RESEARCH & DEVELOPMENT: NEW DRUGS IN NEUROLOGY AND UROLOGY GETTING CLOSER TO MARKET

SCHWARZ PHARMA’s strategic R&D focus is on the treatment of neurological and urological disorders. The need for medicines is particularly high in the field of neurology, since many neurological disorders are not, or not sufficiently, treatable today. What is more, demographic changes and an ageing population are leading to an increasing demand for medicines, especially in these fields. Both patients and their doctors feel and express the need for new medical solutions and expect the researching pharmaceutical manufacturers to come up with corresponding innovations. SCHWARZ PHARMA meets this challenge head on – with passionate commitment and a high sense of responsibility.

We have set ourselves the target of developing innovative medicines for the benefit of patients, and bringing these medicines to market.

SCHWARZ PHARMA has been developing innovative medicines for the treatment of neurological and urological disorders since 1999. SCHWARZ PHARMA’s research and development teams are grouped together under SCHWARZ BIOSCIENCES with sites in Monheim/Germany, Shannon/Ireland, Research Triangle Park, North Carolina/USA, and Tokyo/Japan. SCHWARZ BIOSCIENCES employs more than 650 experts who are focused on searching for new active ingredients internationally and intercontinentally and are responsible for managing the international partnerships, advancing preclinical, pharmaceutical, and clinical drug development, and submitting marketing applications.

Since 1999, SCHWARZ PHARMA has been making closer to achieving its objective of marketing new and innovative medicines from its own development pipeline. Research and development costs have more than doubled since 1999: from €91.5 million to a record high of €258 million in the past fiscal year.

In 2005, SCHWARZ PHARMA conducted 35 international clinical trials involving a total of 11,624 patients and had six advanced projects in clinical development, for treating

- Parkinson’s disease (two projects),
- neuropathic pain,
- epilepsy,
- restless legs syndrome (RLS), and
- overactive bladder syndrome.
In December 2005, our first neurology drug, the Parkinson’s patch rotigotine (Neupro®), for the treatment of the signs and symptoms of early-stage idiopathic Parkinson’s disease as monotherapy (i.e. without levodopa) received a positive opinion from the European marketing approval authority. We received marketing approval for the European market in the first quarter of this year. This means the new drug can now be marketed throughout all 25 member states of the European Union.

Almost 4 million patients worldwide suffer from Parkinson’s disease, with approximately 400,000 new cases being added each year. Parkinson’s disease particularly occurs in older age and is characterized by a diverse range of symptoms. Typical symptoms are, for example, a shaking of the extremities (tremor), a slowing down of all movements (bradykinesis) – typical here is a shuffling gait, an increasingly small size of writing, or a seemingly emotion-
less face due to reduced facial expression –, sudden immobility (freezing), and stiffness (rigor). This progressively worsening (chronic-progressive), degenerative disease is one of the most frequently occurring disorders of the nervous system. So far Parkinson’s disease has proved to be incurable. Hence the most important therapeutic aspect is to gain the best possible control of the symptoms with as few side-effects as possible. Modern therapies are usually based on the concept of dopaminergic stimulation; dopamine is a neurotransmitter in the brain which is responsible for coordinating movements. The worldwide market for Parkinson’s drugs has a volume of some US$2.5 billion and has an annual growth rate of around 6%, last but not least due to demographic effects.

Neupro®, the first Parkinson’s patch, combines the benefits of the non-ergoline dopamine agonist rotigotine with a transdermal patch formulation. A transdermal delivery system has many benefits compared to other formulations: firstly, it is non-invasive, and secondly it provides the benefit of continuous receptor stimulation over a 24-hour delivery period. In addition, absorption via the skin circumvents effects of gastrointestinal activity on absorption. A patch can also be used in the case of patients who suffer from clouding of consciousness (absence) within the course of the disease or in cases of poor compliance. It is also well-suited to treating patients with swallowing problems, which is a frequently occurring secondary symptom.

