



ANNUAL REPORT 2006





Our objective: to be a worldwide best-in-class group of innovative drugs, addressing unmet medical needs in its targeted therapeutic areas: oncology, endocrinology and neuromuscular disorders.



MORE THAN **20**  
R&D PROGRAMMES,  
including 9 new  
chemical entities  
in clinical development

€**178.3**  
MILLION OF R&D  
EXPENDITURE IN 2006

€**861.7**  
MILLION OF SALES  
IN 2006

€**945.3**  
MILLION OF TOTAL  
REVENUES IN 2006

## Facing up to the future

Ipsen is an innovation driven international specialty pharmaceutical group with over 20 products on the market and a total worldwide staff of nearly 4,000. The company's development strategy is based on a combination of products in targeted therapeutic areas (oncology, endocrinology and neuromuscular disorders) which are growth drivers, and primary care products which contribute significantly to its research financing. This strategy is also supported by an active policy of partnerships. The location of its four Research and Development centres (Paris, Boston, Barcelona, London) gives the Group a competitive edge in gaining access to leading university research teams and highly qualified personnel.

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## KEY FIGURES 2006

A solid performance despite a challenging environment

**+7.6%**

Drug sales

**+10.2%**

Volume of drugs sold

**+13.4%**

Specialist care product sales

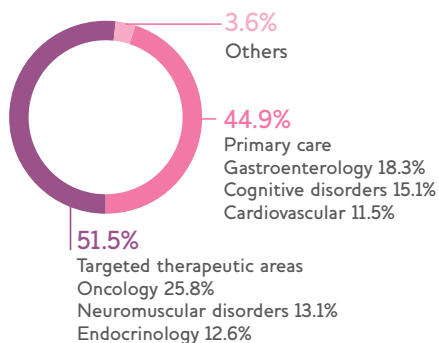
**+19.3%**

Sales outside major Western European countries

2006/2005 growth rates

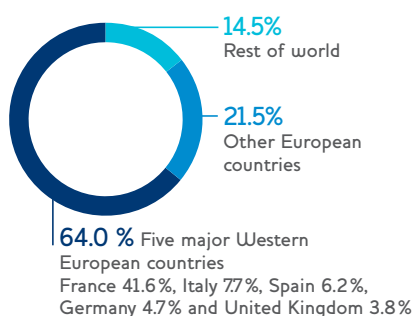
### SALES

by therapeutic area



### SALES

by geographical area



### Net sales of Group's leading products (€ million)

|                     | 2006  | 2005*<br>on a comparable<br>structure basis | Change<br>2006/2005<br>on a comparable<br>structure basis |
|---------------------|-------|---|---|
| Decapeptyl®         | 221.9 | 210.6                                       | +5.4%   |
| Tanakan®            | 129.9 | 121.0                                       | +7.4%   |
| Dysport®            | 113.3 | 92.5  | +22.5%  |
| Somatuline®         | 92.2  | 81.8  | +12.8%  |
| Smecta®             | 80.3  | 67.5  | +18.7%  |
| Nisis® and Nisisco® | 50.7  | 41.5  | +22%  |
| Forlax®             | 46.3  | 42.8  | +8.3%   |
| Ginkor Fort®        | 41.7  | 61.2  | -31.8%  |
| NutropinAq®         | 14.7  | 5.7   | +156.6%   |

\* All financial information for 2005 is shown on a pro forma basis. The pro forma consolidated statements present the Group's activity as if the legal reorganisation of the Group, completed in June 2005, had taken place on 1 January 2002.



### Total revenues (€ million)

2005// 887.9

2006// 945.3

+ 6.5%

In 2006, total revenues reached €945.3 million. They include:

- the revenue made by the sale of pharmaceutical products, active ingredients, raw materials, industrial manufacturing as well as other elements, after deduction of all discounts and rebates (on quantities and prices), and once deducted the financial discounts;
- royalties received from commercial and distribution agreements;
- milestones or up-front payments;
- co-promotion incomes;
- other incomes (for example: retrocession of margin as prescribed by a commercial, research or development agreement and the cost of re-invoicing).

### Sales (€ million)

2005// 807.1

2006// 861.7

+ 6.8%

The increase of consolidated sales was fuelled by the growth of products in targeted therapeutic areas and strong sales momentum in international markets, despite the negative impact of downward price pressure in major Western European countries.

### Research and development expenditure (€ million)

2005// 169.0

2006// 178.3

+ 5.5%

Research and Development expenditure represented 20.7% of sales in 2006, compared with 20.9% of sales in 2005.

### Recurring operating profit (€ million)

2005// 177.8

2006// 204.1

+ 14.8%

The Group's operating income stood at €1872 million, up 1.0% year-on-year despite €16.9 million of non recurring negative impact, notably payment of €8.4 million to Inamed for the recovery of all rights related to Reloxin® and a €7.3 million impairment charge relating to Testim®. Therefore, operating income stood at 21.7% of sales compared with 23.0% in 2005. Excluding non recurring charge previously mentioned, the Group's recurring operating profit stood at €204.1 million, up 14.8% year-on-year, reaching 23.7% of sales, compared with 22.0% of sales a year ago.

### Recurring consolidated profit (€ million)

2005// 128.9

2006// 148.9

+ 15.6%

The consolidated profit reached €144.5 million (€144.0 million attributable to equity holders of Ipsen S.A.), down 3.0% year-on-year, including the one-offs mentioned above. The recurring consolidated profit increased by 15.6% in 2006 to reach €148.9 million, from €128.9 million in 2005.

## MESSAGE FROM THE CHAIRMAN

Since the IPO, Ipsen has achieved all its strategic and financial targets.

2006 was unquestionably a year of achievements and progress. Ipsen met and even surpassed the objectives that it had set itself at the IPO in December 2005. The Group is now a major player in its three targeted therapeutic areas: oncology, endocrinology and neuromuscular disorders.

**Most importantly, the Group has set up its commercial platform in North America**, the world's leading pharmaceutical market.

Ipsen granted Medicis the rights to develop, distribute, and commercialise the Group's botulinum toxin product in the United States, Canada and Japan for aesthetic use by physicians. Under the terms of this agreement, the Group received in the region of \$125 million in 2006, and could receive an additional payment of up to \$105 million depending on the progress of clinical development and the outcome of the regulatory review of the product by the FDA. This partnership is a clear illustration of Ipsen's ability to generate significant financial resources to support growth in its three strategic targeted therapeutic areas.

In endocrinology, we joined forces with Tercica in North America and created a global franchise for patients suffering from growth disorders with Increlex<sup>®</sup> and Somatuline<sup>®</sup> Autogel<sup>®</sup>. The latter molecule has been approved in Canada in the treatment of acromegaly. This is our first ever market authorisation in North America. We have also submitted Somatuline<sup>®</sup> Autogel<sup>®</sup> for registration with the FDA in the treatment of acromegaly. Once the market authorisation has been granted, Somatuline<sup>®</sup> will become the Group's first global product. Tercica, in which Ipsen now owns a 25% stake, will then market a comprehensive offer for use by endocrinologists. Together with Somatuline<sup>®</sup> Autogel<sup>®</sup> and our botulinum toxin (Dysport<sup>®</sup> and Reloxin<sup>®</sup>), Ipsen will be able to offer a complete range of drugs in the North American market in the upcoming years.

**In 2006, our Research and Development expenditure reached €178.3 million**, accounting for 20.7% of consolidated sales, which is a clear sign of the chief importance we place on R&D. With a team of 700 employees working

essentially throughout our centres in Paris, Boston, London and Barcelona, Ipsen is recognised for its expertise within the scientific community and by its peers, capable of discovering and developing innovative drugs for the benefit of patient care.

This is a sign of the vitality and ambition of our R&D programmes: today, nine new molecules are in clinical development, some of which appear to be extremely promising. This portfolio includes both OBI-1, our recombinant factor VIII, which is in phase II clinical trials for the treatment of certain types of haemophilia, and BN 83495, a selective inhibitor of the sulphatase enzyme, which is currently in phase I clinical trials for the treatment of breast cancer in post-menopausal women.

**Based on its long established international reputation for excellence in R&D**, the Group has been very active in 2006 in closing partnerships and alliances with leading international players. For example, Roche chose to exercise its option on our GLP-1 analogue and to finance the development of this promising molecule in the treatment of diabetes. Similarly,

in oncology, Ipsen acquired the rights from GTX, Inc. for the development and commercialisation of Acapodene<sup>®</sup>, a selective oestrogen receptor modulator, to be used for the prevention of prostate cancer in high-risk men and the treatment of multiple side effects from androgen deprivation therapy in advanced metastatic prostate cancer.

**Alongside our strong development, we strive to improve productivity** in order to maintain our profitability in an ever more stringent economic and regulatory environment, and also aim to bring new drugs to the market or to extend the indications of our existing range. The Group has submitted several drugs for approval with the EMEA in Europe, including febuxostat in the treatment of symptomatic hyperuricaemia, NutropinAq<sup>®</sup> in the treatment of idiopathic short stature, and Increlex<sup>®</sup> (submitted by Tercica) in the treatment of severe primary IGF-1 deficiency.

**2007 will be another year of important progress.** Together, we will continue to expand our commercial presence in North America, to fully leverage our research efforts and to pursue our strategy of profitable growth.

During the first quarter of 2007, the Group has already signed three strategic agreements. We have chosen Galderma to market our botulinum toxin in its aesthetic medicine indications in Europe and certain other territories. Ipsen has also acquired a patent application owned by Erasmus University in Rotterdam for the co-administration of a somatostatin analogue with a growth hormone antagonist for the treatment of acromegaly. Finally, the Group signed a co-marketing agreement with MSD, which grants Ipsen the rights to market Adavance<sup>™</sup> in France, in the treatment of osteoporosis.

We are also close to submitting Reloxin<sup>®</sup> and Dysport<sup>®</sup> for approval in the United

States, and will determine the strategy to market and distribute our botulinum toxin for therapeutic indications in North America.

Due to our strong results we maintain an extremely robust financial position, which gives us the financial flexibility to achieve our development goals. Despite tough competition in the pharmaceutical industry, Ipsen is well placed to pursue its development, thanks to its financial health, excellent R&D, commercial momentum and active alliance strategy.

I take this opportunity to express my sincere gratitude to the Group's teams for their daily input, to our shareholders for their support, and finally to the medical world and to patients for their confidence, enabling us to perform our public health mission.



**Jean-Luc BÉLINGARD**  
Chairman and CEO

## CORPORATE GOVERNANCE

Ipsen complies with the internal control legislation and its policy abides by principles of good corporate governance.

## Board of Directors

Chairman, Chief Executive Officer

Jean-Luc BÉLINGARD

Members

Anne BEAUFOUR

Henri BEAUFOUR

Alain BÉGUIN

Hervé COUFFIN

Antoine FLOCHEL  
(Vice-President)

Gérard HAUSER

Pierre MARTINET

René MERKT

Yves RAMBAUD

Klaus-Peter SCHWABE



## Executive Committee



**Jean-Luc BÉLINGARD**  
Chairman and Chief  
Executive Officer



**Éric DRAPÉ**  
Executive Vice-President,  
Manufacturing and Supply  
Organisation



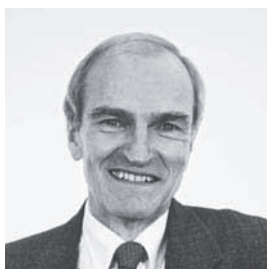
**Claire GIRAUT**  
Executive Vice-President,  
Chief Financial Officer



**Alain HAUT**  
Executive Vice-President,  
Human Resources



**Christophe JEAN**  
Executive Vice-President,  
Chief Operating Officer



**Jacques-Pierre MOREAU**  
Executive Vice-President,  
Chief Scientific Officer



**Stéphane THIROLOIX**  
Executive Vice-President,  
Corporate Development

## Committees of the Board of Directors

The Board has created four permanent committees: strategic committee, audit committee, appointments committee and compensation committee.

