**Press release**

# Positive Top-line Results from Two Phase 3 Clinical Trials that Assessed Zubsolv® (buprenorphine/naloxone CIII sublingual tablet) for Induction of Buprenorphine Maintenance Therapy

**Uppsala, Sweden – June 23, 2014** – Orexo AB (publ) announces the results of two clinical trials assessing Zubsolv for induction of buprenorphine maintenance therapy in patients with opioid dependence. Combined data from the Induction, STabilization, Adherence and Retention Trial (ISTART) (Study OX219-006) and Study OX219-007, in 1068 opioid dependent patients, showed that over 90% of patients treated with Zubsolv were retained in treatment at Day 3 using a 30% lower dose of buprenorphine. The two studies had similar structure during the three-day induction phase to enable a combined analysis of the induction results, with the ISTART being the most important contributing with 70% of the patients. These results enable Orexo to pursue a regulatory submission of an expanded label of Zubsolv to include initiation of treatment in the US.

Nikolaj Sorensen, Chief Executive Officer of Orexo, noted "We know a main barrier for DATA2000 certified physicians to start treating opioid dependent patients, is perceived difficulties in the initiation phase of treatment. With an expanded label Orexo can take an active role to encourage and educate the certified, but not active, prescribers in initiation of treatment and improve access to treatment for patients suffering from opioid dependence"

An analysis of the combined data from the ISTART and OX219-007 studies found no difference when comparing Zubsolv and generic buprenorphine monotherapy when used as treatment for the induction of buprenorphine maintenance therapy. In the combined per protocol set, 92.3% (422/457) of patients in the Zubsolv group were retained in treatment at Day 3 compared to 93.4% (424/454) of patients receiving generic buprenorphine (p=0.54). Similar results were observed in the combined full analysis set where 90.9% (489/538) of patients in the Zubsolv group were retained at Day 3 compared to 92.6% (491/530) generic buprenorphine group (p=0.30).

"These results support that Zubsolv is effective as an induction treatment for patients entering recovery from opioid dependence," said Michael Sumner, Chief Medical Officer of Orexo. "These two studies represented the largest clinical trial program ever conducted with buprenorphine in addiction medicine. When you look at the combined results, over 90% of patients were retained during the induction phase and patients demonstrated a clinical response to treatment that continued to the end of the study. These studies also establish that precipitated withdrawal is not a common occurrence in patients treated with Zubsolv as an induction therapy."

The co-primary endpoint of the large ISTART trial (758 patients) compared retention in treatment at Day 3 in patients receiving Zubsolv and generic buprenorphine monotherapy. There were no differences in retention at Day 3 in the per-protocol [Zubsolv arm: 93.3% (309/329); generic

buprenorphine arm: 92.6% (302/326); p=0.512] or full analysis set [Zubsolv arm: 93.2% (357/383); generic buprenorphine arm: 91.7% (344/375); p=0.440]. Clinically and statistically significant improvements were observed in Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), and opioid cravings VAS (Visual Analogue Scale) total scores.

In the smaller study OX219-007 (310 patients) Zubsolv was assessed for induction of buprenorphine maintenance therapy compared to generic buprenorphine monotherapy. In the per-protocol set, 91.8% (235/256) of patients were retained at Day 3 [generic buprenorphine group: 95.3% (122/128); Zubsolv group: 88.3% (113/128); p=0.040]. In the full analysis set, 90.0% (279/310) of patients were retained at Day 3 [generic buprenorphine group: 94.8% (147/155) Zubsolv group: 85.2% (132/155); p=0.005]. Clinically and statistically significant improvements were seen from baseline throughout the study on COWS, SOWS, and Craving VAS scores for patients in both randomized groups. In addition, improvements in these scores during the blinded phase demonstrated no clinical difference between products. Overall, Zubsolv exhibited a solid safety profile and was well-tolerated in the majority of patients. No significant differences were observed between the safety profiles of Zubsolv and generic buprenorphine during blinded induction phase.

