

News Release

New single dose study shows: Generic extended release nifedipine not bioequivalent to Adalat[®] XL[®]

- Total exposure to generic nearly 20 per cent lower when taken after meal
-

Toronto, February 3, 2010 – An extended release generic nifedipine product (Mylan-Nifedipine extended release 60 mg formerly Gen-Nifedipine extended release 60mg, Genpharm ULC) is not bioequivalent to the Canadian originator product, Adalat[®] XL^{®1}, according to the results of a study recently published in the International Journal of Clinical Pharmacology and Therapeutics.² Based on the study results from in vitro and in vivo tests, the generic extended release nifedipine product has a delayed onset of drug release compared to the originator which is especially noticeable in the fed state. When the tablet is taken after a standard high fat meal, the total exposure to the generic nifedipine is almost 20 per cent lower than with Adalat[®] XL[®].

“With drugs like nifedipine, we see a close relationship between plasma concentration and efficacy. A change in bioavailability could impact blood pressure,” said principal investigator Dr. Frank Donath from SocraTec R&D, Oberursel, Germany. “Since it is widely accepted that small reductions in blood pressure can reduce long-term mortality, these findings may be relevant to physicians treating hypertensive patients.”

The single centre, open-label, randomized phase I study was carried out with 26 healthy male subjects. Using a 4-period crossover study design, the participants were given 60 mg of either a Canadian marketed batch of the generic product (Mylan-Nifedipine extended release 60 mg formerly Gen-Nifedipine extended release 60mg, Genpharm ULC) or Bayer’s once-daily nifedipine product (marketed in Canada as Adalat[®] XL[®]) either in a fed or a fasting state. Blood sampling was conducted regularly throughout the study to determine the plasma concentration of nifedipine. An in vitro dissolution test was carried out prior to the study. The in vitro dissolution

curves show a later onset and considerably lower quantity of nifedipine release from the generic nifedipine compared to Bayer's once-daily nifedipine product. These differences in the completeness of drug release were also observed in the pharmacokinetic study. The total exposure of the generic nifedipine was nearly 20 per cent lower than with Bayer's once-daily nifedipine product in the fed state and almost 10 per cent lower in the fasting state.

"It is fairly common to assume that prescription medicines that become available on a generic basis can automatically be used in place of the original product," said Shurjeel Choudhri, Head, Medical and Scientific Affairs, Bayer Inc. "These study results indicate that the generic version does not match the unique pharmacokinetic properties of Adalat[®] XL[®]. As a company, we encourage health care providers to carefully evaluate their patients who switch to this generic medication to determine if optimal results are being achieved."

While a number of previous studies have shown that several generic nifedipine products are not bioequivalent to Adalat[®] XL[®], this study is the first and only published one to compare the originator head to head with a generic nifedipine formulation based on the gastro intestinal therapeutic system (GITS) principle.

About Adalat[®] XL[®]

Adalat[®] (nifedipine) is a well-established calcium channel blocker (CCB) that has been widely used as an anti-hypertensive and anti-anginal agent for many years. The unique formulation, also known as gastro intestinal therapeutic system (GITS), means that Adalat[®] XL[®] consists of a drug reservoir surrounded by a semi-permeable membrane, which has a single precision-laser-drilled pore on the drug-reservoir side. The Adalat[®] XL[®] formulation delivers a constant plasma level of nifedipine over 24 hours, avoiding unwanted side effects that may be seen with shorter-acting agents. The clinical efficacy of Adalat[®] XL[®], including in patients with increased cardiovascular risk, has been demonstrated in a number of important clinical trials. ACTION3 extended the evidence base for Adalat[®] XL[®] established by the INSIGHT4 and the ENCORE trials.^{5,6} In addition to its blood pressure lowering effect, these studies confirmed that Adalat[®] XL[®] has vascular-protective properties that help further reduce cardiovascular risk, which translates into improved clinical outcomes. Recent research suggests that the results of studies like INSIGHT and ACTION, can only be applied to Adalat[®] XL[®] since generic long-acting formulations of nifedipine have different pharmacokinetic and pharmacodynamic properties.^{2,7,8} Adalat[®] XL[®] is also branded in some markets as Adalat[®] OROS (Oral Release Osmotic System) or Adalat[®] GITS (Gastro-Intestinal Therapeutic System).

