

13 September 2006

# Restless Legs Syndrome

Pan European Equity  
Germany  
Life Sciences  
Pharmaceuticals

**SUBSTANTIALLY UNDER-TREATED MARKET PROVIDES MASSIVE GROWTH OPPORTUNITIES**

## The future looks bright

High patient prevalence and improved diagnosis and treatment rates may make Restless Legs Syndrome (RLS) an important revenue source for key players and new joiners. We estimate that the market value of RLS treatments will increase from c.\$350m (2006E) to about \$1.7bn by 2015E mainly driven by increased diagnosis and treatment rates. We see GSK and Schwarz Pharma as key potential stock market listed beneficiaries.

- **The disease.** RLS is a movement disorder of neurological origin characterized by an irresistible urge to move one's legs and uncomfortable sensations in the legs. About 9% of the American population are thought to be affected and c. 6-7% in Europe.
- **Market forecasts.** On the basis of our expectation of increased diagnosis and treatment rates as well as our pricing assumptions, we forecast that the total number of RLS patients treated may increase from 380k to 2.2m by 2015E, driving the total market value from around \$350m to about \$1.7bn in 2015E.
- **GSK's ropinirole – likely to remain a growth driver for the company.** Requip was launched many years ago for Parkinson's disease treatment, but with its new Restless Leg Syndrome indication, for which it obtained FDA approval in May 2005, the drug is currently among the fastest-growing drugs in the portfolio. Our unchanged estimates assume that sales of Requip will grow from £156m in 2005 to £534m by 2010 or at a CAGR of 15% 2005-10E (includes both indications – PD and RLS). We retain our Add recommendation and price target of £17 for the stock.
- **We see Rotigotine in RLS as an important drug for Schwarz Pharma,** and this is reflected in our €410m peak sales forecast which represents c. 20% of total pipeline peak sales. Our expectations are substantially ahead of company guidance (€300m peak sales), and we have decided to move our probability of launch from 75% to 90% based on strong Phase IIb data released so far and in expectation of similarly strong Phase III data (due Q4 2006). Hence, we have raised our NPV for the project from €8 to €11/share and price target from €76 to €79. We upgrade to Add from Hold.

### GSK: Add; price 1479p, target 1700p

in %	1m	3m	12m
Absolute	1.9	-0.7	8.4
Relative	1.2	-6.6	-0.3
12 month price range	1577.00p – 1354.00p		
Net cash/share YE	13.7p		
NAV/share YE	129.3p		
No. shares in issue	5718.0m		
Free float	100%		
Market cap	£84,569m		
Next event	Q3 results		
Reuters code	GSK.L		
Bloomberg code	GLXO LN		
DJSTOXX	329.41		

### Schwarz Pharma: Add; price €70.2; target €79

in %	1m	3m	12m
Absolute	0.4	6.0	56.8
Relative	-1.1	0.1	39.2
12 month price range	€81.78 - €45.00		
Net cash/share YE	€3.6		
NAV/share YE	€11.2		
No. shares in issue	47.0m		
Free float	40%		
Market cap	€3,298m		
Next event	Q3 Results		
Reuters code	SRZG.F		
Bloomberg code	SRZ GR		
DJSTOXX	329.41		

Unless otherwise stated, share prices are as of market close on 11 September 2006.

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# The potential for RLS treatments

**Restless Legs Syndrome, a substantially under-diagnosed and under-treated movement disorder, is currently the subject of major research efforts which could yield several new drug approvals by the end of the decade. High patient prevalence and improved diagnosis and treatment rates may make RLS an important revenue source for key players and new joiners. We estimate that the market value of RLS treatments will increase from around \$350m (2006E) to about \$1.7bn by 2015E. Amongst others, GSK (ropinirole) and Schwarz Pharma (rotigotine) could be set to benefit, in our view.**

## **Diagnosis and treatment**

A recently published RLS epidemiology study found that only 75% of RLS patients who discussed their symptoms with their primary care practitioner actually received a diagnosis and only 6.2% of patients have been finally diagnosed with RLS. The low rate of diagnosis given to those demonstrating RLS symptoms reflects the current lack of understanding of the disorder in our view. However, newly approved RLS-specific treatments (ropinirole, GSK), anticipated new approvals in the next few years associated with awareness campaigns directed towards doctors and patients are likely to support increased diagnosis and treatment rates.

## **New treatments to come**

Apart from GSK's ropinirole (approved in US/EU) and Böhringer Ingelheim's pramipexole (RLS approved in the EU), we expect a number of new treatments to reach the market by the end of the decade. The most advanced R&D candidates include Schwarz Pharma's rotigotine, Axxonis' Lisuride and XP13512 from Xenoport (all in Phase III trials). Moreover, we have detected an additional six molecules in Phase II clinical testing.

## **Market forecasts**

On the basis of our expectation of increased diagnosis and treatment rates and our pricing assumptions, we forecast that the total number of RLS patients treated may increase from 380k to 2.2m by 2015E, driving the total market value from around \$350m to about \$1.7bn in 2015E.

## **Dopamine agonist likely to become dominant treatment class**

Based on the excellent efficacy and solid safety profiles, we believe dopamine agonists are likely to become the treatment of choice for RLS. We expect ropinirole to remain market leader (25% market share: 2015E) followed by pramipexole (23%) and rotigotine (20%), and that lisuride (14%) is likely to capture a substantial market share.

# Restless Legs Syndrome

## The disease – defining Restless Legs Syndrome

RLS is a movement disorder of neurological origin characterized by an irresistible urge to move one's legs and by uncomfortable, often very unpleasant sensations in the legs, sometimes described as creeping-crawling, burning or twitching.

Most common medical condition nobody has ever heard about

The symptoms typically occur in the evening and may disrupt normal sleep, with rebound effects on alertness the following day. A worsening or exclusive presence of symptoms at rest (lying, sitting) with at least partial and temporary relief by activity is common. Although RLS isn't life threatening, it can be life altering. RLS has been described as "the most common medical condition nobody has ever heard about".

### Specific symptoms reported by Restless Legs syndrome sufferers

Category	Reporting symptoms in %	Reporting symptoms as most troublesome in %
Sensory	88.0	45.7
Sleep	75.5	37.8
Disturbance of daytime functioning	55.5	6.9
Abnormal movements	37.0	3.4
Mood	26.2	2.9

Source REST General Population Study, American Medical Association, June 2005

## Genetics of RLS

Strong evidence for genetic contribution

There is strong evidence for a genetic contribution to RLS. Studies have shown familial aggregation of RLS with c. 50-60% of the patients reporting at least one first degree relative affected with this condition. Several studies found a bimodal distribution of age of onset. Only early-onset patients (< 30 years) revealed a genetic component. Early-onset RLS has recently been found to be genetically different from secondary RLS (onset after age of 30). A study by Allen and Earley found that subjects with RLS symptoms starting before the age of 45 had a greater probability of having a first degree relative affected by RLS than those with late onset of symptoms.