The efficacy, safety, and tolerability of the Parkinson’s patch (Neupro®) has been evaluated in several international clinical trials with a total of 1,500 patients suffering from early Parkinson’s disease. In these clinical trials involving once-a-day administration, Neupro® showed a 24-hour drug delivery and continuous plasma levels over the same period.

The results of phase III clinical trials with Neupro® in patients with advanced stages of Parkinson’s disease using combined therapy with levodopa have shown that the patch is also suited to being used in combined therapy with the drug levodopa for treating patients with advanced stages of Parkinson’s disease. In particular, an improvement in so-called “on” time (without troublesome dyskinesia) was observed. By developing a nasal spray formulation, SCHWARZ PHARMA seeks to provide an additional rotigotine delivery system. The tolerability and safety of the nasal-spray formulation will be evaluated in patients with advanced Parkinson’s disease. These trials will also assess if acute application of the spray leads to an improvement in motor function during “off” episodes. Phase II clinical trials on this formulation began at the start of this year. Results are expected in the first quarter of 2006.
Restless Legs Syndrome (RLS): phase III ongoing

Restless Legs Syndrome is a frequently occurring disorder which has not yet received sufficient attention. It is characterized by an unpleasant urge to move one’s legs, predominantly in the evening and during the night, so preventing a restful sleep. RLS is a chronic disease which occurs about as frequently as migraine or diabetes. Up to 10% of the population suffers from this disease, with women being affected more frequently than men. It is presumed to be caused by a metabolic disorder of the nervous system. Dopamine agonists are considered an effective treatment possibility. The world market for RLS has a current volume of US$500 million, with an expected growth rate of over 25% per year.

The results of phase II trials with rotigotine in patients suffering from mild to severe RLS show a clinically relevant and statistically significant improvement of symptoms. Patients reported of an improved quality of life and a restful sleep. The most common adverse events were nausea, skin reactions and headaches. SCHWARZ PHARMA has been testing the transdermal patch with the active ingredient rotigotine in the final phase of clinical development, phase III, since May 2005. Around 1,000 patients are being treated for six months each within the scope of this international trial program, with first results expected in the first quarter of 2007.

Treatment of Morbus Parkinson with a Patch

![Graph showing plasma concentration over time with patch and oral dosage points](image-url)
Epilepsy: A “new generation” anti-convulsant in development

Epilepsy is the umbrella term given to an entire group of hereditable, trauma-related, or organically related diseases. An abnormal increase in activity in the central nervous system produces so-called epileptic seizures, manifest as a dysfunction of the sensory system, motor functions, emotional state, or objective behavior. Around 0.5 to 1.0% of the population suffer from epilepsy. Anti-epileptic drugs serve to prevent epileptic fits and are usually administered as a permanent therapy. The world market for anti-epileptic drugs amounts to over US$11 billion and has an annual growth rate of 4%.

Lacosamide exhibits an unknown mechanism of action and is a modern anti-convulsant or anti-epileptic drug. SCHWARZ PHARMA has successfully completed the phase II trials program for lacosamide studied as a combination therapy for treating epilepsy. The results of these trials showed a significant and clinically relevant reduction in the number of epileptic seizures. The most common adverse events were dizziness, headache, nausea and fatigue. International phase III clinical trials already began in May 2004, with first results expected in the second quarter of 2006. In addition to the oral, twice-a-day therapy, SCHWARZ PHARMA has also developed an intravenous formulation which is particularly suited to emergencies and times when a tablet cannot be taken. Here the clinical trials program is nearing completion.
Diabetic neuropathic pain:  
A second project for lacosamide

Neuropathic pain is caused by a functional disorder of the central or peripheral nervous system. In contrast to “normal” pain, neuropathic pain does not serve any warning function but occurs without being acutely related to a pathological event. Approximately eleven million diabetics suffer from the consequences of diabetic neuropathic pain. For a long time there was no approved therapy for treating this kind of pain. Doctors and patients therefore frequently use anti-epileptic drugs to alleviate such pain. The market for this area of treatment is estimated at around US$3 billion. Experts expect a market growth rate of 12% p.a.