### Strategic committee

Chairman

**Jean-Luc BÉLINGARD**

Members

**Anne BEAUFOUR**

**Henri BEAUFOUR**

**Hervé COUFFIN**

**Antoine FLOCHEL**

**Klaus-Peter SCHWABE**

### Audit committee

Chairman

**Yves RAMBAUD**

Members

**Alain BÉGUIN**

**Pierre MARTINET**

### Appointments committee

Chairman

**Anne BEAUFOUR**

Members

**Alain BÉGUIN**

**Hervé COUFFIN**

### Compensation committee

Chairman

**Antoine FLOCHEL**

Members

**Gérard HAUSER**

**Yves RAMBAUD**

IPSEN SHARE

# Share price evolution

**Listed on:** Segment A of Eurolist by Euronext™

**ISIN Code:** FR 0010259150

**Mnemonic:** IPN

**FTSE classification:** 486 – Pharmaceuticals

**Sectorial classification ICB:** 4577 – Pharmaceuticals

**Nominal value:** €1

**First trading day:** 7 December 2005

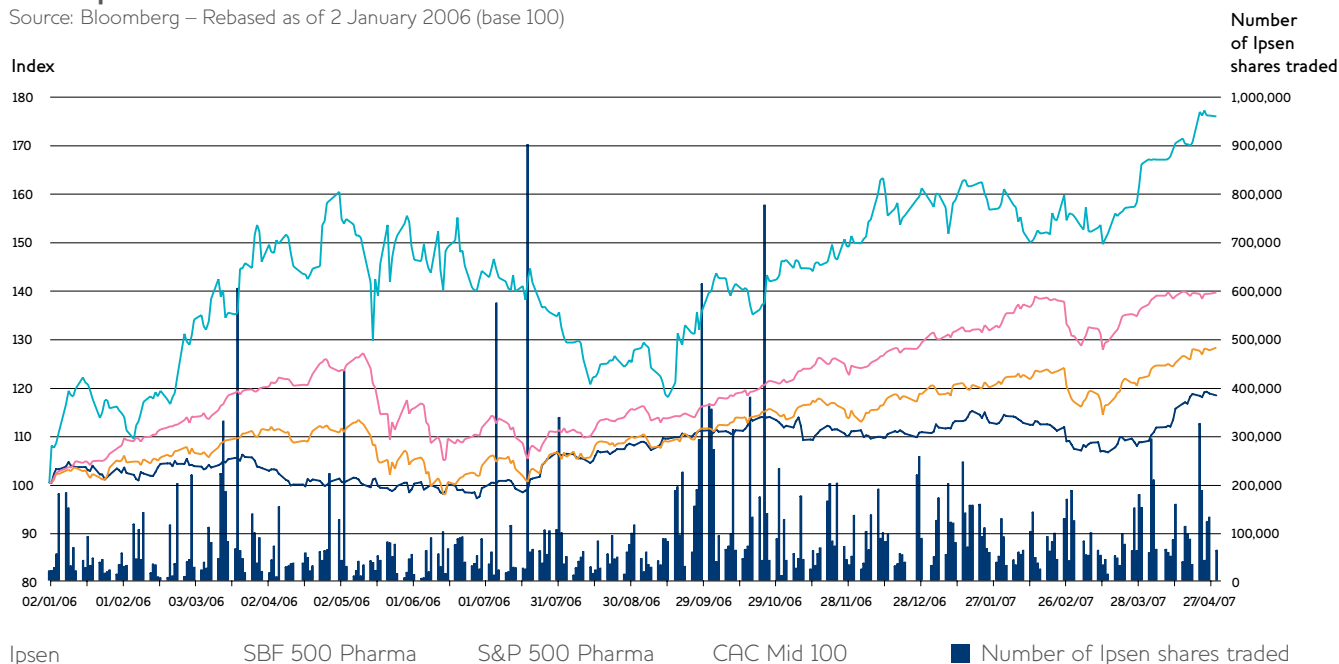
## Share price evolution from 2 January 2006 to 30 April 2007

|                                 |        |
|---------------------------------|--------|
| Closing price on 2 January 2006 | €23.89 |
| Closing price on 30 April 2007  | €38.95 |
| Performance                     | +63.0% |
| Average closing price           | €31.72 |
| Period high (on 25 April 2007)  | €39.23 |
| Period low (on 3 January 2006)  | €23.80 |
| Daily average traded volume     | 85,276 |

Source: Bloomberg

## Share price evolution

Source: Bloomberg – Rebased as of 2 January 2006 (base 100)



On 24 February 2006, Ipsen was added to the SBF 250 index.  
Ipsen entered the *Système à Règlement Différé* (SRD) on 28 March 2007.

### 2006 dividend

(subject to Ipsen shareholders' meeting approval on 6 June 2007 – in euro per share)

€0.60

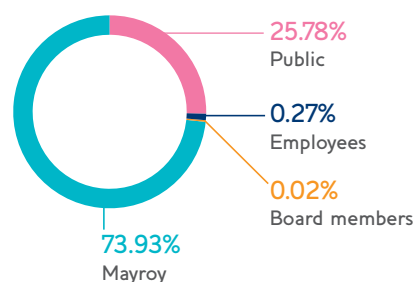
### Recurring earnings per share – fully diluted 2006

(based on the average number of shares outstanding during the fiscal year)

€1.77

### Shareholding structure

as of 31 December 2006  
€84,024,683 split into  
84,024,683 shares of €1 nominal value



### Financial calendar 2007

|                          |  |
|--------------------------|--|
| 1 <sup>st</sup> February | 2006 – full year sales                 |
| 19 March                 | 2006 – results                         |
| 3 May                    | Sales – 1 <sup>st</sup> quarter 2007   |
| 6 June                   | General shareholders' meeting          |
| 1 <sup>st</sup> August   | Sales – 1 <sup>st</sup> half of 2007   |
| 29 August                | Results – 1 <sup>st</sup> half of 2007 |
| 6 November               | Sales – first 9 months of 2007         |

### Investor relations

David Schilansky  
42, rue du Docteur Blanche – 75016 Paris  
France  
Tel.: +33 (0)1 44 30 43 43  
Fax: +33 (0)1 44 30 43 21  
email: investor.relations@ipsen.com

## KEY EVENTS

# A rigorously executed strategy

### July 2006

#### **Roche exercises its option on Ipsen's anti-diabetic medicine for type 2 diabetes**

Further to the agreement signed in October 2003, Roche announced today its decision to exercise its option to exclusively licence, develop and market Ipsen's patented anti-diabetic drug BIM 51077. Roche's decision is supported by the phase I and II results obtained with BIM 51077, a Glucagon-Like Peptide-1 (GLP-1) analogue, and presented at the American Diabetes Association (ADA) scientific meeting in Washington D.C. in June 2006. These data showed that this anti-diabetic compound exhibited an efficacy and safety profile in line with the GLP-1 class of incretins and was compatible with Ipsen's proprietary controlled delivery systems which upon subcutaneous administration could deliver over a period of one day, one week or two weeks.

### September 2006

#### **Ipsen and GTx, Inc. enter into partnership agreement for the European rights of Acapodene®**

GTx, Inc., the Men's Health Biotech Company and Ipsen announced that they have entered into a definitive agreement under which Ipsen will have an exclusive license to develop and market GTx's Acapodene® in all indications except breast cancer, in Europe.

### October 2006

#### **EMA has validated febuxostat's Marketing Authorization Application in the European Union for the management of symptomatic hyperuricaemia**

Further to the agreement signed in July 2003 between Ipsen and Teijin, holder of the product's rights, Ipsen was endorsed to develop and market febuxostat in Europe.

#### **Ipsen and Tercica complete worldwide strategic collaboration agreement in endocrinology**

Under terms of the collaboration announced on 18 July 2006, Ipsen has granted Tercica exclusive rights to sell Somatuline® Autogel®, in the United States, subject to approval by the U.S. Food and Drug Administration (FDA), and in Canada. Tercica has granted Ipsen exclusive rights to sell Increlex®, in all regions of the world except the United States, Japan, Canada, Taiwan and certain countries of the Middle East and North Africa, subject to approval by relevant regulatory authorities.

### December 2006

#### **Initiation of phase III clinical trials with Decapeptyl®'s 4-month sustained release formulation**

The 4-month sustained release formulation of Decapeptyl®, originated from the Group's internal research, is being tested in a phase III clinical trial. This new formulation, aimed at improving patients' quality of life, is



based on Ipsen's proprietary drug delivery system technology and uses the Group's advanced drug delivery platform.

#### **January 2007**

##### **FDA accepts for filing a New Drug Application (NDA) for Somatuline® Autogel®.**

##### **Somatuline® Autogel® is available in Canada.**

The Food and Drug Administration (FDA) has accepted the filing of its NDA for Somatuline® Autogel® (60, 90, 120 mg) in the United States. This acceptance signifies the start of the review process of the NDA with a prescription drug user fee act goal date set for 30 August 2007. Subject to the approval of the drug by the FDA, Ipsen's partner Tercica will market Somatuline® Autogel® in the United States. Moreover, Somatuline® Autogel® is currently being launched by Tercica after having received a marketing approval in Canada.

##### **Agreement between Ipsen and MSD for the co-marketing in France of Adavance™ for the treatment of postmenopausal osteoporosis**

Ipsen and MSD announced the signing of a co-marketing agreement under which MSD grants Ipsen the marketing rights in France for Adavance™, indicated for the treatment of postmenopausal osteoporosis in patients at risk of vitamin D deficiency. Adavance™ reduces the risk of vertebral and hip fractures. MSD currently markets this product under the brand name Fosavance®.

##### **Ipsen strikes alliance with the Erasmus University Medical Centre Rotterdam**

Ipsen announced it acquired an international patent application filed on 13 April 2006 owned by Erasmus University Medical Center Rotterdam (Erasmus MC), the Netherlands, for the co-administration of a somatostatin

analogue with a growth hormone antagonist for the treatment of acromegaly.

#### **February 2007**

##### **Ipsen and Galderma entered into a partnership in aesthetic medicine**

Ipsen and Galderma (a leading global pharmaceutical company focused on dermatology, joint-venture between Nestlé and L'Oréal) announced that they have entered into a partnership for the development, promotion and distribution of Ipsen's botulinum toxin type A for use in aesthetic medicine indications in Europe and certain other territories.



## WORLDWIDE PRESENCE

Our international development, a priority for the future



**36%**  
of sales in 2006  
originated outside  
the major countries  
of Western Europe\*

\* France, Germany, Italy, Spain,  
United Kingdom

**Products marketed  
in more than  
100 countries**



## EUROPE

Ipsen is strongly established in five European countries (France, Spain, Italy, Germany and the United Kingdom), which represent its core market, and through its subsidiaries, also in most of the other European countries, and the rest of world, notably in China, Korea and Australia. In 2006, 36% of sales originated outside the five major countries of Western Europe.

## ASIA

The Group directly markets its products in a number of countries in South-East Asia. It manufactures and markets Smecta® in China. In July 2003, Ipsen entered into a partnership agreement with Teijin to develop and market four Ipsen products, including Somatuline® Autogel®, in Japan.

## NORTH AMERICA

The Group's presence in the United States is mainly based on its research activities, located near to Boston: a new biotechnology unit has been operational at this site since March 2005. The Group's partnership policy (Medicis, Tercica) and Research and Development activities should enable, in the future, to expand its presence in this region, which is the leading pharmaceutical market worldwide. Three products are currently under clinical development in the United States, including two in phase III (Dysport® and Reloxin®). New Drug Application for Somatuline® Autogel® is under review by the Food and Drug Administration.

## INDUSTRIAL SITES

### France

**Dreux:** high-volume oral formulations, 911 million sachets, 767 million tablets, 362 million dry powder capsules, 72.5 million packs for sale, 10,600 tonnes distributed.

Analytical development and production of medicinal products for clinical trials.

**Signes:** sustained-release peptide formulations for injection.

**L'Isle-sur-la-Sorgue:** API plant, manufacturing more than 2,500 tonnes of therapeutic clay per year, used for gastroenterology products.

**Captieux:** plantation and leaf-drying facility (50% share).

**Saint-Jean-d'Ilac:** plantation and leaf-drying facility (50% share).

### United Kingdom

**Wrexham:** preparation of bulk active substances (BAS), purification and formulation of protein-based biological products.

### Ireland

**Dublin:** API plant, solid phase peptide synthesis.

**Cork:** standardised plant extract from Ginkgo biloba leaves (50% share).

### China

**Tianjin:** local market supply for China. The site operates as a joint venture with local partners.

**Lu Yuan:** leaf-drying facility operating in conjunction with local partners.

**Zhong Da:** leaf-drying facility operating in conjunction with local partners.

### Switzerland

**Locarno:** extracts from natural plant sources (including Ginkgo biloba) and related synthetic chemistry for the pharmaceutical and cosmetic industries (50% share).