## Prevalence and different types of RLS

### Prevalence

The US has the highest prevalence rates

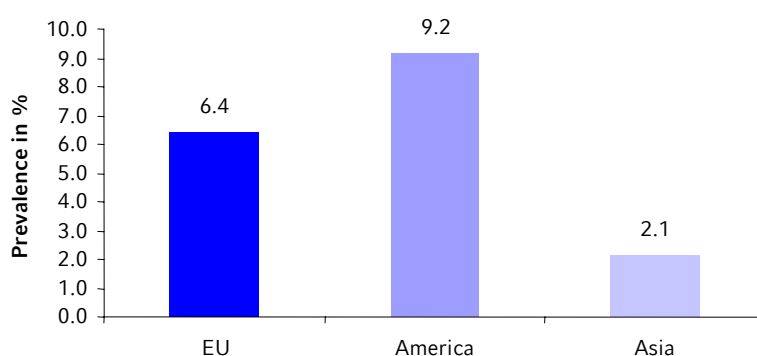
Epidemiological studies have demonstrated a prevalence of c. 10% (or 66.6 million people), according to a study reported in the September 2004 edition of Neurology, the scientific journal of the American Academy of Neurology. Overall literature shows a total of 18 epidemiology studies which on an accumulated basis indicate that the highest prevalence occurs in the US with around 9% of the general population affected and around 6-7% in Europe, whereas prevalence rates in Asia tend to be very modest (2%). The same studies also indicate that prevalence amongst females is about twice as high as in males.

### Prevalence rates of RLS in the general population and primary care

Year	Country	No.	Prevalence (%)	Year	Country	No.	Prevalence (%)
2005	USA, France	15,391	7.20	2001	China	1,157	0.17
2005	France	10,263	8.50	2001	Chile	100	13.00
2004	USA, EUM4	23,052	9.60	2000	Switzerland	668	4.00
2004	Germany	4,310	10.60	2000	Japan	1,000	1.00
2004	UK	3,877	0.25	2000	Germany	738	9.78
2004	Netherlands	1,485	7.10	2000	USA	1,803	10.00
2003	USA	2,099	15.30	1994	Canada	2,019	12.50
2003	Turkey	3,234	3.19	1994	Ireland	100	7.00
2002	EUM5	18,980	5.50	1993	Ireland	307	5.00
2001	Sweden	200	11.00				

Source Epidemiology of Restless Legs Syndrome: The current status, Garcia-Borreguero et al. sleep medicine review

### Prevalence rates of RLS in the general population



Source Epidemiology of Restless Legs Syndrome: The current status, Garcia-Borreguero et al. sleep medicine review 10, 2006, WestLB Research

## Different types of RLS

Clinically Restless Legs Syndrome is divided in two major subforms, the primary or idiopathic form of RLS (most prevalent) and secondary or symptomatic form:

- 1) Primary or idiopathic RLS (60-80% of all RLS) – is defined as cryptogenic, indicating that in most cases the aetiology and pathogenesis are uncertain, but leaving open the possibility of finding the exact origin and mechanisms
- 2) Secondary or symptomatic RLS – some conditions that may cause it include end-stage renal disease, iron deficiency (with or without anaemia), the neuropathies and radiculopathies, rheumatoid arthritis, the myelopathies, syringomyelia, Parkinson's disease, and pregnancy

## Clinically relevant RLS

As regards the severity of RLS, it can be differentiated as a mild disease, which implies that relevant patients suffer from associated symptoms less than twice a week. This group represents the vast majority of RLS sufferers with about 60-65% of all patients diagnosed as having a mild version of the disease. According to epidemiology studies mentioned earlier, those patients who suffer from moderate to severe RLS (symptoms more frequent than two times a week) account for around 35-40% of those diagnosed, which is the patient population targeted by drug companies as these patients may benefit from drug-based intervention.

Drug companies target patients with moderate to severe RLS

## Prevalence of RLS symptoms by country and degree of severity

Country	Questionnaires Distributed	Fully Completed Questionnaires	RLS Symptoms, No. (%) Any Frequency		≥ Once/wk		≥ Twice/wk		≥ Twice/wk and of Moderate or Extreme Distress		
	No.	No.	%	No.	%	No.	%	No.	%	No.	%
France	2,010	1,884	93.7	203	10.8	125	6.6	103	5.5%	79	4.2
Germany	2,040	1,929	94.6	79	4.1	53	2.7	38	2.0%	25	1.3
Italy	2,036	1,768	86.8	119	6.7	74	4.2	55	3.1%	43	2.4
Spain	2,020	1,896	93.9	92	4.9	66	3.5	58	3.1%	37	2.0
UK	2,082	1,950	93.7	167	8.6	109	5.6	95	4.9%	45	2.3
US	6,014	5,964	99.2	454	7.6	346	5.8	289	4.8%	187	3.1
Total	16,202	15,391	95.0	1,114	7.2	773	5.0	638	4.1%	416	2.7
EUM5	10,188	9,427	92.5	660	7.0	427	4.5	349	3.7%	229	2.4

Source Epidemiology of Restless Legs Syndrome: The current status, Garcia-Borreguero et al. sleep medicine review

## RLS – patient model

More than 50m people worldwide suffer from RLS

Based on key disease prevalence and distribution data we believe more than 50m people suffer from the disease in the US and Europe. We estimate that those characterised as suffering from moderate to severe RLS amount to about 16m, implying a four times higher patient number than Parkinson's disease. However, as misdiagnosis is common and many patients do not seek medical attention, there is no final evidence that indicates the prevalence of patients with moderate to severe RLS.

Epidemiology data gathered in the past 13 years does not strictly indicate an increase of prevalence over time. We note however that disease prevalence increases with age, so that some effect, though small, can be assumed from general demographic trends. Hence, our model assumes an annual prevalence growth rate of a modest 1% p.a.

### RLS patient model

Year	2005	2006E	2007E	2008E	2009E	2010E
<b>US patient model</b>						
Disease prevalence ('000)	26,680	26,947	27,216	27,488	27,763	28,041
Primary RLS ('000)	21,344	21,557	21,773	21,991	22,211	22,433
Prevalence of patients with moderate to severe disease ('000)	8,751	8,839	8,927	9,016	9,106	9,197
<b>EU patient model</b>						
Disease prevalence ('000)	25,600	25,856	26,115	26,376	26,639	26,906
Primary RLS ('000)	20,480	20,685	20,892	21,101	21,312	21,525
Prevalence of patients with moderate to severe disease ('000)	7,168	7,240	7,312	7,385	7,459	7,534
<b>US/EU primary moderate to severe RLS patient population ('000)</b>	<b>15,919</b>	<b>16,078</b>	<b>16,239</b>	<b>16,401</b>	<b>16,565</b>	<b>16,731</b>

Source WestLB Research

## Measurement of disease activity – diagnosis and clinical endpoints

Given that the Restless Legs Syndrome is mainly a subjective disease, the major evaluation in practice uses subjective rating scales to determine disorder incidence and its severity. Moreover, instrumental tools are available to confirm the diagnosis.

### Diagnosis

#### Clinical features

Main symptom is the urge to move the legs

The diagnosis of RLS has been undergoing a gradual evolution, but remains anchored in a 'gold standard' of an expert clinical interview. The most recent standards emphasize the

presence of one main symptom – the urge to move – and three key modulators: rest, activity, and time of day. Beyond establishing these key features, the major diagnostic challenge is to eliminate mimics. Objective tests can be helpful in doubtful cases, but have not become accepted as diagnostic criteria. For a diagnosis of RLS, all four of the diagnostic features must be present (see table).

