compete against the greater resources of "Big Pharma"?**

This may sound provocative, but I don't believe that successful R&D is primarily based on financial resources; it is now clear that there is no direct correlation between money spent and the number of new medicines discovered. Success is more a function of creativity and the ability to identify new opportunities.

Today, the centralized research organizations of "Big Pharma" are so large and unwieldy that it is difficult for them to maintain an overview – let alone identify and nurture new ideas. Moreover, they segregate disciplines, preventing the interactions that are essential to creative discovery. Small scientific teams that are prepared to look for the unexpected and pursue new opportunities have a much greater chance for real breakthroughs.

## “We are prepared to look for the unexpected”

In R&D, we have discovered that small, interdisciplinary teams are the best way to make real breakthroughs. These teams share insights, challenge individual assumptions and pursue the unexpected. The result is a working environment that fosters creativity, the source of our success and the engine of our future.

That's why many pharmaceutical companies have outsourced much of their R&D. These large companies are now concentrating on what they do best – clinical development and marketing – leaving the discovery of new drugs to the biotechs.

### **How is Serono tapping into the revolutionary field of genomics?**

Decoding the human genome is a revolutionary step in understanding the “engineering plans” for human life. However, the list of human genes and the proteins they code for is of limited value without knowing the function of these proteins. At Serono, we have a long history of studying proteins and their role in human health and disease. Unlike many biotechnology companies, we have closely linked our traditionally strong departments of pharmacology and toxicology to our genomic efforts. This link allows us to rapidly test new proteins for their function, currently about 400 per month.

### **Which of Serono's current therapeutic areas could be strengthened by the discovery pipeline?**

We have a number of new molecules with potential in the field of neurology, our fastest growing therapeutic area. For example, our IKK-2 and JNK inhibitors, orally active small molecules, have both shown very positive results in experimental models of multiple sclerosis. In addition, we are developing a molecule designed to treat Alzheimer's disease, a neurological disorder that affects some 25 million people and is likely to increase as the world's population ages.

In reproductive health, we are developing another multi-functional cytokine protein, LIF, to improve embryo implantation in assisted reproductive therapies. We have also discovered a small molecule antagonist of the oxytocin receptor that we are testing for the prevention of premature childbirth – a serious cause of illness in infants with life-long repercussions (see also page 39).

### **Are you working on molecules that could open up new therapeutic areas?**

The most likely new indication for us is rheumatoid arthritis (RA), a debilitating disease that affects millions of people, particularly women. Large Phase 2 clinical studies with interferon-beta 1a (IFN $\beta$ -1a) and TNF binding protein (TBP-1) were started during 2001 and will yield results in 2002. A study of TBP-1 in patients with psoriasis or psoriatic arthritis has just commenced patient enrollment. Another protein therapeutic that we are developing, IL-18 binding protein, has also shown good results in models of RA and is now in Phase 1 clinical trials. Gastroenterology could also become a new therapeutic area for us – TBP-1 and IFN $\beta$ -1a are both in Phase 2 studies in Crohn's disease and the latter is also being tested in ulcerative colitis.

### **Which R&D project do you personally find the most exciting?**

Several innovative and creative R&D projects deserve mention. If I had to pick just one, I would choose the protein refolding peptides being investigated in our Geneva lab. These molecules have the potential to treat a number of devastating diseases. Currently, we are evaluating them as a potential therapy for Alzheimer's disease and variant Creutzfeldt Jakob (vCJD) disease, the human equivalent of bovine spongiform encephalopathy or “mad cow” disease. Right now this team is racing to identify an additional substance in the brain that makes normal human proteins change their shape, thereby causing vCJD. If this turns out to be a good drug target, we may be able to treat other brain diseases as well. This project is a good example of how a small, creative team and an elegantly simple idea have put Serono at the cutting edge of science.