### United States

**Sumter, South Carolina:** plantation and leaf-drying facility (50% share).



Decapeptyl®  
Tanakan®  
Dysport®  
Somatuline®  
Smecta®  
Nisis® and Nisisco®  
Forlax®  
Ginkor Fort®  
NutropinAq®  
...

# PRODUCTS

A diversified portfolio with more than twenty field proven drugs.

A strategic focus in three targeted therapeutic areas (oncology, endocrinology, neuromuscular disorders), strengthened by a longstanding presence in primary care.

# A leader in its targeted therapeutic areas

## > Oncology

## Decapeptyl®

*Decapeptyl® is a peptide formulation for injection that was initially developed and continues to be used mainly in the treatment of advanced prostate cancer. Additional indications developed subsequently include the treatment of uterine fibroids (a benign tumour of muscle tissues in the uterus), endometriosis (proliferation of endometrial tissue, the mucous membrane that lines the uterine wall outside the reproductive tract) prior to surgery or when surgery is not deemed appropriate, as well as early-onset puberty and female infertility (in vitro fertilisation). Decapeptyl® is available in monthly or quarterly sustained-release formulations, as well as a daily formulation.*

### Marketing

Decapeptyl® was initially launched in France during 1986. At 31 December 2006, Decapeptyl® had marketing authorisations in over 60 countries, including 25 in Europe. Decapeptyl® was launched in the United Kingdom in late 2003 and in Germany during 2004 (under the Pamorelin® brand). In 2006, 64.4% of Decapeptyl® sales were generated in the Major Countries of Western Europe.

### Research and Development

To manage the life cycle of Decapeptyl®, the Group is pursuing the following developments:

- under the aegis of the International Breast Cancer Study Group, the Group is participating in a study of the treatment of pre-menopausal breast cancer comparing the standard treatment regimen with a hormone therapy combining Decapeptyl® with oestrogen-suppressing agents, such as Aromasin®, which is marketed by Pfizer. Hormone therapy for breast cancer offers a better tolerated option than traditional chemotherapy and is particularly suitable for long-term treatment;

- development of sustained-release formulations over a period of at least four months.

### Active substance

The active substance in Decapeptyl® is triptorelin, a decapeptide analogue of GnRH, a hormone secreted by the hypothalamus, which initially stimulates the release of pituitary gonadotrophins (hormones produced by the pituitary gland), which in turn control hormonal secretions by the testes and ovaries.

### Indications

Prostate cancer, uterine fibroids, endometriosis, in vitro fertilisation, early-onset puberty.





## > Endocrinology

# Somatuline®

*Somatuline® and Somatuline® Autogel® are sustained-release formulations for injection containing lanreotide, a somatostatin analogue (a hormone that inhibits the release of growth hormone). Somatuline® was initially developed and continues to be used mainly in the treatment of acromegaly (disorder caused by the over-production of growth hormone or prolactin due to a benign tumour of the anterior pituitary gland). This product subsequently underwent further development in the treatment of symptoms associated with neuroendocrine tumours (particularly of a carcinoid type).*

### Marketing

Somatuline® was initially launched in France in 1995. At 31 December 2006, Somatuline® and Somatuline® Autogel® were recorded in almost 60 countries and marketed in close to 40 countries (including 24 in Europe) for the treatment of acromegaly and neuroendocrine tumours and in 45 countries (including 26 in Europe) for the treatment of acromegaly alone. In 2006, 68.5% of the sales generated by Somatuline® and Somatuline® Autogel® derived from the Major Western European Countries. Somatuline® Autogel® accounted for 85.9% of total sales of this product.

### Research and Development

The FDA accepted the filing of the New Drug Application (NDA) for Somatuline® Autogel® in the treatment of acromegaly on 29 December 2006, with a prescription drug user fee act goal date set for 30 August 2007. Additional phase III and IV clinical trials

of Somatuline® Autogel® are planned in the treatment of neuroendocrine tumours in the United States and in Europe.

The Group is also pursuing the development of sustained-release formulations for treatment durations of approximately three months. Development of this new formulation is currently at the pre-clinical stage, since a phase I trial with the first candidate formulation proved unsuccessful.

In Japan, the Group's partner, Teijin, started phase II clinical trials of Somatuline® Autogel® in the symptomatic treatment of acromegaly at the beginning of 2007.

### Active substance

The active substance in Somatuline® and Somatuline® Autogel® is lanreotide, which inhibits the growth and secretion of several endocrine, exocrine and paracrine functions. It is particularly effective in inhibiting the secretion of growth and digestive hormones.

### Indications

Somatuline® is prescribed for the treatment of acromegaly and neuroendocrine tumours.

### Somatuline® Autogel®: an improved presentation

Ipsen believes that the Somatuline® Autogel® formulation, to which it holds the patent, represents a major technological advance. As far as the Group is aware, this represents the first semi-solid formulation for injection without any excipient, since the active substance itself controls the sustained release. Somatuline® Autogel® releases the active substance over a period of at least 28 days, thus requiring just one injection per month compared with the two or three injections previously necessary. This product is presented in a pre-filled syringe for easier administration.

## > Endocrinology



# NutropinAq®

*NutropinAq® is a liquid formulation of recombinant human growth hormone, to be used by patients affected by growth delay, which was developed by Genentech. The extension of the indication for the treatment of idiopathic short stature is under review.*

### Marketing

In September 2002, Genentech, a US company specialised in biotechnology, granted the Group exclusive marketing rights for NutropinAq® worldwide outside North America, Mexico and Japan. Genentech has pioneered the development of growth hormone and is currently one of the leading players in the United States market. At 31 December 2006, the Group had marketing authorisations for 31 countries (including 25 in Europe). The product was launched in over 20 countries across Europe during 2005 and 2006.

### Research and Development

Within the framework of its agreement with Genentech signed in September 2002, the Group received from Genentech a copy of the registration dossier compiled by Genentech and filed with the FDA in January 2004 with a view to extending the indication for the treatment of idiopathic short stature. Ipsen filed a dossier in April 2006 with a view

to securing an extension of this indication with the European Medicines Agency (EMA).

The Group is also pursuing Research and Development projects aiming to develop a sustained-release formulation for recombinant growth hormone.

### Active substance

NutropinAq® is a liquid formulation of recombinant human growth hormone to be used with the NutropinAq® Pen. The growth hormone is involved in several physiological processes including growth in stature and bone development.

### Indications

NutropinAq® is prescribed for:

- the long-term treatment of children with growth failure owing to inadequate endogenous growth hormone secretion;
- the long-term treatment of growth failure associated with Turner's syndrome;
- the treatment of prepubescent children with growth failure associated with

chronic renal insufficiency ahead of kidney transplantation;

- the treatment of adults with growth hormone deficiency of either childhood or adult-onset.

> Neuromuscular disorders



# Dysport®

*Dysport®, which acts to block acetylcholine release, hence reducing muscular spasm, was initially developed for the treatment of motor disorders and various forms of muscular spasticity, including cervical dystonia (a chronic condition in which the neck is twisted or deviated), spasticity of the lower limbs (heal) in children with cerebral palsy, blepharospasm (involuntary eye closure) and hemifacial spasm. It was later developed for the treatment of a wide variety of neuromuscular disorders and aesthetic medicine.*

## Marketing

Dysport® was originally launched in the United Kingdom in 1991. At 31 December 2006, Dysport® had marketing authorisations in over 70 countries. In 2006, 44.4% of Dysport®'s sales derived from the Major Western European Countries.

In March 2006, the Group signed an agreement with Medicis, granting the latter the exclusive right to develop, sell and market certain formulations of the botulinum toxin for use in aesthetic medicine indications in the United States, Canada and Japan under a brand other than Dysport®, which could be Reloxin®. In addition, in February 2007, Ipsen granted Galderma the exclusive rights to develop, promote and distribute its botulinum toxin type A product for aesthetic indications in Europe and certain other territories.

## Research and Development

The Group finished recruiting in 2006 for phase III clinical trials with Dysport® in the United States in the treatment of cervical dystonia. Dysport® is currently undergoing phase III clinical trials in the United States for aesthetic medicine indications (frown lines) led by Medicis under the development and distribution agreement entered into by the Group with Medicis. Provided the outcome of these trials is positive, Medicis plans to file regulatory submissions with the FDA during 2007 under a brand name other than Dysport®, which may be Reloxin®.

As far as use of the Group's botulinum toxin type A in aesthetic medicinal indications is concerned, the AFSSAPS (*Agence française de sécurité sanitaire des produits de santé*) regulatory review

process is still ongoing. In this context, Ipsen has decided, in conjunction with its partner Galderma, to optimise the product's profile by including, as soon as possible in 2007 in its marketing authorisation application, the full results of clinical studies in the product's efficacy and safety carried out by its partner Medicis in the United States.

## Active substance

The active substance in Dysport® is a botulinum neurotoxin type A complex, which acts at the level of the neuromuscular junction in the targeted muscle.

## Indications

Cervical dystonia, cerebral palsy in children, blepharospasm / hemifacial spasm.

# Field proven drugs

## > Gastro- enterology



## Smecta®

*Smecta® is an oral formulation devised by the Group. It is used in the treatment of both chronic and acute diarrhoea in adults and children and in the symptomatic treatment of pain associated with oesophageal, gastric, duodenal or colonic disorders.*

### Marketing

The Group launched Smecta® in France in 1977. At 31 December 2006, it held marketing authorisations for Smecta® in over 70 countries. In 2006, 33.2% and 32.6% of Smecta®'s sales derived respectively from France and China, the two main markets for this product.

### Research and Development

In February 2007, the Group submitted an application to the French authorities to modify the file to register a new flavour of Smecta®.

### Active substance

Smecta®'s active substance is diosmectite, a natural clay processed for therapeutic use.



## > Gastro- enterology



## Forlax®

*Forlax® is an oral laxative created by the Group.  
It is used in the treatment of constipation.*

### Marketing

The Group launched Forlax® in France in 1996 and has since obtained marketing authorisations in more than 60 countries. In 2006, 82.7% of Forlax®'s sales derived from the Major Western European Countries.

### Active substance

Forlax® active substance is Macrogol 4000, a linear polyethylene glycol polymer.



## > Cognitive disorders



# Tanakan®

*Tanakan® is an oral formulation of EGb 761®, extracted from the leaves of the Ginkgo biloba tree (dioecious tree in the Ginkgoaceae family) using a standardised and patented process that ensures a consistent composition of the various pharmacologically active substances. It was initially developed in the treatment of various vascular and neurological disorders, mainly the treatment of age-related cognitive impairment, pathophysiological deficiencies, vertigo, tinnitus, acute or chronic hearing difficulties and retinal disorders (visual impairment).*

### Marketing

Tanakan® was initially launched in France in 1975. At 31 December 2006, Tanakan® had been approved for use in over 60 countries, mainly in Europe and Asia. Since 2004, it has been indicated and reimbursed in Belgium in the symptomatic treatment of mild to moderate forms of Alzheimer's-type dementia associated with memory disorders and cognitive disorders. In 2006, 75.2% of Tanakan®'s sales derived from the Major Western European Countries.

### Research and Development

The Group is currently investigating EGb 761®, the Ginkgo biloba extract in Tanakan®, in the treatment of neurodegenerative disorders, such as Alzheimer's disease. Over 8,000 patients are taking part in these research programmes, and eight clinical trials are currently in progress, some being conducted in the United States by the National Institutes of Health, others in Europe by Ipsen (in particular, GuidAge study).

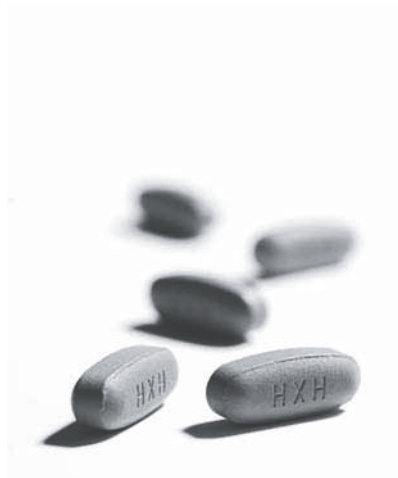
### Active substance

The active substance in Tanakan®, EGb 761®, is extracted from Ginkgo biloba leaves cultivated under controlled conditions in specially designed plantations. It contains natural substances with antioxidant, neuroprotective and vasoactive properties (i.e. it increases the diameter of capillary vessels and hence improves microcirculation).