## Diagnostic features overview

### Key diagnostic features

An urge to move one's legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs

The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting

The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching

The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night

### Supportive clinical features\*

Positive family history

Presence of periodic limb movements (during wakefulness or sleep)

Positive response to dopaminergic therapy

\*These features are not necessary for a diagnosis of RLS to be made; in doubtful cases, they may make it more plausible to consider the diagnosis

*Source Subjective and objective criteria in the diagnosis of the restless legs syndrome, Hening, Wayne, Department of Neurology, Johnson Medical School, New Brunswick, NJ, USA, Oct 2003*

## Diagnosis instruments

A key subjective instrument for RLS diagnosis is the international RLS rating scale, which has recently been validated in an international multi-centre study and has also been used in most of the latest large clinical trials to assess the severity of symptoms. Other questionnaires used include Clinical Global Impression-Improvement (CGI-I) scale, PLMI (Periodic Limb Movement Index – mostly used in DRF-trials) and quality of life assessments (specific to RLS or general). More recently, a clinical trial has been started using a newly developed rating scale for augmentation.

**The IRLS rating scale** consists of a total of 10 questions, and each has to be assigned a score of between 0 (no impact of disease) to 4 (very severe impact), yielding a maximum score of 40. The essential questions are shown below:

1. Desire to move one's limbs associated with paresthesia/dysesthesia
2. Motor restlessness and relief with movement
3. Worsening or exclusive presence of symptoms at rest (lying, sitting) with at least partial and temporary relief by activity
4. Symptoms worsening during the evening/night (circadian patterns)

**Clinical Global Impression scale** – The CGI scale is a clinical-rated instrument that consists of four subscales. The CGI-Improvement is traditionally used as an endpoint in clinical trials for responder analyses (much improved and very much improved patients considered as responders) while the other subscales are less used. The global assessment of the overall severity of illness, the overall therapeutic effect and interference of side

effects with functioning, provides additional information of the overall effectiveness of a drug treatment.

## Diagnosis rates – theory and reality

Lack of understanding of the disorder results in a very low diagnosis rate

One of the most recent RLS epidemiology studies, the REST trial (General Population Study, American Medical Association, June 2005) found that only 75% of RLS patients who discussed their symptoms with their primary care practitioner actually received a diagnosis and that only 6.2% of patients have been diagnosed with RLS. The low rate of diagnosis given to those presenting with RLS symptoms reflects the current lack of understanding of the disorder in our view.

### RLS diagnosis rates (REST study)

	PCP* Consultation rates (among 416 RLS patients)		Any diagnosis for symptoms (among 337 patients, who discussed their symptoms with a PCP)		Received diagnosis of RLS	
	No.	% (n=416)	No.	%	No.	%
within past year	255	61.3%	193	75.7%		
> 1 year ago	82	19.7%	59	72.0%		
<b>Total</b>	<b>337</b>	<b>81.0%</b>	<b>252</b>	<b>74.8%</b>	<b>21</b>	<b>6.2%</b>

Most common diagnosis: poor circulation (18.3%), arthritis (14.3%), back/spinal injury (12.7%), varicose veins (7.5%), depression/anxiety (6.3%), trapped nerve (5.6%)

\* primary care physicians

Source REST General Population Study, American Medical Association, June 2005

## Additional diagnosis tools

Diagnosis of RLS is based on clinical criteria, but some instrumental tools are useful to confirm the diagnosis and sometimes may be of help in differential diagnosis or in doubtful cases. As misdiagnosis is common and many patients do not seek medical attention, there is no clear evidence showing the prevalence of patients diagnosed with moderate to severe RLS.

**Polysomnography (PSG)** – enables the recording of PLMS (Periodic Limb Movement while Sleeping) and periodic/non-periodic leg movements during wakefulness before or after sleep onset

**Suggested Immobilization Test (SIT)** – a new tool to evaluate the effect of immobility on sensory and motor symptoms during a 60-minute period while the subject sits on the bed with legs outstretched and eyes open

**Single Photon Emission Tomography (SPECT) / Positron Emission Tomography (PET) / Magnetic Resonance Imaging (MRI)** – to assess both brain dopaminergic function and topographic functional imaging during sensory symptoms and PLM in RLS

## Clinical endpoints

The primary endpoint of clinical studies today is mainly based on an assessment and analysis of a patient questionnaire. The most widely used questionnaire (IRLS-questionnaire) was established by the International Restless Legs Syndrome Study Group back in 1995. Other questionnaires used include the Clinical Global Impression-Improvement (CGI-I) scale, PLMI and quality of life assessment.

Approvals so far based on 12 weeks trials, now also longer term studies running

The most used primary endpoints for regulatory purposes are IRLS score reductions at the end of the studies and CGI (both endpoints have been used in trials supporting approval of ropinirole and pramipexole in RLS). We note that whereas registrational trials for both ropinirole and pramipexole were looking at a 12-week treatment duration, Phase III trials currently running for other molecules also include longer-term treatment duration.

## Current standard treatments

There are a number of drugs used in clinical practice but at this point the only medicines labelled for the treatment of RLS are GSK's Requip (ropinirole) and Böhringer Ingelheim's Mirapex/Sifrol (pramipexole – only approved for RLS in Europe) as well as Restex/Madopar (carbidopa/benserazide) approved in certain European countries. The following drug categories however are frequently used:

### Dopaminergic agents (DAs)

Dopamine agonists – control the symptoms of RLS

Dopaminergic agents are typically used for the treatment of Parkinson's disease. The hypothesis for the use of dopaminergic agents for the treatment of RLS is based on two elements: 1) SPECT and PET scans indicate that the disease is associated with low dopamine levels in the body, an issue that is tackled by dopamine agonists; 2) there is sufficient evidence in the form of clinical trial results that show that dopamine agonists can control the symptoms of RLS.

Also indicated for the treatment of RLS are Requip (US/EU) and Mirapex/Sifrol (EU), but carbidopa/levodopa combinations and pergolide (1 generation DA) and cabergoline are commonly used.

### Levodopa – limited use in RLS

Levodopa – considered as 2<sup>nd</sup> line treatment in RLS

Levodopa, a substance widely used for the treatment of Parkinson's disease, is metabolised by the body to dopamine and thus also has a positive effect on RLS. However, as a high degree of patients (up to 82%) experience disease augmentation, levodopa and its combination with other agents can be considered as a second-line treatment for RLS.

### Sedatives

Sedatives – treatment of anxiety and ahyponia

Most sedatives act as mild depressants of the central nervous system, lessening general nervous activity or reducing the irritability or activity of a specific organ. Sedative drugs have their primary indication in the treatment of anxiety and ahyponia. Hence, they tend to be effective for improving the sleep of RLS patients.

### Anticonvulsants/Pain relievers

Anticonvulsants – play a minor role for the treatment of RLS

Anticonvulsants are particularly effective for some patients with painful daytime RLS symptoms, whereas pain relievers are used when RLS is severe and relentless. However, both categories tend to play a minor role for the treatment of RLS and are mainly used for the treatment of relapsed patients.

### Iron therapy

It has been found in some clinical trials that RLS is often associated with iron deficiencies and that intravenous administration of iron has a positive impact on RLS. Hence, iron

therapy could represent a low-cost alternative for the treatment of RLS but clinical work needs to be done to establish efficacy and side effects in an accurate manner.

