

Servier puts the accent on innovative, patient-focused research and an ambitious partnership policy

The healthcare sector is in the midst of transformation, with one notable change being the emergence of a comprehensive approach to patient care. A new, patient-centric dynamic is being created.. We are seeing a host of initiatives and technological innovations intended to offer more appropriate treatments, improve monitoring, and promote adherence, comfort and independence. To continue to create value in this sector, it is not just medicines and medical devices that are needed, but also treatment-related services and solutions. Therefore, if the pharmaceutical industry wishes to continue to be a key healthcare stakeholder, it must expand its product offer and become a *Supplier of innovative and comprehensive therapeutic solutions* in which medicines and personalised services go hand in hand, rather than limit itself to being *Creator of medicines*. Alongside this, digital technology is having a major influence on the sector by creating genuine opportunities to innovate in healthcare for the benefit of health professionals and patients alike.

In response to these industrial, commercial and digital challenges, Servier is continuing to transform its research activities through an innovation strategy focused on five areas of excellence, coupled with a dynamic partnership policy. The Group is placing the emphasis on an extensive network of partners to fulfil its needs for specialisation and innovation in new medicinal products, and accelerate research and time to market to best meet patient expectations. Servier currently counts over fifty partnerships – not just with other drug companies but also innovative biotechs, universities and incubators.

The Group also wishes to become involved in digital health by creating and developing eHealth solutions in synergy with, and complementary to, its therapeutic orientations and medicinal products. The creation in November 2016 of its *WeHealth by Servier* department, tasked with entering the digital health market, reflects this ambition.

With 25% of its turnover (excluding generics) ploughed back into R&D year after year, research has always been the top priority for Servier. Armed with its innovation strategy, its expertise, and the excellence of its 2 000 researchers, the Group is well-placed to meet the new challenges generated by a rapidly changing healthcare system, in which the patient is playing an increasingly active role.

> ... to become a major player in oncology and in neuropsychiatric and immune-inflammatory diseases

In oncology, Servier is active on three promising fronts

22 million new cases per year over the next 20 years, according to World Health Organization (WHO) estimates: such is the current scale of cancer. To meet growing patient needs, Servier has made oncology a priority component of its Research and Development (R&D) policy. The proportion of R&D dedicated to oncology has risen from 14% in 2015 to 37% in 2017 and is expected to reach 50% in the next two years.

The Group's R&D oncology programmes explore three avenues: targeted therapies, apoptosis and immuno-oncology, to maximise efficacy for the benefit of patients.

In terms of targeted therapies, the focus of Servier's research is tyrosine kinases¹, a family of enzymes implicated in cancer progression. Inhibitors of these enzymes block the abnormal events that cause cancer cell deregulation. The Group is currently trialling its compound S49076, a MET and AXL kinase inhibitor, in patients with certain types of non-small cell lung cancer.

The second avenue is apoptosis, where the challenge is to induce the death of cancer cells. Various research conducted worldwide has demonstrated that the BCL-2 protein family is over-represented in cancer cells, preventing these cells from entering apoptosis and therefore dying. As such, these research programmes aim to precision-target these proteins to restore this mechanism. This research, conducted in collaboration with the Walter & Elisa Hall Institute in Melbourne (Australia), has been published in the prestigious journal *Nature*².

Servier's third research avenue is immuno-oncology. The principle is to restore and stimulate the immune system so that it can recognise and destroy cancer cells. This involves using biological approaches based on the body's natural defence mechanisms. This is field in which Servier is a pioneer with UCART 19, the first allogeneic cell therapy in clinical trials, developed in partnership with Pfizer.

¹ Tyrosine kinases are a group of enzymes implicated in the signalling pathways that contribute to cancer cell propagation. A kinase inhibitor has the ability to block the action of one or more kinases.

² "The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models". 538, 477-482, 2016.

**FOCUS ON INNOVATION****UCART 19: immunotherapy, a pioneering field in the fight against cancer**

Servier joined forces with Cellectis in 2014, followed by Pfizer in 2015, to develop UCART 19 in the treatment of adult and paediatric relapsed or refractory acute lymphoblastic leukaemia (ALL). The objective is to develop a new generation of immuno-oncology treatments which use allogeneic T-cells to fight haematological malignancies. This approach remedies the shortcomings of the existing autologous therapies (in which the patient's own cells are engineered) by providing a therapy that uses allogeneic T-cells from healthy donors and whose production can be industrialised to obtain an "off-the-shelf" product available for all patients.