### Indications

Age-related cognitive disorders, pathophysiological deficiency, cochleovestibular disorders, retinal deficit.

> Cardiovascular



## Nisis<sup>®</sup> and Nisisco<sup>®</sup>

*In 2003, the Group added Nisis<sup>®</sup> and Nisisco<sup>®</sup>, two antihypertensive products, to its portfolio by signing an agreement with Swiss group Novartis, to market the products in France, Andorra and Monaco.*

### Marketing

Nisis<sup>®</sup> and Nisisco<sup>®</sup> were initially launched in France by sanofi aventis. Following the contracts entered into with Novartis and sanofi aventis in March 2003, the Group holds marketing authorisations and has marketed Nisis<sup>®</sup> and Nisisco<sup>®</sup> in France since May 2003. In 2006, these two products generated sales of €50.7 million.

### Active substance

Nisis<sup>®</sup> is an oral formulation containing valsartan, while Nisisco<sup>®</sup> contains valsartan and hydrochlorothiazide. These products are used in the treatment of arterial hypertension. The active substance in Nisis<sup>®</sup> and Nisisco<sup>®</sup> is valsartan, a synthetic angiotensin II antagonist compound.





- 700 people in Research and Development
- Expenditure in 2006: 20.7% of consolidated sales
- Centres of Research and Development: Paris, Boston, Barcelona and London

# RESEARCH AND DEVELOPMENT

Research and Development focused on hormone-dependent diseases, peptide and protein engineering, and innovation in advanced drug delivery systems.

The Group's Research and Development activities are focused on the discovery and development of new molecules as well as on programmes relating to life cycle management for products already marketed by the Group (development of new formulations or extension of indications and product registrations in new geographical areas). The significant R&D effort is complemented by an active partnership policy.

## RESEARCH AND DEVELOPMENT

# Integrated technological platforms

*Integration of technological platforms drives the discovery of innovative products for the treatment of severely debilitating or life-threatening diseases in the Group's targeted therapeutic areas.*

### Peptide engineering

This technology focuses on the modification through synthesis of derivatives of naturally occurring neuropeptide hormones. This research is conducted by the Boston Research and Development centre (United States).

The Group's R&D programmes are based on four technological platforms: peptide engineering, protein engineering, medicinal chemistry and advanced drug delivery systems. This array of technologies is necessary to meet the Group's objectives:

- fulfil unmet medical needs;
- optimise the efficacy of active substances;
- provide patients with better quality of life;
- facilitate the use of these products by healthcare personnel.

### Protein engineering

It aims to improve the therapeutic properties of naturally occurring proteins through the selective modification of their sequences. This research is conducted by the Boston Research and Development centre (United States).

### Medicinal chemistry

Its mission: discover enzyme inhibitors, mitochondrial protective agents and non-peptide ligands (molecules that attach preferentially to one or more receptors) for specific hormone receptors. Medicinal chemistry research is conducted by the Group's research facilities in Paris (France). The acquisition of UK-based Sterix in February 2004 has given the Group access to additional expertise in the development of medicinal products derived from steroid hormones. In addition, under the agreements with Spirogen (United Kingdom) in 2003, the Group has expanded use of its

medicinal chemistry platform by securing access to a technology making it possible to target specific regions of genes that control their expression.

### Advanced drug delivery

It aims to create and develop innovative formulations for new or existing products in order to optimise the efficacy of the active substances while improving patient quality of life and facilitating the use of the products by healthcare professionals. These research activities are conducted at the Group's research centre in Barcelona (Spain). One of Ipsen's research specifications lies in a converging approach between creating new chemical entities and developing controlled release formulations.

## RESEARCH AND DEVELOPMENT

# International teams and network



*The Group has established an international network of Research and Development centres, located in areas providing access to considerable expertise in academic research and to employees skilled in technology and development processes.*

### **Paris (France)**

The Paris Research and Development centre specialising in medicinal chemistry was opened in 1969. New facilities were built more recently in 1996, with a research team (chemists, biologists and pharmacologists) essentially working on discovering new chemical entities and having access to high-throughput screening and combinatorial chemistry techniques and the early characterisation of their distribution and elimination properties in the body. Its key areas of research are molecular and cellular oncology, together with neuromuscular disorders. The Group also has a clinical development team in Paris that coordinates its clinical trials around the world. Analytical development and production of medicinal products for clinical trials are carried out at the Group site located in Dreux (France).

### **Boston (United States)**

The Boston Research and Development centre specialises in protein and peptide research. Its scientists mainly work in three areas: synthetic chemistry, pharmacology and biotechnology. The centre boasts extensive knowledge about hormone-dependent pathophysiological mechanisms in which neuropeptides are involved. The Group also has a clinical research and development team dedicated to the coordination of the Group's clinical research in North America and regulatory activities with the FDA in the United States. In March 2005, Ipsen inaugurated a new biotechnology unit complementing the activities of the Boston centre. This site houses a team specialising in the development processes specific to genetic engineering, industrial development, analysis and formulation of proteins, production, quality assurance and quality control. One of the main activities

of this site is to modify the structure of endogenous proteins and peptides to enhance their properties. Replacing certain protein sequences with different sequences may reduce antigenicity (detection by existing antibodies), toxicity or immunogenicity (formation of new antibodies) and increase the duration of action, specificity or compatibility with controlled-release formulations.

### **London (United Kingdom)**

Located near London, which is home to the EMEA, the clinical development and regulatory affairs departments devise development and regulatory approval strategies and implement preclinical and clinical development programmes in line with these strategies. They coordinate multicentre international clinical trials, collect data, analyse results and file dossiers and registration applications with the interna-



tional regulatory authorities to ensure that the Group obtains the necessary approvals to market its products in the shortest possible time. The main objective of the clinical development teams is to execute or commission execution of clinical trials complying strictly with the regulatory standards and able to provide high-quality and extensive data about the efficacy and safety of using Ipsen's products. Successful registration requires the consolidation, on a Group level, of all regulatory data necessary for a dossier.

### Barcelona (Spain)

The Barcelona centre specialises in the discovery, design and development of advanced drug delivery systems. Its main objective is to determine optimum methods for the delivery of highly potent medicinal products. Its teams were, for instance, behind the development of the Somatuline® Autogel® formulation, which releases the active substance, without any excipient other than water, over a period of at least 28 days. This research plays a critical role in improving the quality of life of patients by providing them with convenient therapeutic regimens and delivery systems that minimise discomfort. The Barcelona centre employs researchers, together with scientists and technicians specialising in drug delivery systems, and is supported by a pharmacokinetics department integrated with the worldwide clinical development group.

## > Oncology: strong franchise and active life cycle management of products

### Research programmes

The Group's technological platforms in peptide and protein engineering and medicinal chemistry enable it to explore and develop new approaches in cancer treatment under hormonal control, such as:

- key enzyme inhibitors in the biosynthesis of steroids;
- growth factors, notably including prolactins, Growth Hormone Releasing Hormone or Mullerian Inhibiting Substance;
- enzymes regulating cell cycles (notably phosphatases);
- factors involved in the transduction of the intracellular signal and angiogenesis.

These research programmes are conducted internally with assistance from university and industry specialists. The February 2004 acquisition of Sterix has opened up new opportunities for Ipsen in the development of medicinal products derived from steroids. Steroid hormones play an essential role in the processes controlling vital functions. Having signed a partnership agreement with the Group, the team from the University of Bath in

the United Kingdom discovered a chemical modification which, when applied to steroids and their derivatives, enables the selective inhibition of enzymes that convert precursor steroids into their biologically active form. Through its collaboration with Imperial College London and the University of Bath, the Group intends to leverage the use of this technological platform in the field of hormone-dependent cancers. The agreement signed with Spirogen in May 2003 has provided the Group with access to a technological platform with the potential to identify the genes involved in serious therapeutics such as cancer. Ipsen has exclusive access to this technology for several genes involved in cancers refractory to conventional therapies.

### Development programmes

#### Decapeptyl®

With regard to managing the life cycle of Decapeptyl®, Ipsen is pursuing the following developments:

- the Group is participating in three phase III studies conducted under the auspices of the International Breast Cancer Study Group in the treatment of breast cancer in premenopausal women, comparing the conventional treatment methods with hormone therapy combining Decapeptyl® with oestrogen suppressant agents, such as Aromasin®, marketed by Pfizer. These trials are due to take place until 2015. Hormone therapy for cancer offers a better tolerated option than traditional chemotherapy and is particularly suitable for long-term treatment;
- development of sustained-release formulations for treatment durations longer than three months. A formulation for a minimum treatment duration of four months is currently undergoing phase III clinical trials and a sustained-release formulation for a duration of 6 months is currently in phase I clinical trials.

**Acapodene®**

The Group has acquired from GTx, Inc., a biotech company specialised in men's health, an exclusive licence for the development and marketing of Acapodene® (toremifene citrate) for all indications except breast cancer in Europe (European Union, Switzerland, Norway, Iceland, Lichtenstein and the Commonwealth of Independent States). Acapodene® can modulate the activity of the oestrogen receptors ("SERM"). Developed in the context of a new strategy to modulate oestrogen receptors, Acapodene® is currently undergoing phase III development programme in two different clinical settings:

- treatment of the numerous side effects linked to androgen-deprivation therapy in advanced prostate cancer (80mg);
- chemoprevention of prostate cancer in individuals with high-grade prostatic intraepithelial neoplasia (20mg).

The Group detains the marketing rights for the first indication and an option for the second one.

**BN 83495 (STX 64)**

BN 83495 and similar molecules acquired through the acquisition of Sterix, are selective inhibitors of the sulphatase enzyme involved in a key stage of the biosynthesis of oestrogens, one of the principal factors contributing to breast cancer in post-menopausal women. A first phase I clinical trial in patients with breast cancer has been completed and the results demonstrate the inhibition of the sulphatase enzyme at the dosages tested in tumour biopsies.

**Angiomates (STX 140)**

The angiomates refer to a family of small molecules acquired through the acquisition of Sterix which are multitargeted anticancer agents, exhibiting both antiproliferative (killing cancer cells) and antiangiogenic properties (inhibiting the



blood vessels network supporting the tumour) or cytotoxic. These molecules are currently at the preclinical development stage and will target the treatment of hormone-dependent tumours and possibly some hematological malignancies.

**BIM 46187**

BIM 46187 is an innovative anti-tumour compound that acts on cellular signals by the receptors attached to Proteins G (the most common form of receptors for neuropeptide hormones and neurotransmitters). This compound is at the preclinical stage. BIM 46187 may be used either alone or in combination with other cancer therapies in the treatment of

solid tumours, such as lung and prostate cancer.

**BN 2629 (SJK-136)**

BN 2629, a product originating from Spirogen, is a synthetic molecule that has demonstrated during preclinical studies its ability to block the cellular proliferation process characteristic of cancer. This product is being studied in three phase I studies of different administration regimens in patients with metastatic tumours resistant to certain types of chemotherapy. The Group is pursuing ex vivo research using this molecule in leukaemia resistant to other treatments.

The Group is looking for a partner with which to continue the development of a patented class of cytotoxic agents:

- **Diflomotecan.** Diflomotecan (BN 80915) is a cytotoxic agent (cell killer) that inhibits the topoisomerase 1 enzyme. Two phase II clinical trials in lung cancer have been completed, but failed to achieve their safety and efficacy targets in this indication for the dosages tested. During phase I clinical trials, diflomotecan showed high oral bioavailability, low gastrointestinal toxicity and no cumulative haemotoxicity. Investigations into other indications are due to be carried out.

- **Elomotecan.** Elomotecan (BN 80927) is a cytotoxic (cell killer) inhibitor of topoisomerase 1 and 2 enzymes, intended for the treatment of certain types of advanced metastatic cancers (colon, breast and prostate). Elomotecan is currently undergoing phase I clinical trials.

Development of these cytotoxic agents was carried out in conjunction with Roche under the licensing and partnership agreement of December 2002. The Group and Roche terminated this partnership in May 2005.