## Data-tracking difficult – but trends are visible

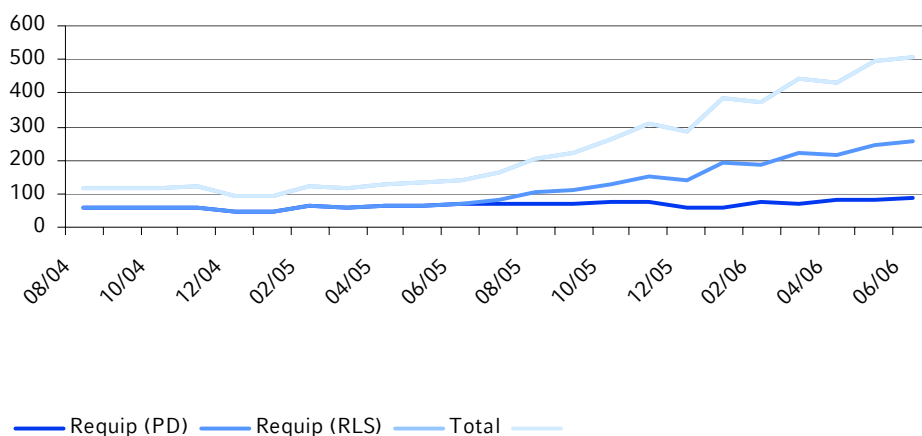
As stated before, in the US GSK's Requip is currently the only approved drug for the treatment of RLS. As Requip is already on the market for the treatment of Parkinson's disease and given that most other drugs used in this indication find their primary label in indications elsewhere, data tracking from IMS regarding prescription trends appears to be rather difficult.

Requip – the only approved drug for the treatment of RLS in the US

However, we have analysed US prescription data of Requip, which was granted approval in October 1997 for the treatment of PD and in May 2005 was also labelled for RLS treatment. Most recently, TRx have been growing by more than 200% yoy.

We have analysed the data by looking at prescription growth prior to any release of clinical data or awareness campaign. At that time, Requip was growing at a rate of around 25% yoy and we have assumed excess growth to be solely attributable to RLS. On this basis, we believe that at present about twice as many patients have Requip prescribed for RLS than for PD. Some evidence can be found when tracking quarterly sales per prescription, which have trended downwards for at least the past four quarters, as the monthly treatment cost for RLS is substantially lower than for PD due to lower dosage.

### Requip TRx IMS data



Source IMS Health, WestLB Research

### Ropinirole life-cycle management

The US base patent is set to expire in December 2007 and GSK has exclusivity in RLS until May 2008. However, GSK is currently in Phase III clinical trials for an extended release version of ropinirole and a filing in US/EU is expected by end-2006, potentially making it possible to switch a decent number of patients from the immediate release version.

Whereas both versions are administered once-daily, we believe the XR-formulation could have the advantage of a lower rebound risk for patients, given the relatively short half-life of the molecule.

It appears that GSK is currently running a total of at least three Phase III trials looking at the efficacy and safety of Requip XR vs. Requip and switching regimens. As no clinical data is yet available on the XR-version, the new formulation is not discussed in the following section.

## Global RLS R&D pipeline

[There are only three drugs approved for the treatment of RLS worldwide](#)

As stated earlier, there are currently only three drugs approved for the treatment of RLS, Requip (ropinirole, GSK) in the US and Europe and Mirapex/Sifrol (pramipexole, BI) in Europe and Restex/Madopar, approved in certain European countries. Our pipeline overview (see table) shows that there are a number of drugs in late stage clinical trials which are expected to reach the market in two years from now. We have found a total of four molecules in Phase III clinical trials/registration and six in Phase II. We have excluded Topamax (topiramate) from our table as the drug was investigated in a Phase IV trial with data due in 2005, but no evidence could be found about a filing in this indication.

### Global RLS R&D pipeline

Drug	Mechanism of action	Company	Status	Expected Launch	Comment
Ropinirole XR	Dopamine agonist (oral)	GSK	Phase III	2007/8	Extended release formulation
Pramipexole	Dopamine agonist (oral)	Böhringer Ingelheim	in registration	2006	Approved in Europe since April 2006, filed in the US
Rotigotine	Dopamine agonist (patch)	Schwarz Pharma	Phase III	2008/9	First Phase III trial to report in Q4 2006
Lisuride	Dopamine agonist (patch)	Axxonis	Phase III	2008	First data expected H1 2007, Europe only
XP13512	Gabapentin prodrug	XenoPort	Phase III	2009/10	Phase III trials enrolment start March 2006, NDA expected for H2 2008
KW-6002 (Istradefylline)	adenosine A2A receptor antagonist	Kyowa	Phase II	2010/11	US Phase IIa RLS trials started July 2005; data disclosure October 2006; NDA filing for PD expected for H2 2006
Safinamide	multiple mechanisms	Newron	Phase II	2010/11	Phase IIa completed in January 2005
SEP-226330	NE + DA reuptake inhibitor	Sepracor	Phase II	2010/11	Not mentioned in recent pipeline presentation
Radafaxine (353162)	NE/DA reuptake inhibitor; Bupropion metabolite	GSK	Phase II	2010/11	
Dorsiflex (mephenoxalone)	Muscle relaxant; Anti-spasmodic	Will-Pharma	Phase II	2010/11	
Keppra (Levetiracetam)	Antiepileptic	UCB	Phase II	2010/11	Last follow-up in Oct 2005

Source WestLB Research

We discuss available clinical data in depth for all Phase III compounds in the following section. The limited data released on those projects currently in Phase II are as follows:

[KW-6002 – an adenosine A2A receptor antagonist in Phase II clinical trials](#)

**KW-6002** – Kyowa's Istradefylline (KW-6002) is an adenosine A2A receptor antagonist currently in Phase II clinical trials. A2A receptors are localized on several neurons and are thought to modulate the neurotransmission of gamma-aminobutyric acid (GABA), thereby supporting control of motor behaviour. However, no clinical data has been published according to our knowledge, but a Phase II trial registered under clinicaltrials.gov with 160 RLS patients is set to complete in November 2006, with data hopefully available by end-2006.

Safinamide – remarkable performance combined with excellent tolerability

**Safinamide** – Newron’s safinamide is a drug with several different modes of action as it inhibits the uptake of dopamine as well as monoamine oxidase (MAO) B combined with potent sodium (Na+) channel blocking activity and calcium (Ca2+) channel modulation. Data from a small pilot study (n=10) in severe RLS patients showed a substantial reduction of the IRLS score by 10 points after two weeks, a remarkable performance in our view combined with excellent tolerability according to the company. We believe that safinamide could reach the market by 2010/11. Any assessment about the drug’s potential in the RLS is impossible in our view as there is limited data available at this stage.

Levetiracetam – likely no further efforts to get approval for RLS treatment

**Levetiracetam** – Keppra is UCB’s market leading anti-epileptic drug and is under investigation for the treatment of RLS. A small Phase II study (n=20) started in 2003 with the last follow-up in October 2005. No data has been released post the finalisation of the study and we believe that UCB is unlikely to try and obtain approval for Keppra for RLS.

## Clinical data analysis and product profiling

Meaningful clinical data is available for analysis from a number of Phase III and Phase IIb trials. We have taken these trials in order to compare the efficacy and safety of the relevant marketed RLS treatments and those drugs which are in late-stage clinical testing. Of course, the comparison of different clinical trails leads to some limitations and accurate comparison may only be possible on the basis of head-to-head trials, which have not yet been revealed.