The drug candidate obtained Investigational New Drug status in the US in March 2017.

In February 2014, Servier acquired exclusive rights to UCART19 from Cellectis. In 2015, the Group sold Pfizer the exclusive rights to develop and commercialise UCART19 in the US while maintaining exclusive rights to the other countries. Following these agreements, Servier and Pfizer entered a joint clinical development programme alliance for this anti-cancer immunotherapy.

Checkpoint inhibitors, or how to unblock immune controls

In January 2017, Servier and Pieris Pharmaceuticals entered a strategic co-development alliance in immuno-oncology.

The aim is to offer a series of new molecules, including a number of bispecific antibodies, modulators of immune "checkpoints". To understand these more clearly, one must be aware that the immune system acts via a series of checkpoints which activate or inhibit the immune system. At these checkpoints, cancer cells protect themselves by deceiving and blocking immune cells that are no longer able to identify them as dangerous and destroy them. Several years ago, researchers identified monoclonal antibodies, called checkpoint inhibitors, which can prevent tumours from evading the immune system. The excellent clinical efficacy of these inhibitors is nevertheless limited because a majority of patients fail to respond to approved therapies. Pieris' technology is particularly innovative because it allows coupling two antibodies that simultaneously block various checkpoints on the same cell, thereby significantly increasing treatment efficacy.

Under the terms of this agreement, Servier and Pieris can jointly conduct a number of bispecific research programmes.



Servier 2017 oncology pipeline

- **3 products** for healthcare professionals and patients: Muphoran, Pixuvri and Lonsurf
- **12 drug candidates** in development

> ... to focus on the most incapacitating neuropsychiatric conditions

With its over 40 years of expertise in neuropsychiatry, Servier has decided to focus its research activities on neurodegenerative disorders by targeting the proteinopathies - diseases characterised by an abnormal build-up of certain proteins, such as in Alzheimer disease or Parkinson disease. In addition to being particularly incapacitating for the patients, these diseases also directly impact their families. Alongside this, Servier is also committed to the development of treatments for high therapeutic need neuropsychiatric conditions, such as multiple sclerosis, autism, and depression.



FOCUS ON INNOVATION

Multiple sclerosis: targeting causes, rather than symptoms, gives hope to patients

Signed in November 2014, the partnership between GeNeuro and Servier involves an innovative approach which acts prior to neuroinflammation and neurodegeneration, unlike existing treatments which target the actual neuroinflammation and symptoms, therefore not addressing the cause.

For this, Servier and GeNeuro are working on the development of a monoclonal antibody which neutralises pHERV-W env, a toxic protein thought to be a causal factor in neuroinflammation and neurodegeneration, present in patients with multiple sclerosis. Following the Phase 1 and 2 clinical trials, Servier can exercise the option to licence the product for all markets, excluding the USA and Japan.

The 6-month results from the CHANGE-MS Phase 2b study confirm its good safety profile. The second half of the study is currently underway, with final results expected in the first quarter of 2018.



FOCUS ON INNOVATION

Autism: promising results in children

Research by Neurochlore has demonstrated that bumetanide acts on the high chloride levels in neurons observed in certain neurodevelopmental disorders such as autism. A Phase 2B trial conducted by the biotech in almost 90 children (2-18 years) in six French centres has yielded promising results.

While no treatment currently exists for autism, bumetanide could become the first overall therapy to manage its core symptoms of social deficit and repetitive behaviour.



Servier 2017 neuropsychiatry pipeline

- 4 products for healthcare professionals and patients: **Arcalion, Trivastal, Stablon and Valdoxan**
- 3 drug candidates in development

> ... to target its efforts in three immune-inflammatory diseases

Immuno-inflammatory and autoimmune diseases encompass numerous conditions triggered or characterised by an inappropriate immune system response directed against the body's own cells.

