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Press Release

Four studies published in *The Lancet* show roflumilast (Daxas[®]), a new oral approach to COPD, improves lung function and reduces exacerbations

- Once-a-day tablet Daxas[®] (roflumilast) is a first-in-class treatment under development targeting inflammation, the underlying cause of chronic obstructive pulmonary disease (COPD)

Nycomed and Forest Laboratories today announced that results of four phase III trials have been published in the prestigious peer-reviewed medical journal *The Lancet* showing that roflumilast, a phosphodiesterase 4 (PDE4) inhibitor, improved lung function and reduced exacerbations in patients with moderate to severe COPD.

COPD is an under-diagnosed progressive lung disease that may lead to death. Worldwide, COPD kills four people every minute and the World Health Organization (WHO) predicts that it will be the third leading cause of death by 2030. WHO estimates that 80 million people have moderate to severe COPD.

Roflumilast, a once-a-day oral tablet, would be the first in an entirely new class of treatment for COPD if it receives regulatory approval from the authorities in Europe (EMA) and the US (FDA). The phase III placebo-controlled trials of roflumilast evaluated the treatment in two 12-month (*Lancet* 2009; 374: 685–694) and two six-month studies (*Lancet* 2009; 374: 695–703), involving 4,500 patients in ten countries. Details of the results of the four studies will be published in *The Lancet* on August 29.

The two 12-month studies published in *The Lancet* demonstrated that roflumilast produced a statistically significant and clinically relevant reduction in exacerbations (lung attacks that need treatment with systemic steroids or lead to hospitalisation), even for patients who were also taking long-acting bronchodilators. The studies showed a reduction in moderate to severe exacerbations by 17 percent per patient per year (rate of 1.14 events per year with roflumilast vs. 1.37 per year with placebo, $p < 0.001$). The reduction in exacerbations was irrespective of concomitant treatment with long-acting beta-2 agonists, a standard bronchodilator therapy.

When added to standard bronchodilator therapies in the two six-month studies, a clear trend for the reduction of exacerbations was observed with roflumilast, over and above what was achieved with these therapies alone. There was also a statistically significant difference with roflumilast in other prespecified endpoints, including median time to first exacerbation (moderate to severe in the salmeterol study, and mild, moderate and severe in the tiotropium study) and in the proportion of patients in both studies experiencing a mild, moderate, or severe exacerbation.

Lung function, as measured by FEV₁ (how much volume can be exhaled in one second), was the primary or co-primary endpoint in all four studies. Across the studies, roflumilast demonstrated a statistically significant improvement in pre-bronchodilator FEV₁, in the range of 48 to 80 mL (p<0.001).

Nausea, diarrhoea and weight loss were the most common adverse events recorded in patients in the four trials, but they were generally mild to moderate in intensity and generally occurred in the first weeks of treatment.

Professor Peter Calverley, Professor of Respiratory Medicine, University of Liverpool, UK, and the lead author of the 12-month studies, said: "COPD can devastate people's lives and exacerbations can be extremely frightening, so a novel tablet like roflumilast is really exciting for those of us treating patients. Roflumilast acts differently to bronchodilators as it acts on the underlying condition, not primarily impacting on everyday symptoms. It acts slowly and the effects, as we saw in our studies, are gradual and sustained."

"Roflumilast could be an important new treatment for COPD," added Professor Fernando Martinez, University of Michigan, also a lead author of the 12-month studies. "We clearly need new options for patients with COPD and the results of these studies, published in *The Lancet*, confirm that roflumilast is beneficial. It reduced exacerbations, or lung attacks, and significantly improved lung function, in a patient population whose lung function is very poor."

Professor Leonardo Fabbri, Professor of Respiratory Medicine, University of Modena and Reggio Emilia, Italy, and lead author of the six-month studies, said: "Roflumilast has a novel mode of action and has the potential to become the first of a new class of drugs and potentially the only completely new treatment option for COPD in the next several years. These eagerly awaited results, published this week in *The Lancet*, show that in addition to confirming the sustained statistically significant improvements in lung function, roflumilast also showed a trend to reducing exacerbations when given in addition to long acting inhaled bronchodilators. The results of the two six-months trials examining the additive effect of roflumilast on top of salmeterol or tiotropium support and extend the findings of the 12-month trials, by showing a clinically relevant lung function improvement in patients with impaired lung function on top of maximum bronchodilation."