## > Endocrinology: a first-class portfolio for the treatment of growth disorders

### Research programmes

In pituitary disorders, Ipsen is involved in several programmes, chiefly in pituitary adenomas, such as acromegaly. The Group is also continuing its efforts to identify second-generation somatostatin analogues and growth hormone antagonists. Acromegaly used to be treated by surgical removal of the benign tumour followed by radiotherapy. If the tumour did not respond sufficiently, a somatostatin analogue was administered. However, because of the heterogeneity of the tumour, new therapies are needed since a substantial number of patients still do not receive satisfactory treatment. The Group is currently investigating molecules with a broader spectrum of activity and hopes that they will not only provide a symptomatic treatment for acromegaly, but also offer the possibility of reducing tumour size, thereby eliminating many of the limitations associated with existing treatments (dopastatin). The Group is also exploring the role of certain peptide hormones (ghrelin, MSH/MC4) in regulating food intake and the gastro-intestinal function with the priority objective of treating cachexia (lack of appetite), which is often the cause of functional disorders in the elderly, cancer patients and patients with chronic illnesses (ghrelin, MSH/MC4). The Group is continuing to pursue the programmes it initiated in 11 $\beta$ HSD enzyme inhibitors with a view to developing a therapy for the related metabolic syndromes



associated with obese patients with hyperinsulinemia, which principally manifests itself in the form of greater cardiovascular risks. In conjunction with Asterion, Ipsen is also continuing to develop growth hormone antagonists.

## Development programmes

### Somatuline® Autogel®

With regard to managing the life cycle of Somatuline® Autogel®, the Group is pursuing the following developments:

- the phase III clinical trials in the United States with Somatuline® Autogel® for the treatment of acromegaly have ended. The FDA accepted the NDA filing on 29 December 2006. The date closing the prescription drug user fee act is forecast for 30 August 2007;
- additional phase III and IV clinical trials of Somatuline® Autogel® are in progress with a co-administration of pegvisomant marketed by Pfizer; other are planned in the treatment of neuroendocrine tumours in the United States and in Europe;
- Ipsen is also pursuing the development of sustained-release formulations for treatment durations of more than two months. Development of this formulation is currently at the preclinical stage, since a phase I trial with the first candidate formulation proved unsuccessful;
- in Japan, the Group's partner, Teijin, has started phase II trials of Somatuline® Autogel® in the symptomatic treatment of acromegaly.
- Ipsen envisages securing additional marketing authorisations for Somatuline® Autogel® shortly, in Poland and Russia for the treatment of acromegaly and neuroendocrine tumours, and in France and Germany for the treatment of neuroendocrine tumours.

### NutropinAq®

With regard to managing the life cycle of NutropinAq®, the Group is pursuing the following development work:

- within the framework of its agreement with Genentech signed in September

2002, the Group received a copy of the registration dossier compiled by Genentech and filed with the FDA in January 2004 with a view to extending the indication for the treatment of idiopathic short stature. The Group filed a dossier in April 2006 with a view to securing an extension of this indication with the EMEA;

- the Group is pursuing Research and Development projects that aim to develop a sustained-release formulation for recombinant growth hormone.

### BIM 51077

BIM 51077 is an analogue of peptide hormone GLP-1 (Glucagon Like Peptide-1). Further to the agreement signed in 2003, Roche announced in July 2006 its decision to exercise its option to exclusively licence, develop and market Ipsen's patented anti-diabetic drug. This decision is supported by the phase I and II results obtained with BIM 51077, and presented at the American Diabetes Association (ADA) scientific meeting in Washington D.C. in June 2006. These data showed that this anti-diabetic compound exhibited an efficacy and safety profile in line with the GLP-1 class of incretins and was compatible with Ipsen's proprietary controlled delivery systems. This subcutaneous way of administration could make the product be delivered over a period of one day, one week or two weeks. In Japan, the Group's Japanese partner (Teijin) has completed a phase I trial with BIM 51077 and is now preparing to hold further phase I trials with sustained-release formulations.

### Increlex®

Increlex® (mecasermin [recombinant DNA origin] injection) is a substitution treatment of human insulin like growth factor (rhIGF-1) produced by a recombinant DNA technology, indicated in the long term treatment of growth failure in children with severe primary insulin-like growth factor-1 deficiency (IGFD). The main active substance of Increlex® is identical to the natural hormone IGF-1 produced by the body in response to a stimulation by the growth hormone.

IGF-1 is the principal hormonal mediator of statural growth and must be present so that children's bones, cartilage and organs grow normally. If the IGF-1 is not present in sufficient quantities, the child will not reach its normal stature. Increlex®, approved by the FDA in August 2005 for the treatment of IGF-1 deficiency, is available to patients in the United States. Furthermore, in December 2005, Tercica submitted an application for marketing authorisation for Increlex® in the European Union. Increlex® has received orphan drug exclusivity.

> **Neuromuscular disorders: strategic positioning in therapeutic indications and partnerships in aesthetic medicine**

### Research programmes

The Group's research programmes in neuromuscular disorders mainly focus on the identification of new botulinum toxin formulations. For neurodegenerative conditions, Ipsen has synthesised several original classes of chimeric compounds, i.e. compounds capable of performing several pharmacological activities simultaneously and used to protect mitochondria (intracellular organelles responsible for the production of energy) in connection with neurodegenerative conditions, such as Parkinson's, amyotrophic lateral sclerosis and Huntington's disease.

### Development programmes

#### Dysport®

With regard to managing the life cycle of Dysport®, Ipsen is pursuing the following developments:

- in August 2005, the Group initiated phase III clinical trials of Dysport® in the United States in the treatment of cervical dystonia. Ipsen envisages filing for registration with the FDA in 2007;
- Dysport® (Reloxin®) is currently under-



going phase III clinical trials in the United States for aesthetic medicine indications (frown lines) led by Medicis within the framework of the development and distribution agreement entered into with the company. Provided the outcome of these trials is positive, the Group plans to file regulatory submissions with the FDA during 2007 under a brand name other than Dysport®, which may be Reloxin®;

- as far as use of the botulinum toxin in aesthetic medicinal indications is concerned, the AFSSAPS regulatory review process is still ongoing. In this context, Ipsen has decided, in conjunction with its partner

Galderma, to optimise the product's profile by including, as soon as possible in 2007 in its marketing authorisation application, the full results of clinical studies in the product's efficacy and safety carried out by its partner Medicis in the United States.

## > Other programmes

### Cognitive disorders

#### Tanakan®

Ipsen is endeavouring to validate the clinical benefits of Tanakan® in the treatment of age-related cognitive impairment and behavioural disorders. The Group is thus involved in the assessment of EGb 761®, the extract of Ginkgo biloba present in Tanakan®, for the treatment of neurodegenerative disorders such as Alzheimer's disease. More than 8,000 patients are enrolled in the research programmes, and eight clinical studies are currently underway:

- the National Institutes of Health (United States) are currently sponsoring four clinical trials:
  - a study on the prevention of Mild Cognitive Impairment (MCI) in patients aged over 85;
  - a study on the primary prevention of Alzheimer's disease in "healthy" patients aged over 75 ("GEM"). The 3,000 patients for this study have now been recruited, and they will be treated at least until 2008;
  - two pilot studies on the cognitive disorders caused by cancer treatments (chemotherapy or radiotherapy);

- the Group is also the sponsor of four other studies in Europe, including:
  - the GuidAge study assessing the effectiveness of EGb 761® in the prevention of Alzheimer's disease in patients of more than 70 years of age presenting with a spontaneous memory complaint; the 2,800 patients were recruited by September 2004 and their treatment will continue for five years. The results of this study are likely to be available in 2010;
  - a study evaluating the efficacy of EGb 761® in cognitive disorders in patients with Alzheimer's disease and related behavioural and psychological disorders (Behavioural and Psychological Symptoms in Dementia);
  - two pilot studies aiming to study the efficacy of EGb 761® in cognitive impairment related to various disorders, such as multiple sclerosis and the consequences following a stroke.

All of these clinical studies, with the exception of the GuidAge study, are proof-of-concept studies. If successful, they will have to be confirmed by further clinical studies before a new indication can be registered. If the GuidAge trial is successful, its results may be used for the purpose of securing an indication for EGb 761® in the prevention of Alzheimer's disease in patients over 70 with spontaneous memory impairment.

### Haematology

Ipsen also boasts longstanding expertise in haemostasis (blood coagulation). Its research has enabled it to establish partnerships with Emory University (United States) and Octagen, in order to develop a recombinant version of porcine factor VIII using its protein engineering platform. This product (OBI-1) is intended for the treatment of congenital or acquired haemophilia resistant to human factor VIII. OBI-1 is currently in its phase II trials in the United States. OBI-1 is produced by Ipsen at its biotechnology unit in Boston.

### Rheumatology

Within the framework of the partnership established in July 2003 with Japanese group Teijin in endocrinology, the Group signed a specific agreement to develop in Europe febuxostat, a drug intended for the treatment of symptomatic hyperuricaemia, currently in the process of being registered by Takeda Abbott Pharmaceuticals (TAP) in the United States. The FDA issued an approvable letter in October 2005 followed by a second one in August 2006. With a view towards possibly launching the compound in Europe, after assessing the submissions filed by TAP with the FDA in February 2006 in response to this approvable letter, the Group has decided to submit for marketing authorisation the European authorities. This application was accepted by the EMEA in October 2006 and is currently being reviewed.



## RESEARCH AND DEVELOPMENT

# 9 new chemical entities in clinical development

*The Group is currently pursuing the preclinical and clinical development of several innovative compounds and new formulations of existing drugs. The following table provides a summary of the Group's principal development programmes. Ipsen believes that it is one of the few pharmaceutical companies able to pursue a significant number of Research and Development projects in its targeted therapeutic areas.*

### The preclinical and clinical phases

• **Preclinical stage.** The Group's research scientists study, usually for two to four years, the effects of innovative drug candidates on cell systems or organs in isolation, in vitro or in animal models, to gain a better understanding of their pharmacological and toxicological properties. An analysis of the results of these studies helps to determine whether the compound meets the therapeutic objectives laid down. If so, further development through clinical trials must be subject to the approval of the competent regulatory authorities, as well as ethics committees.

The purpose of clinical trials is to establish proof that the drug candidate is safe to use and effective in humans.

• **Phase I.** The purpose of phase I is to conduct a short-term assessment on healthy volunteers (or on patients in oncology) of the safety profile of the drug candidate based on dosage administered and to establish preliminary pharmacokinetic (absorption, metabolism, distribution, elimination) and pharmacodynamic profiles. These results combined with those of preclinical trials

help to verify the drug's tolerance profile and to confirm the dosage and optimum treatment regimen maximising efficacy while minimising side effects.

• **Phase II.** The purpose of phase II is to assess on patients the pharmacological properties of the drug candidate and identify the therapeutic index (ratio between the active and toxic doses) in one or more of the administered dosages identified during phase I. At this stage, if the drug candidate's therapeutic efficacy and its tolerance profile are confirmed, a decision may be taken to hold phase III trials.

• **Phase III.** Phase III trials represent the final stage of clinical trials conducted before an application for marketing authorisation is filed. These trials are normally conducted on a much larger number of patients than are used for phase II trials, and their purpose is to provide reliable clinical and statistical data regarding their tolerance and efficacy.

A STRONG PIPELINE\*  
TO FUEL FUTURE GROWTH

### Preclinical Oncology Angiomates

Cytotoxics

**BIM 46187**

Cytostatics, solid tumours

### Endocrinology Human sustained-release growth hormone

Long term treatment of growth failure in children and growth hormone deficiency in adults

**Dopastatine**

Pituitary adenomas

\* As of 31 March 2007.

## Phase I Oncology

**BN 83495 (STX 64)**  
Post-menopausal breast cancer  
expressing oestrogenic receptors

**BN 2629 (SJG-136)**  
Advanced metastatic cancer

**Elomotecan (BN 80927)**  
Advanced metastatic cancer

## Phase II Oncology

**Diflomotecan (BN 80915)**  
Advanced metastatic cancers

## Endocrinology

**BIM 51077**  
Type 2 diabetes (in partnership with  
Roche since July 2006)

## Haematology

**OBI-1**  
Haemostase

## Phase III Oncology

**Acapodene®**  
Treatment of side effects induced by  
androgen-deprivation therapy

**Decapeptyl®**  
Combined hormone therapy for premenopausal  
breast cancer

**Decapeptyl®**  
Prostate cancer 4-month formulation

## Endocrinology

**Increlex®**  
Long term treatment of growth failure in  
children with severe IGF-1 deficiency  
*Europe: regulatory review*

**Somatuline® Autogel®**  
Asymptomatic neuroendocrine tumours

**Somatuline® Autogel®**  
Co-administration with pegvisomant

**Somatuline® Autogel®**  
Acromegaly  
*United States: regulatory review*

**NutropinAq®**  
Idiopathic short stature  
*Europe: regulatory review*

## Neuromuscular disorders

**Dysport®**  
Cervical dystonia  
United States: NDA filing planned in 2007

**Reloxin®**  
Aesthetic medical purposes  
*Europe: regulatory review*  
United States: partnership with Medicis - NDA  
filing planned in 2007

## Rheumatology

**Febuxostat**  
Symptomatic hyperuricaemia  
*Europe: regulatory review*

## Cognitive disorders

**Tanakan®**  
Age-related cognitive impairment



Ipsen, a recognised strategic partner by the pharmaceutical and biotechnology industry

# PARTNERSHIPS

## Develop strategic partnerships

Active policy of partnerships: Ipsen has built a strong network of centres of excellence in research and industry leaders.