Adalat® XL® is contraindicated in: pregnancy, during lactation, and in women of childbearing potential; in patients with severe hypotension or cardiovascular shock and in patients with hypersensitivity to Adalat® XL®. Nifedipine must not be used in combination with rifampicin because insufficient plasma levels of nifedipine may result due to enzyme induction.

In hypertension, the most common adverse events reported with Adalat® XL® were edema, which was dose-related and ranged in frequency from approximately 10 to 30% in the 30 to 120 mg dose range, headache (16.6%), fatigue (6.2%), dizziness (4.4%), constipation (3.5%) and nausea (3.5%).

In angina, the most common adverse events reported were edema (10.1%), headache (3.1%), angina pectoris (3.1%).

For complete information, please see the Product Monograph.

About Bayer Inc.

Bayer Inc. (Bayer) is a Canadian subsidiary of Bayer AG, an international research-based group with core businesses in health care, crop science and innovative materials. Headquartered in Toronto, Ontario, Bayer Inc. operates the Bayer Group's HealthCare and MaterialScience businesses in Canada. Bayer Crop Science Inc., headquartered in Calgary, Alberta operates as a separate legal entity in Canada. Together, the companies play a vital role in improving the quality of life for Canadians - producing products that fight diseases, protecting crops and animals, and developing high-performance materials for applications in numerous areas of daily life. Canadian Bayer facilities include the Toronto headquarters and offices in Montréal and Calgary.

Bayer Inc. has approximately 900 employees across Canada and had sales of \$908 million CDN in 2008. Globally, the Bayer Group had sales of over 32 billion Euro in 2008. Bayer Inc. invested approximately \$36 million CDN in research and development in 2008. Worldwide, the Bayer Group spent the equivalent of over 2.6 billion Euro in 2008 in R&D. For more information, go to www.bayer.ca.

For more information, please contact:

Laura Burns
Senior Business Communications Partner
Bayer Inc.
(416) 240-5466
laura.burns.b@bayer.com

Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

¹ Marketed in some countries as Adalat[®] OROS or Adalat[®] GITS (Gastro Intestinal Therapeutic System).

² Anshütz et al. Differences in bioavailability between 60 mg of nifedipine osmotic push-pull systems after fasted and fed administration. *International Journal of Clinical Pharmacology and Therapeutics*; Vol. 48 – No. 2/2010 (158-170): <http://www.dustri.com/nc/journals-in-english/mag/int-journal-of-clinical-pharmacology-and-therapeutics/vol/volume-48/issue/february-17.html>

³ Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004;364:849–57.

⁴ Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;356:366–72.

⁵ ENCORE I Study Group. Effect of nifedipine and cerivastatin on coronary endothelial function in patients with coronary artery disease: the ENCORE I study (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function). *Circulation* 2003;107:422–8.

⁶ Luscher T, Pieper M, Tendera M, et al. A randomized placebo-controlled study on the effect of nifedipine on coronary endothelial function and plaque formation in patients with coronary artery disease: the ENCORE II study. *Eur Heart J* 2009;30:1590–7.

⁷ Wonnemann M, Schug B, Anshütz M, et al. Comparison of two marketed nifedipine modified-release formulations: an exploratory clinical food interaction study. *Clin Ther* 2008;30:1–11.

⁸ Brown M, Toal C. Formulation of long-acting nifedipine tablets influences the heart rate and sympathetic nervous system response in hypertensive patients. *Br J Clin Pharmacol* 2008;65:646–52.