"The lung function improvements on top of current bronchodilation clearly indicates that roflumilast improves lung function over and above what can be achieved with other COPD treatments alone. It also demonstrates that roflumilast works in a different way to current treatments and supports roflumilast's potential to change how COPD is managed," added Professor Klaus Rabe, Professor of Medicine at Leiden University Medical Center, also a lead author of the six-month studies.

Nycomed's Executive Vice President R&D, Anders Ullman, said: "We are very pleased with the results published in *The Lancet* this week. In four studies, two 12-month studies and two six-month studies, roflumilast showed clear therapeutic potential, decreasing exacerbations and improving lung function. The uniformity of the results is really encouraging and gives us great hope that our faith in roflumilast has been confirmed. We are now undergoing the regulatory review process with the European and US authorities."

"Based on the results from the pivotal studies published this week, it appears that roflumilast provides added activity on top of other commonly used treatments for COPD," said Lawrence S. Olanoff, President and Chief Operating Officer of Forest Laboratories. "Roflumilast represents the first in a new class of agents to treat COPD and, if approved, would be the first oral anti-inflammatory maintenance treatment for the disease."

About Roflumilast (Daxas[®])

Roflumilast is an orally administered phosphodiesterase 4 (PDE4) enzyme inhibitor targeting cells and mediators in the body believed to be important in the COPD disease process. Roflumilast is expected to act on the underlying mechanism of COPD and related inflammatory diseases. If approved, roflumilast, a once-a-day oral tablet, will be the first in an entirely new class of treatment for COPD. It will also be the first oral anti-inflammatory treatment for COPD patients. Current treatment for COPD patients includes the use of inhaled bronchodilators and inhaled corticosteroids.

About COPD

COPD is an under-diagnosed progressive lung disease that may lead to death. Worldwide, COPD kills four people every minute and the World Health Organization (WHO) predicts that it will be the third leading cause of death by 2030. WHO estimates that 80 million people have moderate to severe COPD.

Symptoms of COPD include breathlessness, chronic cough and excessive production of phlegm. A significant worsening of symptoms called an exacerbation or lung attack can last several weeks. Breathing becomes severely compromised and patients may need to be admitted to hospital. Exacerbations are frightening events resulting in increased patient anxiety, worsening health status, lung function decline and increased risk of death.

Smoking is a major contributory factor in western countries, and pollution from fires for cooking and heating is an additional contributory factor in less developed countries. Industrial and chemical pollutants can also cause COPD.

Chronic inflammation in the lungs plays a significant role in COPD. Current medications used to treat the condition deal mainly with symptoms rather than the underlying disease. Roflumilast is a new PDE4 inhibitor being developed specifically to target the chronic inflammation which is COPD-related.

About Nycomed

Nycomed is a privately owned global pharmaceutical company with a differentiated portfolio focused on branded medicines in gastroenterology, respiratory and inflammatory diseases, pain, osteoporosis and tissue management. An extensive range of OTC products completes the portfolio.

Its R&D is structured around partnerships and in-licensing is a cornerstone of the company's growth strategy.

Nycomed employs 12,000 associates worldwide, and its products are available in more than 100 countries. It has strong platforms in Europe and in fast-growing markets such as Russia/CIS and Latin America. While the US and Japan are commercialised through best-in-class partners, Nycomed plans to further strengthen its own position in key Asian markets.

Headquartered in Zurich, Switzerland, the company generated total sales of €3.4 billion in 2008 and an adjusted EBITDA of €1.2 billion.

For more information visit www.nycomed.com

About Forest Laboratories

Forest Laboratories (NYSE: FRX) is a U.S.-based pharmaceutical company with a long track record of building partnerships and developing and marketing products that make a positive difference in people's lives. In addition to its well-established franchises in therapeutic areas of the central nervous and cardiovascular systems, Forest's current pipeline includes product candidates in all stages of development and across a wide range of therapeutic areas. The company is headquartered in New York, NY. To learn more about Forest Laboratories, visit www.FRX.com.