### Efficacy analysis

In order to assess the performance of currently marketed treatments and late stage clinical compounds, we have analysed IRLS-rating scale improvement as reported in individual clinical studies as well as CGI data. Quality of life data have not been reported for all trials analysed.

#### Above 50% relative improvement achieved by all drugs

The summary of the clinical efficacy of the drugs mentioned below mainly stems from Phase III trials (ropinirole, pramipexole) and from Phase IIb studies (rotigotine, lisuride). All drugs showed a more than 50% reduction of IRLS scores relative to baseline, indicating strong efficacy which in all trials compared favourably with placebo, which showed a range of improvement in all trials of 27-45% (average 35%) vs. baseline and 6.1-9.8 in absolute improvement.

All drugs showed strong efficacy

#### RLS drug efficacy overview (IRLS score reduction)

Drug	No. of trials	Treatment duration (weeks)	Average baseline score	Average improvement	Relative improvement (%)	Range av. improvement	Range rel. improvement
Ropinirole	4	12-52	22.9	12.0	52.5	10.9-13.5	45-61
Pramipexole	2	3-12	23.1	14.2	62	11.9-17.0	53-73
Rotigotine	1	6	27.9	15.8	57	14.9-17.3	53-62
Lisuride	1	12	28.8	17.3	60	14.7-18.9	51-66

Source Abstracts, WestLB Research

#### Pramipexole appears to be the strongest, but...

Pramipexole seems to be the strongest, but low evidence

Boehringer Ingelheim’s pramipexole appears to be the strongest dopamine agonist when looking at relative IRLS improvements of 62% on average on our data analysis. However, we note that there were only two trials available for assessment, one of which had a very

short duration of only three weeks. Nonetheless, looking at the pramipexole 12-week Phase III trial it appears that with a relative improvement of 58%, or 13.5-point IRLS-score reduction, the drug shows a similar efficacy to ropinirole. The European authorities approved the drug based on four Phase III trials (total of approx. 1000 patients) observing a 60% IRLS improvement vs. 40% for placebo. CGI responder rates (very much improved or much improved) of 51% (placebo) and 72% (pramipexole) were also statistically significant.

### **DA patches with competitive edge**

The potential new joiners of the RLS market also seem to have a competitive efficacy profile. The essential feature of DA patches is that they deliver constant dopaminergic stimulation and therefore are hoped to have better therapeutic coverage. However, rotigotine from Schwarz Pharma (non-ergoline D2/D3 dopamine agonist patch), has shown significant IRLS-score improvements of 57% vs. baseline, with the 15cm<sup>2</sup> patch (-62%) appearing to be the most reasonable dose (Phase IIb range 5-20cm<sup>2</sup>). The first Phase III data is expected in Q4 2006 and will be interesting as the trial is designed for a 24-week treatment duration, compared to 6 weeks in the Phase IIb trial. We currently expect the drug to be filed by end-2007.

Lisuride, the second dopamine agonist patch (iso-ergoline), has also reported very robust Phase IIb data with an improvement vs. baseline of 60%. Axxonis has reformulated the molecule which has already been on the market for several years as an oral formulation for the treatment of Parkinson's disease. The company is set to reveal Phase III results in H1 2007, potentially allowing for a launch in Europe by end-2008.

### **DAs – duration of action potentially key differentiation criteria**

One of the issues when taking DAs is the coverage duration determined by the half life of a drug. In this context, ropinirole is considered to have a relatively short elimination half life of around 6 hours while pramipexole is eliminated by the body in 8-12 hours. This, however, implies that symptoms may only be suppressed for a limited period of time and rebound could occur late at night or early in the morning.

Both DA patches seem to have the benefit of providing better coverage as the patch systems release the active ingredient over at least 24 hours. Hence, these products may be particularly suitable for those patients who suffer regular rebound to oral DAs. Moreover, due to permanent drug release, early onset of action may be a feature which is not significant for patches.

### **XP13512 – too early to judge**

Phase IIa data of the gabapentin prodrug XP13512 from XenoPort was presented recently at SLEEP 2006. The data on 34 evaluated patients showed XP13512 significantly improved the IRLS score at the end of two weeks (change from baseline = -12.1 vs. -1.9), investigator CGI, the number of awakenings per night due to RLS symptoms and the number of hours awake per night due to RLS symptoms (all p<0.0001). XP13512 was generally well tolerated without serious adverse events recorded. The most common side effects were somnolence and dizziness.

Potential new RLS drug  
rotigotine expected to be  
filed by end-2007

Phase IIb data presented showed that XP13512 led to a 16.1-point reduction (1200 mg) of the IRLS scale over two weeks compared to an 8.9-point reduction of placebo. CGI data suggests responder rates of 81% compared to 48% of patients on placebo.

Whereas we regard the first Phase II data as promising, we believe the database is not sufficient to accurately assess the future profile of the drug. Phase III trials began in March 2006 involving more than 700 patients, and XenoPort is targeting an NDA filing in H2 2008, potentially allowing the drug to reach the market in 2010.

### **Responder rates**

Responder rates are typically measured on the basis of the CGI scale and patients who are considered as responders are those who have much improved or very much improved. Reported data show that 53-60% of patients on ropinirole have responded to treatment, while data for pramipexole seem to be in a similar range at 63%. Again, competitive edge could be proven for the DA patches, with responder rates of 74-81% and 59-80% respectively reported for rotigotine and lisuride in their Phase IIb data. (We note that both pramipexole and rotigotine data came from 6-week trials, whereas the remainder came from 12-week studies.)

### **Conclusion: head-to-head on efficacy of dopamine agonists**

Overall we conclude that both oral DAs and the next products to enter the market – DA patches – appear to have a similar efficacy profile based on the clinical data available. Unlike Parkinson's disease, we believe that the patch formulations do not represent a substantial USP as RLS patients do not tend to take as many pills as PD sufferers. Dosages used in RLS tend to be about 50% of the maximum doses used in PD.

### **Safety profiles**

All dopamine agonists mentioned appear to have excellent tolerability, which is generally visible in discontinuation rates similar to placebo. However, specific issues relating to individual drugs are outlined below:

**Pramipexole** – Most commonly reported adverse events (>5%) in RLS trials include nausea, headache and fatigue. Uncommonly reported but included in the label is the occurrence of excessive daytime somnolence and sudden sleep onset periods, which may relate to the long half-life of the drug. Disease augmentation (tendency of symptoms to develop earlier in the day) has been observed in approx. 33% of patients treated, but has been generally treatable with higher doses earlier in the day.

**Ropinirole** – The EMEA review on the filing of Adartrel (ropinirole trade name in Europe) noted the most common adverse drug reaction was nausea (approx. 30% of patients) and vomiting. Also common were nervousness, somnolence and dizziness. In addition, a few events of hallucinations were reported in longer-term trials as well as disease augmentation. As with pramipexole, the label includes a warning about sudden sleep attacks. The impact on the degree of disease augmentation has not been established yet.

**Rotigotine** – The most common adverse events reported in the Phase IIb trial (incidence >5%) were, as expected, application site reactions due to the patch system (occurred in 17.5% of patients in the Phase IIb trial (all active dosages) and in 16% and 20% of patients on the 10cm<sup>2</sup> and 15cm<sup>2</sup> patches respectively). However, only three patients

(1% of those on active treatment) discontinued. Other side effects included nausea, fatigue, influenza-like symptoms, and headache.