- Asterion
- Auxilium
- Bayer
- CEA
- Debiopharm
- Galderma
- Genentech
- GTx, Inc.
- Health Protection Agency (HPA)
- Indena
- Inserm
- Massachusetts General Hospital
- Medicis
- Merck Sharp & Dohme
- Novartis
- Octagen and Emory University
- Radius
- Roche
- Schwabe
- Spirogen
- Teijin
- Tercica
- Tulane University

## PARTNERSHIPS

# Active policy of partnerships throughout the world

## Oncology

### **GTx, Inc.** (Memphis, United States)

On September 2006, GTx, Inc. granted the Group an exclusive licence to develop and market Acapodene®, a Selective Estrogen Receptor Modulator (SERM) and all other products containing toremifene for all its indications, except treatment and prevention of breast cancer, in Europe (European Union, Switzerland, Norway, Iceland, Lichtenstein and the Community of Independent States).

### **Spirogen** (London, United Kingdom)

In May 2003, the Group signed a partnership agreement with Spirogen, a UK biotechnology company. This partnership comprises, on the one hand a development and licensing agreement covering the development and marketing by the Group of a patented anti-cancer drug, namely BN 2629 (SJG-136) and on the other hand, a research agreement for other anti-cancer compounds through

implementation of a gene targeting technology patented by Spirogen.

### **Massachusetts General Hospital** (Boston, United States)

In June 2005, the Group signed a partnership agreement with the General Hospital Corporation, which runs Massachusetts General Hospital, to conduct a Research and Development programme into the use of Mullerian Inhibiting Substance hormone in the treatment of cancer.

Pursuant to this agreement, the Group holds an exclusive worldwide option on the patents held by the General Hospital Corporation on the antimullerian hormone and an option on an exclusive worldwide licence to use research results belonging to the General Hospital Corporation.

### **Inserm** (Paris, France)

In October 2005, Ipsen signed a partnership agreement with Inserm (French national health and medical research institute) to conduct a R&D programme in the treatment of breast and prostate cancer.

## Endocrinology

### Auxilium

(Philadelphia, United States)

In March 2004, the Group entered into a licensing agreement with Auxilium to distribute Testim® 50mg Gel, a gel applied to the skin, worldwide, except for the United States, Mexico, Canada and Japan. This product was developed by Auxilium using patents belonging to Bentley Pharmaceuticals. The Group will hold any marketing authorisations awarded. The licence also includes the right to use the Testim® brand name, which belongs to Auxilium.

### Genentech

(San Francisco, United States)

The exclusive distribution agreement entered into in September 2002 with Genentech covers NutropinAq®, a liquid formulation of human growth hormone produced using recombinant DNA technology. Under this agreement, the Group has the exclusive right to market worldwide (with the exception of North America, Mexico and Japan) NutropinAq® and the NutropinAq® Pen Cartridge® (i.e. the configuration used for the daily administration of the liquid formulation of NutropinAq®) and any improvement made to these products.

In November 2004, Ipsen signed a R&D agreement covering the development of sustained-release formulations of recombinant growth hormones using the technology platforms of Genentech, Ipsen or third parties.

### Roche (Basel, Switzerland)

Pursuant to the licensing agreement signed by the Group in October 2003 with various companies in the Roche group, on 19 July 2006, Roche exercised its option on an exclusive licence to the rights to develop and market BIM 51077, the patented anti-diabetic drug discovered by the Group's research activities. This GLP-1 analogue has shown its efficiency and the

latest data from the phase I and II clinical trials have shown that the molecule could potentially be administered more easily than other molecules in its class, which would facilitate patient compliance. These rights are granted exclusively to Roche worldwide with the exception of Japan where these rights are shared with Teijin (the Group's Japanese partner) and in France where the Group may decide to exercise its co-marketing rights.

### Teijin (Tokyo, Japan)

In July 2003, Ipsen entered into a R&D partnership with Teijin. This partnership covers on the one hand, the development and the marketing of four Ipsen's products, including Somatuline® Autogel® and BIM 51077 and on the other hand, the development and marketing by Ipsen in Europe of febuxostat, a product owned by Teijin and used in the







treatment of the symptoms associated with hyperuricaemia.

**Tercica** (Brisbane, California, United States)

On 12 October 2006, the General Meeting of the shareholders of Tercica approved the agreements entered into in July 2006 with the Group consisting of two cross licensing agreements and the acquisition by the Group of a 25% stake in Tercica's capital, with certain rights to increase this stake. This transaction was finalised on 13 October 2006.

Ipsen granted Tercica the exclusive license to develop and market Somatuline® Autogel® (leading drug in Europe to treat

acromegaly) in the United States and Canada; Tercica granted Ipsen the exclusive license to develop and market Increlex® (leading drug in the United States to treat severe primary insulin-like growth factor-1 deficiency) worldwide except for the United States, Japan, Canada, Taiwan and certain countries in the Middle East and North Africa. Moreover, each company has granted to the other the rights to pursue development of new indications and improvements to Somatuline® Autogel® and Increlex®.

## Agreements around the botulinum toxin

**Medicis** (Scottsdale, United States)

In March 2006, the Group entered into a development and distribution agreement with Aesthetica Ltd, a fully controlled subsidiary of Medicis, covering certain botulinum toxin formulations for aesthetic medicine in the United States, Canada and Japan under a brand name other than Dysport®, which may be Reloxin®.

### **Galderma** (Lausanne, Switzerland)

Ipsen granted Galderma Pharma SA, a Swiss company jointly owned by Nestlé and L'Oréal, exclusive rights to develop, promote and distribute specific formulations for the aesthetic medicine indications of its botulinum product in the European Union, Russia (subject to an additional payment) and certain territories in Eastern Europe and Central Asia, Israel and the Lebanon.

## **Other agreements**

### **Merck Sharp & Dohme Ltd** (Hoddesdon, United Kingdom)

The Group signed an agreement in January 2007, for the use in France of Adavance™, within the framework of a co-marketing agreement. This fixed association of alendronate sodium trihydrate and colecalciferol is used in the treatment of post-menopausal osteoporosis for patients at risk with low vitamin D levels. Pursuant to this 10-year agreement, the Group will market and sell this product under the name Adavance™ in France which it will purchase exclusively from Merck Sharp & Dohme Ltd.

### **Novartis** (Basel, Switzerland)

In March 2003, the Group signed a series of agreements, including one with sanofi aventis for the transfer of Nisis® and Nisisco® brand names and a distribution agreement with Novartis concerning the anti-hypertensive Nisis® and Nisisco® in France; these drugs were previously exploited and distributed by Aventis. The transfer of marketing authorisations was completed on 30 April 2003.

### **CEA** (Paris, France)

In October 2005, Ipsen signed a letter of intent with the French atomic energy commission, CEA, to carry out research programmes related to the treatment of Parkinson's and Alzheimer's diseases.

### **Radius** (Cambridge, United States)

In September 2005, Ipsen signed a licensing agreement with Radius under the terms of which the Group granted Radius the exclusive right to develop, manufacture and distribute a compound belonging to the Group known as BIM 44058

(as well as its analogues) using the sustained-release formulation technology developed by the Group for the development of a drug used in the treatment of osteoporosis.





A strategy respectful of working conditions, environment and dissemination of knowledge

# OUR COMMITMENT: SOCIAL AND ENVIRONMENTAL RESPONSIBILITY

Ipsen, conscious of its social and environmental responsibility, aims to provide good working conditions for its employees and to respect the planet.

To contribute to the dissemination of scientific knowledge, Ipsen created in 1983 *La Fondation Ipsen* under the patronage of *La Fondation de France*, which mission is to develop exchanges between researchers and clinical practitioners.



## SOCIAL RESPONSIBILITY

# Knowledge sharing and skills valuation

*Ipsen has structured its human resources strategy around four lines of expertise: training/development, compensation and benefits, recruitment and social relations. According to a functional and matricial structure, which makes it possible to support the whole of activities of the Group in all the countries where it is established, the teams of human resources support the employees within the framework of this policy and the respect of the principles of equity and merit.*

The Group decided to formalise certain practices which had been in use for some time already, and provide a common framework to its actions. "Vision, Mission and Values" are Ipsen's cultural references.

### Group's values

In a context of growth, this framework should help to focus Ipsen projects, formalise organisational changes already initiated for some years, to reinforce the sense of belonging to the Group and value its ethical dimension.

These cultural references are defined by:

- one vision: innovation for patient care;
- one mission: an innovation driven international specialty pharmaceutical group;
- and five values:
  - **Commitment:** we recognise patients, prescribers, regulatory authorities, payers,

business partners, suppliers, shareholders, and employees are the heart of everything we do and we are committed to meeting their needs and expectations.

– **Drive:** we create new opportunities by nurturing innovation and welcoming change. We deliver agreed objectives and quality work on time. We demonstrate a competitive spirit, resilience, flexibility, compliance and drive to succeed.

– **Teamwork and respect:** we work together as one Group and share our knowledge across hierarchies, functions, businesses and countries. Our diversity and mutual respect strengthen our performance. We encourage individual and team development, foster expertise and reward success.

– **Value creation:** we invest in our future through a strategy of clarity, consistency and market intelligence based on an accurate knowledge of the patients and

the medical profession needs. We pursue competitive growth and are all accountable custodians of company assets.

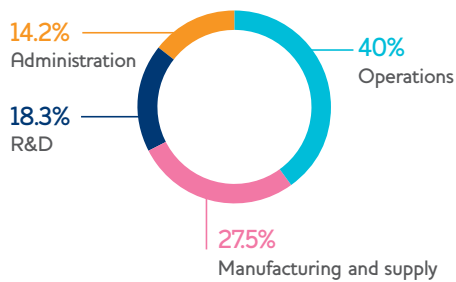
– **Ethics:** we earn the trust of others by consistent honesty, truthfulness and acting responsibly. We adhere to the highest standards of ethics, social responsibility, personal integrity and safety.



## Nearly 4,000 employees worldwide in 2006

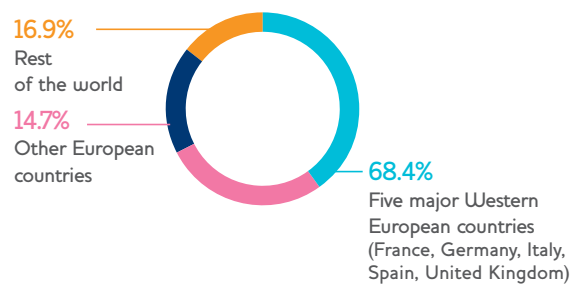
### Headcount staffing

by division

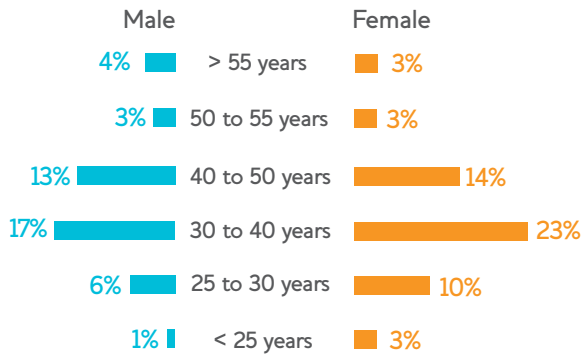


### Headcount staffing

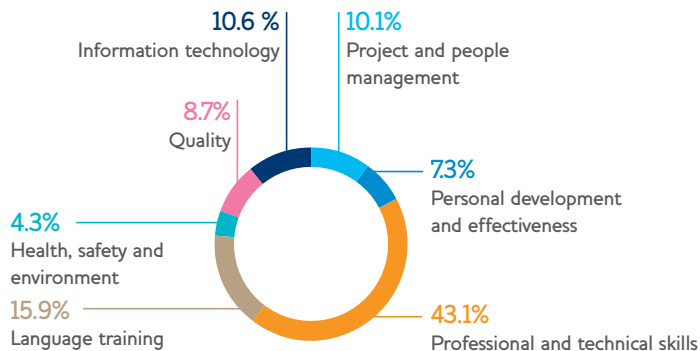
by geographical area



### Distribution by age



### Distribution of training costs



Total training investment

**€6.8 million**



## Training and development

The Group consistently aims to provide its employees with high-quality training tailored to the specific features of each business. Training can be broken down into two types: at central level, training programmes are organised to promote the development of managerial expertise and the cohesion of the Group, and at local level technical training is provided linked to business expertise. In 2006, the Group devoted €6.8 million to continuous professional training, representing 2.92% of its total payroll costs.