Servier has opted to focus its research efforts on three conditions with high unmet needs: systemic lupus erythematosus, systemic sclerosis - which affects around 30 000 patients in Europe, and Sjögren's syndrome, which is the second most common autoimmune disease and affects around 190 000 patients in Europe.

Their treatment is limited to corticosteroids and immunomodulators. In recent years, a certain level of progress has been achieved with biotherapies, but this remains insufficient. These treatments are not curative. On average, only one-third of treated patients will enter clinical remission, but sometimes not without many side effects and a high risk of treatment failure.

In this context, research programmes are underway with OSE Immunotherapeutics in Sjögren's syndrome and ILTOO Pharma in systemic lupus erythematosus to begin with, to be later followed by programmes in other autoimmune conditions.



Servier's 2017 immuno-inflammatory diseases pipeline

- 4 drug candidates in development

> ... to strengthen its leading positions in cardiovascular diseases and diabetes

Servier: No. 2 in Europe in cardiovascular diseases and No. 1 in hypertension

Cardiovascular diseases, affecting the heart and blood vessels, are the leading cause of mortality worldwide. Given their major public health impact, Servier has always made these diseases the core focus of its research and development activities. The Group is currently Europe's second leading pharmaceutical industry player in fighting them, offering doctors and patients 14 medicinal products for the treatment of heart failure, hypertension, coronary artery disease and venous disease. Each day, over 17 million cardiovascular patients are treated with Servier drugs worldwide.

In 2016, Servier signed an agreement with a US partner, AMGEN, to market its new chronic heart failure candidate, omecamtiv mecarbil, in the European Union and Community of Independent States, including Russia. This drug represents a highly innovative approach in the treatment of chronic heart failure, which affects over 23 million people worldwide. In the wake of the positive results of COSMIC-HF^[1], a Phase 2 trial evaluating this treatment in patients with this condition, Servier and Amgen have decided to continue the development programme of omecamtiv mecarbil into Phase 3, in collaboration with US biopharmaceutical company, Cytokinetics.



Servier 2017 cardiovascular diseases and pulmonary hypertension pipeline

- **3 heart failure products** for healthcare professionals and patients: Procoralan, Implicor, Vastarel. Carivalan is awaiting marketing authorisation
- **9 hypertension products** for healthcare professionals and patients, making Servier the only company to offer its patients such a wide range: Coversyl, Cosyrel, Coveram, Natrilix, Natrixam, Preterax, Triplixam, Triveram, Viacoram
- **4 drugs** in development

^[1] Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure

Type 2 diabetes: a more personalised approach

Diabetes is the seventh cause of death worldwide and the leading cause of kidney failure, blindness in adults and lower-limb amputation. That is why treating type 2 diabetes and its complications has always been a priority for the Servier Group.

Without major changes in lifestyles or the introduction of new treatments in the next 10 to 15 years, it is forecast that 642 million people will be diabetic by 2040, representing a 50% rise within only a quarter of a century.

The approaches taken by Servier are expected to more precisely pinpoint the origin and progression of the disease and identify the types of patient in whom an adapted and tailored therapeutic strategy would be possible.

Servier is participating in the Innovative Medicines Initiative (IMI), the fruit of a partnership between the European Commission and the pharmaceutical industry. The Group is also participating in three other programmes intended to promote access to innovation in diabetes: DIRECT, IMIDIA and RHAPSODY. Their purpose is to elucidate why the disease progresses more rapidly in some patients and not others.



Servier 2017 diabetes pipeline

- 1 product for healthcare professionals and patients: Diamicon (various forms)
- 1 drug candidate in development
- 4 research programmes underway

> Research 3.0

WeHealth: a new eHealth department for better fulfilment of patient needs

WeHealth by Servier is the Group's new eHealth department. Its purpose is to improve patient support in their daily lives by offering innovative and connected services for better monitoring and increased reactivity should treatment adjustment be required. For Servier, it is about entering the connected healthcare field by co-developing simple-to-use products and services, based on innovation spearheaded by start-ups around the globe.



FOCUS ON INNOVATION

Cardioskin, a connected T-shirt

In conjunction with the start-up BioSerenity, *WeHealth by Servier* has developed Cardioskin, a connected garment as light as underwear and washable up to 35 times. Designed to be worn 24 hours a day, its integrated sensors detect heart rhythm disorders in real time.