**Lisuride** – During the clinical studies with Lisuride TDS, local and reversible skin reactions have been detected which were graded in general as mild and well tolerated. A higher rate of skin reactions seen in a first dose-finding study mainly due to more frequent re-exposition could not be confirmed in a large double-blind trial (n=335), where 28.2% of the patients showed skin reactions, which is in a range known from other transdermal systems.

## Conclusion

Overall, we believe that side effects of oral DAs vs. DA patches tend to be relatively similar. While we see a small advantage for the patches in that they seem not to be associated with sudden daytime sleep attacks and provide sustained drug release (potentially positive impact on rebound), patients on patches have to cope with application site reactions. Unlike with Parkinson's disease, we believe this may be a marginal disadvantage as RLS patients have a tendency to take much less medication than PD sufferers. The impact of patches on disease augmentation has not been investigated yet, but may be unlikely given the constant dopamine delivery of these systems.

## RLS market forecast

### Patients

As outlined earlier, we believe that around 42m people in Europe and the US suffer from primary RLS and approx. 16m from its moderate to severe form. Our model does not include Asia/Japan given the very modest prevalence in this area. We assume that only about 38.5% of patients are currently diagnosed and that this rate will increase to about 50% by 2015E due to awareness programmes initiated by the industry that focus on patients and doctors. As a result, we expect the number of patients diagnosed to increase from 6m to about 8.8m by 2015, yielding an annual growth rate of around 4% (CAGR).

### Treatment rates forecast

As already stated, RLS is very much an under-treated disease. Treatment rates are expected to increase substantially, again driven by awareness campaigns and a greater arsenal of drugs potentially available in the medium term. Hence, we have assumed that treatment rates (as a percentage of diagnosed patients) will move up from around 6% currently to c. 26% by 2015E, implying an annual patient growth rate of around 22%. On that basis, we forecast that around 2.2m patients will be treated at the end of our forecast period compared to around 380k currently (2006E).

### Pricing considerations

Given that dosing in RLS tends to be substantially lower than for Parkinson's disease and looking at the pricing of ropinirole in the US (due to lower dosing), we believe that daily treatment costs may be around \$2-\$2.5 per day compared to more than \$5 for PD.

A different scenario however applies to Europe, where pricing in key countries tends to be higher than the US – which is visible in the PD setting. Interestingly, even though GSK has launched a dual brand strategy in Europe where ropinirole's trade name is Adartrel,

Due to campaigns by the industry the diagnosis rate will increase to about 50% by 2015E

Due to a greater arsenal of drugs the low treatment rates will move up fast

The price level in Europe tends to be higher compared to the US

according to Gelbe Liste data it has chosen a similar pricing per mg to the PD-brand Requip. Overall, however, pricing in Europe varies substantially, from around €2.5 per day to around €5 per day. We believe that rotigotine is most likely to achieve the latter price.

### **Assumed annual treatment costs**

Generally, the cost per daily dose for Requip/Adartrel in RLS would result in annual treatment costs of about €600-€720 per patient. However, for model purposes, we have assumed that patients will only stay on drug therapy for around nine months a year as good disease control is likely to result in a certain irregularity of medication use.

### **Market value**

On the basis of our earlier-mentioned patient, treatment and pricing assumptions, we estimate that the global market for RLS treatments is currently worth around \$350m and will grow to about \$1.7bn in 2015E. However, in reality the value of this market may be impacted by generic competition for ropinirole and pramipexole.

### **Market share forecasts**

Regarding market share distribution, we estimate that the four dopamine agonists mentioned in this report will dominate the RLS market in the next decade and will replace those drugs which are currently used but not specifically trialled and labelled for this indication.

Given the relatively similar clinical profiles of the newer dopamine agonists we assume that time to market may be a critical issue. Hence, we forecast that ropinirole, the first approved drug for this indication, will gain the greatest market share of 25% (2015E), followed by pramipexole (23%) and rotigotine (20%), whereas we estimate that lisuride may capture a 14% market due to prejudice about it belonging to the ergot-family of DAs. We note that our forecasts assume that both DA patches will be partnered with large cap pharma companies in order to gain sufficient marketing power to access GPs.

Estimated market value of \$1.7bn in 2015

Due to the first-mover advantage ropinirole will be the market leader

## Global RLS patient & treatment model

Year	2006E	2007E	2008E	2009E	2010E	2011E	2012E	2013E	2014E	2015E
Disease prevalence ('000)	52,803	53,331	53,864	54,403	54,947	55,496	56,051	56,612	57,178	57,750
Primary RLS ('000)	42,242	42,665	43,091	43,522	43,957	44,397	44,841	45,289	45,742	46,200
Prevalence of patients with moderate to severe disease ('000)	16,078	16,239	16,401	16,565	16,731	16,898	17,067	17,238	17,410	17,585
As % of total population	2.3	2.4	2.4	2.4	2.4	2.4	2.5	2.5	2.5	2.5
Patients diagnosed with moderate to severe RLS	6,190	6,496	6,889	7,289	7,529	7,773	8,022	8,274	8,531	8,792
as % of prevalence mod. to severe	38.5	40.0	42.0	44.0	45.0	46.0	47.0	48.0	49.0	50.0
<b>Patients treated ('000)</b>	<b>383.8</b>	<b>454.7</b>	<b>620.0</b>	<b>947.5</b>	<b>1,204.6</b>	<b>1,399.2</b>	<b>1,604.3</b>	<b>1,820.3</b>	<b>2,047.5</b>	<b>2,286.0</b>
as % of patients diagnosed	6.2	7.0	9.0	13.0	16.0	18.0	20.0	22.0	24.0	26.0
<b>Patients &amp; sales per treatment</b>										
Patients treated with Restex	115	105	130	171	193	210	225	228	225	229
Share of total patients (%)	30	23	21	18	16	15	14	13	11	10
Patients treated with pramipexole	19	50	93	171	161	336	394	429	462	515
Share of total patients (%)	5	11	15	18	13	24	25	24	23	23
Patients treated with ropinirole	68	105	158	260	325	371	410	455	503	561
Share of total patients (%)	18	23	25	27	27	27	26	25	25	25
Patients treated with rotigotine	0	5	23	72	135	205	266	328	398	457
Share of total patients (%)	0	1	4	8	11	15	17	18	19	20
Patients treated with lisuride	0	0	0	4	28	81	150	207	264	318
Share of total patients (%)	0	0	0	0	2	6	9	11	13	14
Patients treated with other drugs (incl. RLS pipeline)	181	191	216	270	270	196	160	174	196	206
Share of total patients (%)	47	42	35	28	22	14	10	10	10	9

Source WestLB Research estimates

# GSK

## Add recommendation; target price £17

Although Requip was launched many years ago for Parkinson's disease treatment, with its new Restless Leg Syndrome indication, for which it obtained an FDA approval in May 2005, the drug is currently among the fastest growing drugs in the portfolio. We estimate sales of Requip will grow from £156m in 2005 to £534m by 2010 or at a CAGR of 15% 2005-10E (includes both indications – PD and RLS).