The Group-wide framework (IDEA: Ipsen Development and Education Academy) implemented in end 2005 to facilitate the development of Training, Development and Education -TD&E- initiatives continues to evolve in order to support the philosophy of the culture of company and the development of employees. IDEA is oriented toward six principal goals:

- **core competencies**, to facilitate the development and advancement of a corporate culture;
- **integration of new employees**, using a common standard implemented at local level, by plant and by geographical region; it will be complemented by e-integration via the intranet and a specific programme for managers;
- **young professionals development programme**, which aims to attract, secure the loyalty and accelerate the development of high-potential graduates who will be involved in key roles within the Group's various divisions;
- **the managers college**, which aims to raise the performance of supervisors and managers to a high level guaranteeing the consistency of management practices within the Group;
- **the leaders college**, which aims to hone the leadership skills of senior executives in long-term strategic areas;

- **the Group's image**, to bolster the Group's credentials as an employer of choice in the current market through its image and clear communication of the Group's human resources practices and management initiatives.

To optimise continuous investment in the TD&E initiatives, the network of training staff specifically trained to deliver the Group's programmes will be strengthened during 2007.

The Ipsen Performance Appraisal Process, which was introduced during 2006, encourages the identification of training and development needs to meet personal and business goals. It facilitates regular discussions regarding personal and development objectives between employees and their managers.

## Compensation and benefits

Ipsen's compensation and benefits policy is based on a Global Total Reward approach, which endeavours to value all functions, as well as measure the performance of its employees. It is based on four main principles: an assessment of the positions using a model applicable to all the Group's positions; competitiveness at regional, national and international level; equal internal opportunities; and performance-based compensation. These principles are applied in countries where the Group operates, and the way they are implemented is adapted to the local socio-economic and legal environment.

From 2006 onwards, annual pay increases are implemented using a common framework and identical schedule for the entire Group.

Employees performing a management role are eligible to a bonus system. The proportion of "variable" compensation has been increased with efforts by the Group to foster a performance-based culture.





Trends in compensation and benefits paid by Group companies depend on local circumstances.

### Recruitment and internal promotion

Group's employment policy aims at attracting and maintaining a suitably qualified, well trained and motivated workforce to perform, as efficiently as possible, the various tasks and roles inherent to the Group's business activities.

A specific attention is paid to recruitment policy which is made in the respect of the Group's values. Thus, in 2006, 695 new employees have joined Ipsen, including 579 for permanent jobs.

Internal promotion is one the key ways to motivate employees and their supervisors (4.8% of employees had a promotion in 2006)

### Social relationships

Employees are represented at each Group company in accordance with the applicable local legislation. In France, employees' representation is now organised within the framework of an economic and social entity, with a unique central works council for all employees. This entity model allows to legitimate and perpetuate the central negotiation model in place since 2004 within the Group in France.

The frequency of meetings between management and employee representatives also depends on the applicable local legislation. The Group ensures that the rights and freedoms of employee representatives are strictly observed and that they enjoy the same promotion and training opportunities as other employees. In France, since 2006, to safeguard equal wage and promotion opportunities, employee representatives have the oppor-

tunity of a specific interview with their line and human resources managers. A specific agreement was reached in 2006 in relation to employees who are medical sales representatives, for them to maintain their variable compensation opportunities while they exercise their employee representative activities.

Where there are relevant local regulations, the Group applies collective bargaining agreements or industry agreements for the pharmaceutical sector. In addition, companies negotiate specific agreements according to their individual characteristics and requests of employee representatives and union organisations. Management continues its policy to develop the social dialogue.

ALMOST  
**700**  
PEOPLE JOINED  
IPSEN in 2006

## ENVIRONMENTAL RESPONSIBILITY

# Investment respectful of environment

*Since environmental protection remains a permanent priority for the Group, it regularly invests in this area. Ipsen pursued campaigns during 2006 at most of its facilities to raise users' awareness about energy consumption, and all energy-consuming investments are now assessed and undergo an energy review by the Group's industrial department.*

Responsibility for environmental protection at each plant is assigned to named individual. In 2006, 21 members of staff were involved in this organisation across the Group as a whole. It is managed by the head of the Health-Safety-Environment function for the whole of the Group's manufacturing and supply organisation.

### **Energy consumption: further efforts to achieve greater energy efficiency**

The Group's energy consumption increased by 5% (compared with a rise of 8.3% between 2004 and 2005), attributable to the strong rise in production volumes at most facilities and growth totalling 9.1% in sales volumes. Consumption trends at individual plants mirrored trends in production volumes, albeit with a generally favourable and significant differential. This improved

energy efficiency was the result of deliberate efforts to reduce consumption at most plants.

### **Water consumption: consumption tightly controlled in spite of growth in sales**

Water consumption was reduced of 2.4%. Thanks to the initiatives taken to recycle manufacturing and washing process water, and also to systematic investigations to detect water losses, water consumption is better controlled.

### **Solid and liquid waste**

Production of waste increased by 0.3%, a much slower rate of growth than that seen in production volumes over the same period. The proportion of recycling is thus steadily increasing, while incineration and

landfill volumes are moving in the opposite direction. Significant efforts are underway or being developed by the majority of facilities to reuse a larger proportion of their waste. For instance, more and more organic waste is being composted in Cork (Ireland), paper and cardboard recycling is developed in Tianjin (China) since 2005 and in Isle-sur-la-Sorgue (France) since 2006, and dichloromethane recycling was rolled out at the Signes (France) plant during 2005.

### **Improvement in quality of discharges into the air**

Ongoing efforts have been made over the past few years in this area: scrapping the use of fuel oil in Dublin (Ireland) at the end of 2003 and at Dreux (France) from 1 January 2005 and the plan to do the same in 2007/2008 in Tianjin (China) all contribute to the decrease in sulphur dioxide tonnages following the discontinuation of or reduction in the use of fuel oil.



### **Encouraging trend in the effluent to sales ratio**

Effluent volumes dropped by 12.5%. All the plants recorded lower or stable effluent volumes thanks to specific reprocessing measures or efforts to curb inputs.

### **Noise**

No particular noise issues were reported at the Group's manufacturing facilities that caused nuisance to neighbours (nuisance was restricted to uninhabited environments). Most of our facilities are located far from residential areas and no specific comment was made in the specialised audit carried out in 2006.

### **Soil pollution**

The Group attaches a very high level of importance to the issue of the impact of its operations on the soil in and around its plants. It is therefore very pleased to note that no instances of soil pollution were recorded at the Group's facilities in 2006.



LA FONDATION IPSEN

# Contribute to the development and dissemination of knowledge

*Created in 1983 under the patronage of La Fondation de France, La Fondation Ipsen mission is to contribute to the development and dissemination of scientific knowledge. The long-standing action of La Fondation Ipsen is aimed at furthering the interactions between researchers and clinical practitioners, which are indispensable due to the extreme specialisation of these professions. The ambition of La Fondation Ipsen is not to offer definitive knowledge, but to trigger discussions about the major scientific issues of the forthcoming years. La Fondation Ipsen involves partners from the international academic and scientific communities in each of its actions so that it can independently set out the major issues that it has decided to address and provide an update on the current state of the scientific knowledge.*

## **Medicine and Research seminars**

*La Fondation Ipsen brings together distinguished experts in its Medicine and Research seminars. These annual international meetings are dedicated to the emerging themes of medicine and biology in several fields:*

### **Alzheimer's disease**

Since 1987 there have been 21 conferences on this topic. In 2006, there was a special commemoration to celebrate the 100<sup>th</sup> anniversary of Alois Alzheimer's presentation of the Auguste D. case which took place where the initial presentation was made: Institute of Psychiatry in Tübingen, Germany. All the pioneers of research into

Alzheimer's disease presented the major steps made over the past two decades. The last conference in this series was held on 16 April 2007 and covered the situation of current research, on the synaptic function and plasticity as regards Alzheimer's disease and other degenerative diseases.

### **Neurosciences**

Started in 1990, this set of conferences focuses on the major issues emerging in this field, concerning molecular biology or cognitive sciences. The 14<sup>th</sup> conference of this series took place in April 2006 and covered the molecular and cellular learning mechanisms of the memory. The 2007 conference covered a completely new theme: the role of retrotransposons in neuronal diversity and brain development.

### **Longevity**

Launched in 1987, this topic brings up the issues and paradoxes of a medical approach which is not focused on the disease but on a better resistance to damaging attacks which weaken the physiological systems in ageing.

### **Endocrinology**

This topic, launched in 2002, focuses on the interactions of the endocrine system, and their involvement in the body's functioning. In December 2006, the 6<sup>th</sup> conference in this series dealt with a theme at the crossroads of oncology and endocrinology: hormonal control of the cell cycle. The next conference to be held in December 2007, will discuss the effect hormones have on social behaviour.

### **Vascular tree**

This new topic, launched in 2004, aims at exploring the various stages leading to the development of the vascular system, its smooth growth in relation to the growth of the various organs, its degeneration, its death and its regeneration possibilities. In 2006, the conference was dedicated to the effects inflammation has on the vascular tree.

## Cancer

The first conference in 2005 was based on identifying the aims of therapeutic research, taking into account the fact that cancer is a chronic disease. In 2006, the second meeting discussed the possible link between inflammation and cancer. In 2007, the conference covered metastases and brought together the world's leading specialists including several Nobel prize winners.

## Other international events

*La Fondation Ipsen* organises international meetings in partnership with several international institutions and organisations, which bring together experts in various disciplines, including:

- World Health Organisation (WHO) – Since 1989, a number of meetings on human genetics have addressed some of the most widely debated topics in this field;

- French National Gerontology Foundation: various conferences covered dementia and cognitive ageing. Three new partnerships will be launched in 2007, with:

- The Salk Institute (La Jolla) and Nature magazine: this partnership will set up a series of annual meetings dedicated to biological complexity. The first meeting which took place in January 2007 dealt with transcription, which is a hot topic as demonstrated a few weeks before the meeting by the fact that one of the speakers, Professor Kornberg received the 2006 Nobel Prize in Chemistry;
- Cell magazine and the Massachusetts General Hospital: this series (“Exciting Biologies”) will start in October 2007 with “Biology in Motion”;
- Nature magazine: there will be several meetings in 2007 in the United States under the title “Emergence and Convergence”.

## International publications

The various events of *La Fondation Ipsen* result in the publication of synthesis works published by international publishing houses within various Ipsen Foundation collections:

- Research and Perspectives in Alzheimer's disease;
- Research and Perspectives in Neurosciences;
- Research and Perspectives in Longevity;
- Research and Perspectives in Endocrinology;
- Collection OMS/Fondation Ipsen;
- Collection « *Esprit et cerveau* ».

In addition, *La Fondation Ipsen* has since 1986 published (190 issues released), a periodical dedicated to Alzheimer's disease entitled *Alzheimer Actualités*.

It also publishes the Medicine and Research Conferences reports dedicated to the decryption of the vascular tree and cancer.

## Awards to encourage research

*La Fondation Ipsen* awards prizes for the works of pioneers in the four following fields of research:

- **Neurosciences.** The 17<sup>th</sup> prize in Neuronal Plasticity, which was created in collaboration with Prof. Jean-Pierre Changeux, was awarded in 2006 by an international jury chaired by Prof. Joël Bockaert (Institute of Functional Genomics, Montpellier) to three researchers jointly: Prof. Eckhart D. Gundelfinger (Leibniz Institute for Neurology, Magdeburg), Prof. Mary B. Kennedy (California Institute of Technology, Pasadena) and Prof. Morgan Sheng (Picower Institute for Learning and Memory, MIT, Cambridge) for their works on the synaptic function.

