



## New analyses of phase 3 data for NicOx' naproxcinod presented at the American College of Cardiology (ACC) Annual Meeting

### Oral presentation focused on blood pressure data for naproxcinod in osteoarthritis patients taking commonly used antihypertensive therapies

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NicOx S.A. (NYSE Euronext Paris: COX) today announced that important new results on naproxcinod's blood pressure profile were presented yesterday at the American College of Cardiology (ACC) Annual Meeting in Orlando, Florida, by Professor William B. White, MD from the University of Connecticut School of Medicine, Farmington. The new analyses included detailed assessments of the systolic blood pressure (SBP) changes from baseline in the overall population and hypertensive sub-groups, in addition to statistical modeling figures that describe the probability of developing an SBP  $\geq 140$  mmHg in patients who had normal SBP when they entered the study. The presentation focused on the SBP data for naproxcinod in an important subgroup of hypertensive patients taking renin-angiotensin system (RAS) blockers.

Naproxcinod is a Cyclooxygenase-Inhibiting Nitric Oxide Donating (CINOD) anti-inflammatory agent, which completed a phase 3 clinical program in 2008 in patients with osteoarthritis (OA). The submission of a New Drug Application (NDA) to the US Food and Drug Administration (FDA) is planned for mid-2009. The objective of these analyses of the 301 phase 3 study was to assess the impact of naproxcinod 750 mg bid and 375 mg bid, as well as naproxen 500 mg bid, a widely used traditional non-steroidal anti-inflammatory drug (NSAID), and placebo on the SBP of patients with OA of the knee.

**Pascal Pfister MD, Chief Scientific Officer and Head of Research & Development at NicOx**, commented: *"The results presented yesterday by Professor White show a favorable blood pressure profile for naproxcinod in a large OA population. Given that approximately half of OA patients also have hypertension, these findings may have important clinical implications. We were very pleased that these data were accepted for an oral presentation at the prestigious American College of Cardiology annual conference."*

### Naproxcinod shows no detrimental impact on blood pressure in a sub-group of hypertensive patients taking RAS blockers

Traditional NSAIDs and COX-2 selective inhibitors have been shown to destabilize systolic blood pressure control in patients on RAS blockers, with increases of 3 to 8 mmHg being reported in the literature. RAS blockers comprise a number of antihypertensive classes that target the renin-angiotensin system: Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin-II Receptor Blockers (ARBs) and direct Renin Inhibitors. Together, these drugs represented more than 50% of the antihypertensive sales in the seven major pharmaceutical markets in 2007 [Datamonitor 2008].

In the patients with controlled hypertension who were treated with RAS blockers, naproxcinod 750 mg bid showed a mean reduction in SBP of 5.0 mmHg from baseline at week-13, while naproxen 500 mg bid showed an increase of 1.5 mmHg, resulting in a statistically significant difference of 6.5 mmHg in favor of naproxcinod ( $p < 0.02$ , *post hoc* analysis). Likewise, the SBP reduction from baseline was 2.7 mmHg in the naproxcinod 375 mg group and 4.6 mmHg in the placebo group.

### Categorized SBP changes of individual patients from baseline

Dr. White also presented bar graphs which categorize the SBP changes in individual patients from baseline. These showed the proportion of patients who developed an increase or decrease in SBP of between 0 and 10 mmHg, of between 10 and 20 mmHg and exceeding 20 mmHg, for each treatment group in the overall population and hypertensive sub-groups. In the abstract it was disclosed that in the hypertensive population, 23.3% of the patients receiving naproxen saw their SBP increased by 10 mmHg or more over the 13 weeks of the study. The percentage of hypertensive patients experiencing an increase of SBP  $\geq 10$  mmHg was significantly lower in the naproxcinod 750 mg group (11.5%,  $p < 0.04$  vs. naproxen, *post hoc* analysis). This proportion was 16.0% for the 375 mg dose and 15.3% in the placebo group.

## Probability of developing an SBP $\geq$ 140 mmHg

In addition, statistical modeling figures were presented, which describe the probability of the different treatments leading to an SBP  $\geq$ 140 mmHg in patients with normal or borderline SBP at baseline (SBP <140 mmHg), showing that the probability of becoming uncontrolled was lowest for both doses of naproxcinod.

**William B. White MD, Professor of Medicine and Chief, Division of Hypertension and Clinical Pharmacology in the Cardiology Center at the University of Connecticut School of Medicine, Farmington,** stated: "*The increase in blood pressure seen in OA patients receiving NSAID treatment is believed to be partly due to the indirect inhibition of the vasodilator prostacyclin. The sustained release of nitric oxide from naproxcinod may prevent the induction of blood pressure increase in both normotensive and hypertensive patients and this effect may be particularly useful in patients taking renin-angiotensin blocking agents. The impressive results seen in the RAS blocker subgroup support the notion that RAS blocking agents may depend in part on vascular prostacyclin and nitric oxide for their mechanism of action.*"

William B. White MD is a consultant to NicOx who has provided advice on clinical study design. He was the principal investigator of the 112 study for naproxcinod.

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**NicOx (Bloomberg: COX:FP, Reuters: NCOX.PA)** is a product-driven biopharmaceutical company dedicated to the development and future commercialization of investigational drugs for unmet medical needs. NicOx is applying its proprietary nitric oxide-donating technology to develop an internal portfolio of New Chemical Entities (NCEs) in the therapeutic areas of inflammatory and cardio-metabolic disease.

Resources are focused on the development and pre-commercialization activities for naproxcinod, a proprietary NCE and a Cyclooxygenase-Inhibiting Nitric Oxide-Donating (CINOD) anti-inflammatory agent for the treatment of the signs and symptoms of osteoarthritis. Naproxcinod has completed three pivotal phase 3 studies with positive results and the submission of a New Drug Application (NDA) to the US Food and Drug Administration (FDA) is projected for mid-2009.

Beyond naproxcinod, NicOx has a pipeline containing multiple nitric oxide-donating NCEs, which are in development internally and with partners, including Pfizer Inc and Merck & Co., Inc., for the treatment of prevalent and underserved diseases, such as atherosclerosis, hypertension and widespread eye diseases and respiratory conditions.

NicOx S.A. is headquartered in France and is listed on the NYSE Euronext Paris (Compartment B: Mid Caps).



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*This press release contains certain forward-looking statements. Although the Company believes its expectations are based on reasonable assumptions, these forward-looking statements are subject to numerous risks and uncertainties, which could cause actual results to differ materially from those anticipated in the forward-looking statements.*

*For a discussion of risks and uncertainties which could cause actual results, financial condition, performance or achievements of NicOx S.A. to differ from those contained in the forward-looking statements, please refer to the Risk Factors ("Facteurs de Risque") section of the Document de Reference filed with the AMF, which is available on the AMF website (<http://www.amf-france.org>) or on NicOx S.A.'s website (<http://www.nicox.com>).*

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