The data captured by Cardioskin are transmitted to the patient's doctor, enabling him or her to continuously monitor parameters in their patient and establish an accurate diagnosis.

Cardioskin has obtained CE marking and is scheduled to launch in 2018.



Cardioskin, a connected T-shirt to monitor cardiac activity



FOCUS ON INNOVATION

A telemedicine tool to improve cardiac patient management

WeHealth by Servier has teamed up with CardioRenal to develop a personalised connected outpatient solution. In the form of a small unit, it uses a drop of blood to measure three biomarkers to screen for the warning signs of a heart problem. This medical device has been designed for patients whose treatment is in the process of being stabilised. Analysed by a specific algorithm, the measurements are transferred in real time to the doctor who can react efficiently and quickly, thereby preventing the re-hospitalisation of their patient.

This solution offers a number of major benefits:

- It reduces the rate of re-hospitalisations which are both traumatic for the patient and costly for the healthcare system.
- It optimises patient monitoring and provides reassurance through continuous physician surveillance.
- It offers patients a more personalised and effective solution which takes into account their needs and characteristics.

Deprexis®: an online therapy effective in the management of depression

Servier has partnered with GAIA, a global pioneer in digital therapy, to develop an Internet-based cognitive-behavioural therapy, intended to accelerate return to a normal life. This medical device offers patients tailored therapeutic support by simulating effective, up-to-date and personalised cognitive behavioural therapy interventions.

This medical advancement provides a user-friendly interface associated with artificial intelligence software that, by continuously adapting to the patient's responses to questions asked, adapts to their needs and keeps them engaged.

When used in addition to pharmacological or psychotherapeutic treatments, Deprexis® has demonstrated its efficacy in 9 different trials performed in nearly 2 000 patients.

Already marketed by Servier in Germany, this device for use in conjunction with other treatment is expected to launch in a number of countries in the near future.

A centre dedicated to therapeutic innovation at Saclay, for increasingly innovative and ambitious research

By 2021, the Group's 600 researchers in France will be pooled at one site – the Servier Research Institute at the Paris-Saclay scientific innovation cluster.

With a surface area of around 45 000 m², the new building, representing a 260-million-euro investment, will have the capacity to welcome up to 800 people. Its architectural approach will foster team spirit, transversality and openness, in an environment conducive to the expression of ideas and talents.



The Servier Research Institute at Paris-Saclay

Designed for maximum versatility, the building will be able to adapt to future developments in technology and science, with ecology always a prime consideration.

The future research centre fully reflects the Group's strategic ambition to be a key player in healthcare innovation. Its purpose is to embody the Group's values of team spirit, cross-functionality and openness in an environment conducive to expressing ideas and talents. With a firm focus on *open innovation* and equipped with the best technologies, it will contain laboratories, project rooms and an incubator to host start-ups and innovative projects from all over the world.

Researchers will be able to interact with numerous other healthcare stakeholders, ensuring that the core focus of research continues to remain the patient, who will benefit from the increasingly rapid and effective solutions that it generates.

> Servier R&D in brief



KEY FIGURES FOR 2017

- 25% of turnover (excluding generics) reinvested each year in R&D
- 2 200 researchers at 3 discovery research centres, including 2 in France
- 51 active alliances with biotechs, start-ups and French and international drug companies
- 33 drug candidates in clinical development in 2017, including 20 new molecular entities in 5 major therapeutic areas: cancer, neuropsychiatric and immune-inflammatory diseases, cardiovascular diseases and diabetes

5 MAJOR AVENUES FOR INNOVATION



About Servier

Servier is an international pharmaceutical company governed by a non-profit foundation, with its headquarters in France (Suresnes). With a strong international presence in 148 countries and a turnover of 4 billion euros in 2016, Servier employs 21 000 people worldwide. Entirely independent, the Group reinvests 25% of its turnover (excluding generic drugs) in research and development and uses all its profits for development. Corporate growth is driven by Servier’s constant search for innovation in five areas of excellence: cardiovascular, immune-inflammatory and neuropsychiatric diseases, cancers and diabetes, as well as by its activities in high-quality generic drugs.

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