- **Neuropsychology.** The Jean-Louis Signoret prize was awarded by a jury chaired by Prof. Albert Galaburda (Harvard University, Boston) to Prof. Faraneh Vargha-Khadem (Institute for Child Health, London) in 2006 for her research in showing that a mutated gene is involved in language disorder in children.

- **Longevity.** In 2006 this prize was awarded to Prof. Cynthia Kenyon (University of California, San Francisco) for her work on the genetic decoding of the ageing of the *C. elegans* genome.

- **Endocrinology.** The international jury chaired by Prof. Iain Robinson (National Institute for Medical Research, London) in 2006 selected Prof. Roger Cone (Oregon Health and Science University, Portland) for his works on peptides involved in metabolism and obesity.







Solid performances in 2006 despite a challenging environment

# 2006 CONSOLIDATED FINANCIAL STATEMENTS

Recurring operating margin above objectives: 23.7% of consolidated sales.

Strong increase in recurring consolidated profit: +15.6%.

All time high cash flow from operating activities: €328 million.

The pro forma consolidated statements present the Group's activity as if the legal reorganisation of the Group, completed in June 2005, had taken place before 1 January 2002.

## CONSOLIDATED INCOME STATEMENTS

| (in thousands of euros)  | 31/12/2006     | 31/12/2005<br>Pro forma | 31/12/2005     |
|--|----------------|-------------------------|----------------|
| Sales of goods   | 861,676        | 807,114                 | 788,709        |
| Other revenues   | 83,581         | 80,738                  | 75,046         |
| <b>Total revenue</b>   | <b>945,257</b> | <b>887,852</b>          | <b>863,755</b> |
| Cost of goods sold   | (181,377)      | (171,042)               | (176,833)      |
| Research & Development expenses  | (178,348)      | (169,025)               | (167,571)      |
| Selling expenses   | (307,795)      | (295,358)               | (292,586)      |
| General and administrative expenses                                      | (75,220)       | (68,777)                | (66,787)       |
| Other operating income and expenses                                      | (8,223)        | 1,169                   | 1,185          |
| Restructuring costs  | 190            | 530                     | 530            |
| Impairment losses  | (7,265)        | –                       | –              |
| <b>Operating income</b>  | <b>187,219</b> | <b>185,349</b>          | <b>161,693</b> |
| Investment revenue   | 7,974          | 1,952                   | 1,312          |
| Cost of financing  | (2,142)        | (7,870)                 | (7,701)        |
| <b>Net finance cost</b>  | <b>5,832</b>   | <b>(5,918)</b>          | <b>(6,389)</b> |
| Other financial income and expenses                                      | (5,707)        | (632)                   | (291)          |
| Income tax   | (40,891)       | (34,208)                | (32,643)       |
| Share of (loss)/profit of associated companies                           | (1,666)        | –                       | –              |
| <b>Revenues from continuing operations</b>                               | <b>144,787</b> | <b>144,591</b>          | <b>122,370</b> |
| Revenues from discontinued operations                                    | (290)          | 4,416                   | 4,416          |
| <b>Consolidated revenues</b>   | <b>144,497</b> | <b>149,007</b>          | <b>126,786</b> |
| – attributable to equity holders of Ipsen S.A.                           | 144,006        | 148,638                 | 119,230        |
| – attributable to minority interests                                     | 491            | 369                     | 7,556          |
| Basic earnings per share, continuing operations (in euros per share)     | 1.72           | 2.14                    | 1.71           |
| Diluted earnings per share, continuing operations (in euros per share)   | 1.72           | 2.14                    | 1.71           |
| Basic earnings per share, discontinued operations (in euros per share)   | 0.00           | 0.06                    | 0.06           |
| Diluted earnings per share, discontinued operations (in euros per share) | 0.00           | 0.06                    | 0.06           |
| Basic earnings per share (in euros per share)                            | 1.71           | 2.20                    | 1.77           |
| Diluted earnings per share (in euros per share)                          | 1.71           | 2.20                    | 1.77           |

## CONSOLIDATED BALANCE SHEETS – BEFORE ALLOCATION OF NET PROFIT

| (in thousands of euros)                                    | 31/12/2006       | 31/12/2005     |
|--|------------------|----------------|
| <b>ASSETS</b>  |                  |                |
| Goodwill   | 188,836          | 188,836        |
| Other intangible assets                                    | 68,203           | 39,800         |
| Tangible assets  | 198,186          | 187,769        |
| Equity investments   | 1,825            | 2,656          |
| Investments in associated companies                        | 50,832           | –              |
| Other non-current financial assets                         | 30,601           | 2,671          |
| Deferred tax assets  | 64,025           | 13,096         |
| <b>Total non-current assets</b>                            | <b>602,508</b>   | <b>434,828</b> |
| Inventories  | 78,947           | 74,390         |
| Trade receivables  | 191,702          | 164,681        |
| Current tax assets   | 2,665            | 10,951         |
| Other current assets                                       | 44,601           | 42,966         |
| Cash and cash equivalents                                  | 285,459          | 202,034        |
| <b>Total current assets</b>                                | <b>603,374</b>   | <b>495,022</b> |
| <b>Assets of discontinued operations</b>                   | <b>8,391</b>     | <b>12,659</b>  |
| <b>TOTAL ASSETS</b>  | <b>1,214,273</b> | <b>942,509</b> |
| <b>EQUITY and LIABILITIES</b>                              |                  |                |
| <b>Share capital</b>                                       | <b>84,025</b>    | <b>84,025</b>  |
| Share premiums and consolidated reserves                   | 506,244          | 420,591        |
| Net profit for the year                                    | 144,006          | 119,230        |
| Foreign exchange differences                               | (7,789)          | (4,080)        |
| <b>Equity attributable to equity holders of Ipsen S.A.</b> | <b>726,486</b>   | <b>619,766</b> |
| Minority interest  | 1,419            | 1,334          |
| <b>Total equity</b>  | <b>727,905</b>   | <b>621,100</b> |
| Retirement benefit obligation                              | 9,299            | 8,032          |
| Long-term provisions                                       | 11,421           | 8,266          |
| Bank loans   | 6,286            | 37,751         |
| Other financial liabilities                                | 15,313           | 15,508         |
| Deferred tax liabilities                                   | 2,371            | 1,358          |
| Other non-current liabilities                              | 172,270          | –              |
| <b>Total non-current liabilities</b>                       | <b>216,960</b>   | <b>70,915</b>  |
| Short-term provisions                                      | 5,323            | 3,309          |
| Bank loans   | 6,973            | 7,074          |
| Financial liabilities                                      | 2,251            | 1,760          |
| Trade payables   | 100,269          | 107,045        |
| Current tax liabilities                                    | 27,215           | 2,223          |
| Other current liabilities                                  | 114,824          | 113,525        |
| Bank overdrafts  | 1,716            | 1,470          |
| <b>Total current liabilities</b>                           | <b>258,571</b>   | <b>236,406</b> |
| <b>Liabilities of discontinued operations</b>              | <b>10,837</b>    | <b>14,088</b>  |
| <b>TOTAL EQUITY AND LIABILITIES</b>                        | <b>1,214,273</b> | <b>942,509</b> |



## CONSOLIDATED STATEMENT OF CASH FLOWS

| (in thousands of euros)   | 31/12/2006       | 31/12/2005<br>Pro forma | 31/12/2005       |
|---|------------------|-------------------------|------------------|
| <b>Net profit for the period</b>  | <b>144,497</b>   | <b>149,007</b>          | <b>126,786</b>   |
| Net profit from discontinued operations   | 290              | (4,416)                 | (4,416)          |
| Share of loss/profit from associated companies                                      | 1 666            | -                       | -                |
| <b>Net profit from continuing operations before share from associated companies</b> | <b>146,453</b>   | <b>144,591</b>          | <b>122,370</b>   |
| <b>Non-cash and non-profit items</b>  |                  |                         |                  |
| Depreciation, amortisation and impairment losses                                    | 49,940           | 30,603                  | 28,869           |
| Change in fair value of derivative financial instruments                            | 1,562            | 276                     | 276              |
| Net gains or losses on disposal of non-current assets                               | (877)            | 232                     | 215              |
| Share of government grant released to profit and loss                               | (112)            | (135)                   | (81)             |
| Exchange differences  | 694              | (1,238)                 | (1,553)          |
| Change in deferred taxes  | (34,227)         | (4,717)                 | (4,517)          |
| Share-based payment expenses  | 3,282            | 3,355                   | 3,355            |
| Net gains or losses on disposal of treasury shares                                  | 221              | -                       | -                |
| Other non-cash items  | 690              | -                       | -                |
| <b>Cash flow from operating activities before changes in working capital</b>        | <b>167,626</b>   | <b>172,967</b>          | <b>148,934</b>   |
| (Increase)/decrease in inventories  | (4,644)          | (5,315)                 | (8,100)          |
| (Increase)/decrease in trade receivables  | (27,419)         | (6,755)                 | (3,943)          |
| (Decrease)/increase in trade payables   | (7,121)          | 9,192                   | 8,049            |
| Net change in income tax liability  | 33,051           | (15,110)                | (16,357)         |
| Net change in other operating assets and liabilities                                | 166,142          | 21,875                  | 20,970           |
| <b>Change in working capital related to operating activities</b>                    | <b>160,009</b>   | <b>3,887</b>            | <b>619</b>       |
| <b>NET CASH PROVIDED BY OPERATING ACTIVITIES</b>                                    | <b>327,635</b>   | <b>176,854</b>          | <b>149,553</b>   |
| Acquisition of property, plant and equipment  | (40,630)         | (36,479)                | (35,716)         |
| Acquisition of intangible assets  | (41,217)         | (7,944)                 | (6,911)          |
| Proceeds from disposal of intangible assets and property, plant and equipment       | 3,044            | 1,124                   | 1,096            |
| Acquisition of investments in non-consolidated companies                            | (15)             | -                       | -                |
| Acquisition of investments in associated companies                                  | (63,082)         | -                       | -                |
| Convertible note subscriptions  | (20,966)         | -                       | -                |
| Payments to post-employment benefit plans   | (4,226)          | (1,400)                 | (1,400)          |
| Impact of changes in the scope of consolidation                                     | -                | -                       | (51,405)         |
| Treasury shares   | (1,294)          | -                       | -                |
| Other cash flows related to investing activities                                    | (1,028)          | (426)                   | (475)            |
| Change in working capital related to investing activities                           | 5,796            | (7,624)                 | (6,778)          |
| <b>NET CASH USED BY INVESTING ACTIVITIES</b>  | <b>(163 618)</b> | <b>(52 749)</b>         | <b>(101 589)</b> |
| Additional long-term borrowings   | -                | 13,052                  | 13,052           |
| Repayment of long-term borrowings   | (31,824)         | (189,969)               | (200,949)        |
| Net change in short-term borrowings   | (89)             | (3,095)                 | (3,095)          |
| Ipsen S.A. capital increase   | -                | 9,088                   | 133,616          |
| Increase in share premiums or transfer premiums                                     | -                | 182,731                 | 212,652          |
| Dividends paid by Ipsen S.A.  | (50,407)         | (29,303)                | (29,303)         |
| Dividends paid by subsidiaries to minority interests                                | (358)            | (300)                   | (300)            |
| Change in working capital related to financing activities                           | 464              | (1,154)                 | (3,440)          |
| <b>NET CASH USED BY FINANCING ACTIVITIES</b>  | <b>(82,214)</b>  | <b>(18,950)</b>         | <b>122,233</b>   |
| Impact of operations due to be sold or discontinued                                 | 647              | 12,001                  | 12,001           |
| Impact of pro forma restatements  | -                | (10,150)                | -                |
| <b>CHANGE IN CASH AND CASH EQUIVALENTS</b>  | <b>82,450</b>    | <b>107,006</b>          | <b>182,198</b>   |
| <b>Opening cash and cash equivalents</b>  | <b>200,564</b>   | <b>92,763</b>           | <b>17,742</b>    |
| Impact of exchange rate fluctuations  | 729              | 795                     | 624              |
| <b>Closing cash and cash equivalents</b>  | <b>283,743</b>   | <b>200,564</b>          | <b>200,564</b>   |

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Administration and Finance: Claire Giraut  
Public Affairs and Corporate Communications: Didier Véron

Production and Design: Synelog

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