### Threats

For many years it has been known that dopamine agonists such as Requip are able to treat Restless Leg Syndrome successfully, a condition not well diagnosed or treated, but Requip was the first to obtain the marketing approval and start to develop this completely new market. In Europe, under the name Adartrel, the drug obtained a positive recommendation from the CHMP in April 2006 but is still awaiting final approval. Requip is also expected to be launched in Japan towards the end of the year. The key threat to the drug's progression is the patent expiry in the US in December 2007 with several generics already filed.

To counter the generic effect, GSK is currently developing two extended release formulations. For Parkinson's disease, Requip XL was developed in collaboration with SkyePharma and the drug was filed in Europe at the end of last year – it is due for filing in the US this year. For Requip in restless leg syndrome, the company will have product exclusivity until May 2008 in the US, and another extended release formulation – different from the one used for the Parkinson's product – is currently in Phase III trials but also due for filing in the US by the end of this year.

Requip was approved in Europe in 2000 for Parkinson's disease, carrying a 10-year exclusivity, while in the RLS indication (under the different name Adartrel) further protection should be available until 2016 assuming the drug gets final approval later this year. Our model assumes a successful switch to the extended release formulations in both markets. GSK may also try to block the generic by using the Citizen Petition route which has been employed successfully by many companies in the neurology area including Biovail for Wellbutrin XL.

### Valuation and investment case

We regard GSK as currently among the cheapest in the large cap European pharma sector, trading at around 18% discount to its peers based on our 2007 PE valuation, as the generic threat intensified this year with Wellbutrin XL now vulnerable and the expected loss of Zofran in December 2006. On a five-year basis, GSK's EPS CAGR 2005-10 that we forecast at 9.7%, is slightly below the sector's expected 10.8%. On the positive side, GSK has one of the most promising industry pipelines, with four product launches executed so far this year and three more expected by the end of the year. The company also advanced eight new products in Phase III trials, providing significant pipeline momentum, in our view. We believe that the current share price indicates a significant buying opportunity.

We regard GSK as among the cheapest in the large cap European pharma sector

**Forthcoming newsflow**

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<b>Date</b>	<b>Event</b>
Q3 2006	Tykerb filing in the US
Q4 2006	Eltrombopag Phase III and possible filing
Jun 2006	Trexima (Imitrex/naproxen combination) approval and launch
Sep 2006	Retapamulin (Altabax) PDUFA date
Oct 2006	Altabax PDUFA date
End 2006	Avandia outcome trials results (DREAM trial)
Nov 2006	Entereg PDUFA date
Q4 2006	R&D day
Q4 2006	Trexima refiling with FDA
Dec 2006	Zofran off-patent

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Source WestLB Research estimates

# Schwarz Pharma

## Upgrade to Add; price target €79 (€76)

We expect Rotigotine in RLS to be an important drug for Schwarz Pharma, and our €410m peak sales forecast represents about 20% of total pipeline peak sales. Our expectations are substantially ahead of company guidance (€300m peak sales) and we have decided to move our probability of launch from 75% to 90% on the basis of strong data released so far and in expectation of similarly strong Phase III data (due Q4 2006). Hence, we have raised our NPV for the project from €8 to €11 per share and our price target from €76 to €79 per share.

### Phase III data to be seen in Q4 2006

Headline data from the first Phase III trial are expected to be released in Q4 2006. On the basis of what we regard as very strong Phase IIb data (from both the six-week DRF-trial and the open label extension), we remain very optimistic about the outcome of the Phase III studies. Even though it is not clear whether the Phase IIb study is pivotal, a second Phase III trial is set to report results in Q1 2007, potentially allowing for a filing by end-2007 in US/EU.

### Excellent pricing supports our forecasts

The pricing in Germany and UK for the use of the drug in PD in our view already determines the pricing in RLS. We have assumed that a price of €5 per 15cm<sup>2</sup> patch can be realised in Europe and tend to be cautious with regards to the US, where our assumption stands at \$2.5 per patch. Based on our estimate that about 228k patients may be treated with rotigotine (20% market share), we arrive at peak sales of €410m (€390m previously).

### Strong clinical data base allows for model adjustment

Given the relatively strong clinical database of rotigotine in RLS (six-week Phase IIb with 340 patients + 12-month open label extension) we have opted to increase our assumed probability for success from 75% to 90% in expectation of strong Phase III data, leading to an upgrade of our rotigotine RLS NPV from €8 to €11 per share.

### Partner required

In order to have sufficient reach for the marketing of the RLS patch to general practitioners, who are expected to be the main prescribers for patients suffering from RLS, Schwarz Pharma will need to have a strong marketing partner. We believe that the maximum value may be retained in the company with a deal occurring after acceptance of filing (very end-2007/early-2008) and before approval (early-2009).

### Investment thesis and valuation

On the back of our increasingly optimistic stance regarding rotigotine in RLS and the associated change to project NPV, we see now sufficient upside potential to allow for an upgrade from Hold to Add. Our positive fundamental view may be confirmed by substantial newsflow mainly expected for Q4 and later in 2007. Moreover, we believe that a potential delay of lacosamide for its neuropathic pain indication is now reflected in the

We are increasingly optimistic about rotigotine in RLS and this has led to our upgrade from Hold to Add

share price. Our price target of €79 is based on our pipeline NPV of €55 per share, €18 per share for the base business and €4 net cash. We have not reflected in our model the prospect of a timely launch of generic pantoprazole, which carries a potential NPV of €3 per share according to our model.

### Rotigotine RLS sales forecast (€m)

Year	2006E	2007E*	2008E	2009E	2010E	2011E	2012E	2013E	2014E	2015E
Patients treated in the US ('000)	0	5	17	47	86	123	150	180	214	251
Cost per patient/year (\$)	675	675	675	675	675	675	675	675	675	675
US RLS sales (\$m)	0	3	12	32	58	83	101	122	144	170
US RLS sales (€m)	0	3	9	25	45	65	79	95	113	133
Patients treated in Europe ('000)	0	0	6	26	49	82	116	148	184	206
Cost per patient/year (€)	1350	1350	1350	1350	1350	1350	1350	1350	1350	1350
European RLS sales (€m)	0	0	8	35	66	111	156	199	249	278
<b>Total rotigotine RLS sales (€m)</b>	<b>0</b>	<b>3</b>	<b>17</b>	<b>59</b>	<b>111</b>	<b>175</b>	<b>235</b>	<b>294</b>	<b>362</b>	<b>410</b>

\* assumes first off-label use in the US

Source WestLB Research estimates

### Forthcoming newsflow

Date	Event
Q4 2006	Update on filing strategy (lacosamide)
27 October	Q3 results
Q4 2006	Second Phase III trial of lacosamide on epilepsy
Q4 2006	Rotigotine Nasal Phase II data
Q4 2006	First Phase III results of rotigotine in RLS
Q4 2006	Lacosamide/rotigotine fibromyalgie Phase II initiation
Q1 2007	Second Phase II trial of rotigotine in RLS
H1 2007	Approval and launch of Neupro in the US (early PD)
H2 2007	Filing lacosamide in epilepsy*
End-2007	Approval of fesoterodine
End-2007	Filing of rotigotine for the treatment of RLS
2007	Fourth Phase III trial to report results of lacosamide in DNP
2007	Lacosamide partnering
2008	Rotigotine RLS partnering