The results of phase II clinical trials with lacosamide for treating chronic pain caused by diabetic neuropathy have shown a significant reduction of pain symptoms combined with good tolerability. The first results of two clinical trials within the ongoing phase III program also verify a significant reduction of neuropathic. A trial conducted in the USA showed a statistically significant improvement compared with placebo as regards the primary variable, measured at the beginning and end of the trial. A second trial conducted in Europe also showed a distinct improvement in symptoms, though a statistically significant improvement compared with placebo was not shown for the primary variables. As well as reducing neuropathic pain, both trials showed an improvement of numerous other symptoms (e.g. sleep, everyday activity). The results of both trials showed a good tolerability of lacosamide with the most common adverse events being dizziness, nausea, headache and fatigue. Of patients who completed the trials, 90% decided to continue treatment with lacosamide in an open-label follow-on trial. A further placebo-controlled phase III trial is expected to report results in the second quarter of 2006.
Overactive bladder syndrome/urgent urinary incontinence: marketing application submissions for fesoterodine underway

Overactive bladder syndrome/urgent urinary incontinence is the inability to control the release of urine from the bladder. The main symptoms of overactive bladder syndrome are urinary frequency and uncontrollable urgency, which may be accompanied by involuntary leakage of urine and wetting. Approximately 10% of the population over the age of 40, for the most part women, suffer from this disease. Due to continual voiding of the bladder, uncontrollable urgency, and particularly wetting, patients often also face social isolation. These symptoms are usually treated using anti-muscarinic agents, to which the compound fesoterodine, newly developed by SCHWARZ PHARMA, belongs. The market volume of this area of treatment amounts to approximately US$2 billion. However, due to demographic developments, an annual growth rate of 12% is expected.

In 2005, SCHWARZ PHARMA successfully completed the final stage, phase III, of its international clinical program. The results show a clinically relevant and statistically significant improvement of symptoms. This is particularly true of the symptom which is perceived by patients to be the worst handicap – uncontrollable urgency accompanied by wetting. In keeping with the improvement of symptoms, patients gave distinctly positive evaluations of the successfulness of treatment using a “treatment-benefits scale”. Adverse events were as expected for anti-muscarinic agents with the most common event being dry mouth. Of patients who completed the trials, over 90% of the patients decided to continue treatment with fesoterodine in an open-label follow-on trial. Approximately 1,900 patients were included in this double-blind, placebo-controlled trial program conducted in the USA and Europe to show efficacy, tolerability, and safety of fesoterodine. We submitted the required marketing applications at the end of the first quarter of 2006.
Researching now for the next decade

Thanks to its current development pipeline, SCHWARZ PHARMA is very well positioned. With one product – Neupro® – about to go to market in Europe, another undergoing marketing review procedures, and a total of three projects in the final phase of clinical development, SCHWARZ PHARMA has sufficient potential to generate significant growth in the next few years. To continue to enable growth in the more distant future, we have already expanded our search for new active ingredients in the early stages of drug development. In particular, we wish to identify further areas of treatment concerning the central nervous system with a high medical demand for rotigotine and lacosamide. We shall initiate corresponding tests in 2006.

SCHWARZ PHARMA pursues all promising avenues to find new active ingredients. Not only within our own organization, at SCHWARZ BIOSCIENCES, but outside the company too. Part of the way we see ourselves is defined by our continued pursuit of research and development in cooperation with other players, such as companies or universities. Such a bundling of skills, instruments, and resources, and especially highly qualified personnel, gives all those working within such networks a much improved prospect of success.

This is something we quite deliberately exploit. Whether we support professorial chairs or laboratories, or conduct joint trials with companies covering similar key areas of treatment, our duty as a researching pharmaceutical company is to enter into cooperations which serve the advancement of knowledge. No matter if, having developed a marketable medicinal product at the end of the pipeline, we find ourselves facing competition as a commercial enterprise.