Except for the historical information contained herein, this release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements involve a number of risks and uncertainties, including the difficulty of predicting FDA approvals, the acceptance and demand for new pharmaceutical products, the impact of competitive products and pricing, the timely development and launch of new products, and the risk factors listed from time to time in Forest Laboratories' Annual Report on Form 10-K, Quarterly Report on Form 10-Q, and any subsequent SEC filings.

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Notes to editors

Further details for the four trials will be presented at the European Respiratory Society Annual Congress 2009, in Vienna, Austria, September 12 to 16, 2009.

12-Month Trials

The two replicate, 12-month trials were randomised, placebo controlled and double blind. One 12 month study was conducted in 246 centres in 10 countries and the second was conducted in 221 centres in eight countries.

COPD patients were over 40, and either former or current smokers with a smoking history of at least 20 pack-years. The patients had symptoms of chronic cough and sputum, their post-bronchodilator FEV₁ was ≤ 50% of the predicted value and they had at least one documented moderate to severe exacerbation in the previous year. Approximately 50% of the patients were concomitantly using long acting beta agonists.

Patients were permitted to use short-acting bronchodilators to relieve their symptoms as needed.

Compared with placebo, roflumilast significantly reduced the rate of exacerbations and improved lung function in treated patients. The rate of moderate to severe exacerbations in the study period (pooled data) was 1.14 per year in the patients treated with roflumilast compared with 1.37 per year, in the placebo group. This represents an improvement of 17 per cent (RR 0.83; CI 0.75-0.92, p<0.001).

The pooled data for lung function using the pre-bronchodilator FEV₁ measurement (forced expiratory volume in one second) showed an average increase of 48mL (p<0.001) in roflumilast treated patients compared with the placebo group. The improvement in post-bronchodilator FEV₁ was 55mL (p<0.001) with roflumilast.

The differences found in exacerbation rates and lung function were similar irrespective of whether roflumilast was used with or without a long-acting beta-agonist.

Using another measurement, FVC (forced vital capacity, the lung capacity measured when the patient is exhaling for as hard and as long as possible) roflumilast patients also scored higher with an average increased FVC of 98 mL (p<0.001) compared with the placebo group. These patients had not used a bronchodilator prior to testing. The improvement in post-bronchodilator FVC was 101 mL (p<0.001).

Roflumilast was well tolerated by most patients. Slightly more patients discontinued the trial in the roflumilast group than those taking placebo (14 percent vs 11 percent). Diarrhoea, nausea and headache were the commonest reasons for discontinuation. A reduction in weight, around 2kg, was seen consistently across all the studies published in The Lancet. When patients stopped taking roflumilast the majority regained weight. In addition, in the 12-month studies, only four patients out of 1,547 dropped out because of weight loss.

Six-month trials

In the six-month trial patients used roflumilast or a placebo in conjunction with commonly used long acting bronchodilators (inhalers).

In one trial, patients used salmeterol with roflumilast or placebo. In the second trial, patients used tiotropium, a long-acting bronchodilator which also reduces the production of mucus, with roflumilast or placebo. Patients used "rescue medication" short-acting bronchodilators, as needed.

There were 933 patients in the salmeterol trial and 743 patients in the tiotropium trial. Overall patients had moderate to severe COPD; were over 40, current or former smokers with a history of smoking at least a pack a day for 10 years. In contrast to the 12-month trials, patients in the six-months trials did not require a history of exacerbations. Patients recruited to the tiotropium study were more symptomatic than those in the salmeterol study as they were required to have daily chronic cough and sputum production and a documented use of rescue medication.

Patients were seen and measured once a month for the first three months and every six weeks for the last three months of the trial.

Compared with placebo, patients taking roflumilast in addition to salmeterol, had an average increased pre-bronchodilator FEV₁ (forced expiratory volume in one second) of 49mL (p<0.001).

Compared with placebo, patients taking roflumilast in addition to tiotropium had an average increased pre-bronchodilator FEV₁ of 80mL (p<0.001).

There was a similar FEV₁ advantage in both trials when measurements were taken after using a short-acting bronchodilator, an increase of 60mL (p<0.001) in the salmeterol study and 81mL (p<0.001) in the tiotropium study.

Roflumilast was well tolerated by most patients. Slightly more patients discontinued the trials in the roflumilast group than those taking placebo (13 percent vs 8 percent). Diarrhoea, nausea and headache were the most commonly reported adverse events.