\*Assumes the company decides against an early Phase IIb + Phase III filing

Source WestLB Research estimates

### Schwarz Pharma R&D pipeline

Compound	Mechanism	Indication	Current status	Expected launch	Current WLB probability	WLB
Lacosamide	AED	Neuropathic pain	Phase III	2009	75%	13.2
		Epilepsy	Phase III	2008/9	100%	4.5
Neupro	dopamine agonist	Parkinson's disease	Appr. EU/ filed US/	2006/7	100%	13.7
		RLS	Phase III	2008/9	90%	11.0
Fesoterodine	anti-muscarinic	OAB	filed	2007	100%	12.4
<b>Total</b>						<b>54.8</b>

Source WestLB Research estimates

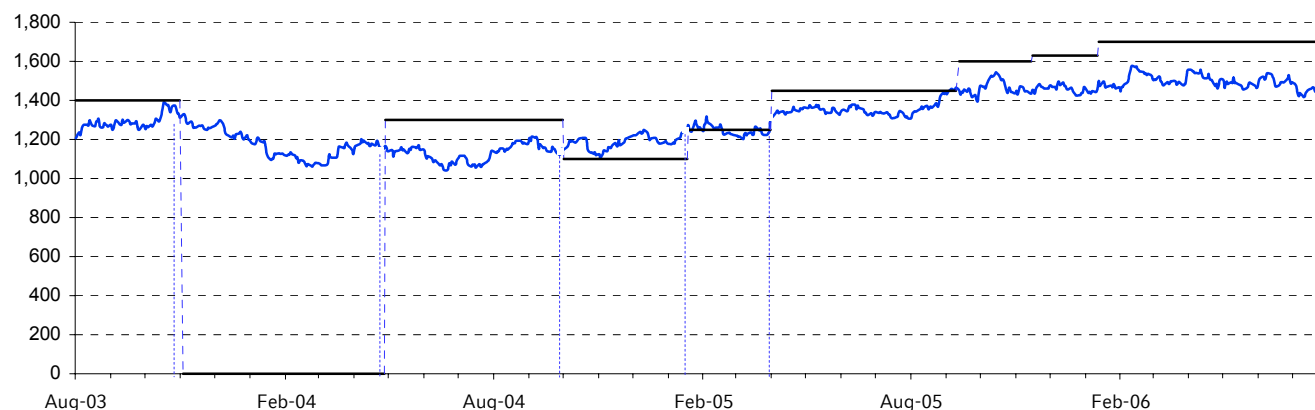
### Schwarz Pharma SOTP model

	Value (€m)	Value per share (€)	Share (%)	Metrix
Base business + bridge products	873	18.4	23	1.1x 2006 sales
Omeprazole + Teva damages	96	2.0	3	NPV
R&D pipeline	2594	54.8	69	NPV
Net cash (debt)	177	3.7	5	2006E
<b>Total</b>	<b>3740</b>	<b>79.0</b>	<b>100</b>	

Source WestLB Research estimates



## GlaxoSmithKline GSK.L



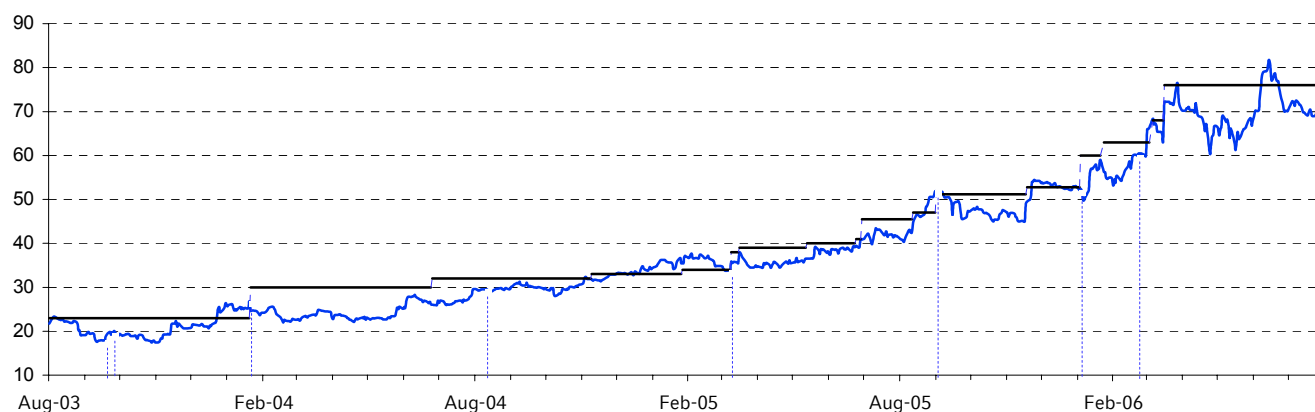
Date	Price	Changed to...	Date	Price	Changed to...	Date	Price	Changed to...
29-Apr-05	1312.00	Add	29-Oct-04	1147.00	Reduce	30-Nov-03	1311.00	No Rating
15-Feb-05	1273.00	Hold	26-May-04	1168.00	Add			

**Coverage History** Rating at 29/08/2003 was Add

Source FactSet/JCF, WestLB Research

Coverage dropped end November 2003

## Schwarz Pharma SRZG.F



Date	Price	Changed to...	Date	Price	Changed to...	Date	Price	Changed to...
22-Mar-06	60.51	Hold	06-Apr-05	35.79	Add	24-Oct-03	20.02	Hold
31-Jan-06	52.40	Add	08-Sep-04	29.50	Hold	17-Oct-03	19.00	Add
29-Sep-05	51.30	Hold	18-Feb-04	24.58	Add			

**Coverage History** Rating at 29/08/2003 was Hold

Source FactSet/JCF, WestLB Research

Reinitiation of coverage with new analyst on 27 July 2001. No coverage 11 Sep 00 to 27 Jul 01.

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Coverage universe	Count	Percent	Inv. Banking Relationships*	Count	Percent
Buy/Add	166	59	Buy/Add	47	72
Hold	88	31	Hold	13	20
Sell/Reduce	27	10	Sell/Reduce	5	8

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**Valuation and Risk assessment; Recommendations.**

Unless otherwise stated in the text of this report, target prices in this report are based on either a discounted cash flow valuation or comparison of valuation ratios with companies seen by the analyst as comparable or a combination of the two methods. The result of this fundamental valuation is adjusted to reflect the analyst's views on the likely course of investor sentiment.

Whichever valuation method is used there is a significant risk that the target price will not be achieved within the expected timeframe. Risk factors include unforeseen changes in competitive pressures or in the level of demand for the company's products. Such demand variations may result from changes in technology, in the overall level of economic activity or, in some cases, in fashion. Valuations may also be affected by changes in taxation, in exchange rates and, in certain industries, in regulations. Investment in overseas markets and instruments such as ADRs can result in increased risk from factors such as exchange rates, exchange controls, taxation, political and social conditions. This discussion of valuation methods and risk factors is not comprehensive – further information is available if required.

Stock ratings are based on the analyst's expectation of the stock's total return during the twelve months following assignment of the rating. This view is based on the target price, set as described above, and on the analyst's opinions on general market and economic developments.

Within that overall framework, a Buy rating means that the total return from the stock is expected to exceed 20%; Add means between 10% and 20%, Hold means movement between 0% and a positive 10%, Reduce means between 0% and minus 10%; Sell means the stock is expected to return less than minus 10%.

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