Nikolaj Sorensen, Chief Executive Officer of Orexo, noted, “I am very satisfied with the positive combined data which encourages Orexo to continue to invest in advancing the treatment of opioid dependence. These studies show that Zubsolv is effective, but more importantly than that, Zubsolv is as effective as buprenorphine monotherapy but with almost 30% less medication during the induction phase. Strengthened by this, we will now continue to analyze the entire study results and initiate a regulatory submission path for an induction label for Zubsolv to create a clear differentiation from the generic alternatives available in the market”.

**For further information, please contact:**
Nikolaj Sorensen, President and CEO
Tel: +46 (0)703-50 78 88, E-mail: **ir@orexo.com**

**About the ISTART Trial**

The ISTART (Induction, STabilization, Adherence and Retention) Trial (Study OX219-006) was a randomized, non-inferiority, multicenter study to assess early treatment efficacy of Zubsolv versus generic buprenorphine monotherapy for induction and versus SUBOXONE® film of opioid maintenance therapy to explore switching between treatments. The primary endpoints were retention in treatment at Day 15 and Day 3. Secondary efficacy assessments included scores on the COWS and SOWS, opioid cravings VAS, and switching between Zubsolv and Suboxone film. Seven hundred and fifty eight opioid dependent, adult subjects were randomized. On days 1 and 2, patients received a blinded, fixed dose of Zubsolv (5.7/1.4 mg and 5.7/1.4 or 11.4/2.8 mg, respectively) or generic buprenorphine monotherapy (8 mg and 8 or 16 mg, respectively). On Day 3, the patients on generic buprenorphine were switched to Suboxone film and

patients in the Zubsolv arm continued to receive Zubsolv. Stabilization doses were titrated to a maximum daily dose of 17.1/4.2 mg and 24/6 mg for Zubsolv and Suboxone, respectively, based upon clinical symptoms. The ISTART study is still being analysed and results from remaining end-points will be shared when finalized.

**About Study 007**

Study OX-219-007 was a prospective, randomized, multicenter, blinded, parallel-group, active-controlled study comparing advanced formulation Zubsolv versus generic buprenorphine monotherapy for induction of opioid maintenance therapy. Three hundred and ten opioid dependent, adult subjects were randomized. On days 1 and 2, patients received a blinded, fixed dose of Zubsolv (5.7/1.4 mg and 5.7/1.4 or 11.4/2.8 mg, respectively) or buprenorphine (8 mg and 8 or 16 mg, respectively). On day 3, all patients received open-label Zubsolv (5.7/1.4 or 11.4/2.8 mg). The primary objective was to demonstrate that induction directly on Zubsolv is non-inferior to induction on buprenorphine monotherapy with regard to retention in treatment. The primary endpoint was retention in treatment at Day 3. Secondary efficacy assessments included scores on the COWS, SOWS, and opioid cravings VAS.

**About Orexo AB**

Orexo is a specialty pharma company with commercial operations in the United States and R&D in Sweden developing improved treatments using proprietary drug delivery technology and commercial operations in the United States. The company is commercializing its proprietary product, Zubsolv®, for maintenance treatment of opioid dependence, in the United States. Zubsolv is a novel formulation of buprenorphine and naloxone using Orexo's extensive knowledge in sublingual technologies. Orexo has a portfolio of two approved and revenue generating products currently marketed under license in the EU and US. Orexo AB, with its headquarters in Sweden, is listed on NASDAQ OMX Stockholm Exchange and its American Depositary Receipts (ADRs) trade on the OTCQX marketplace in the U.S. under the symbol, "ORXOY". The largest shareholders are Novo A/S and HealthCap.

For information about Orexo, please visit **www.orexo.com.**

**About Zubsolv®**

Zubsolv (buprenorphine and naloxone) sublingual tablet (CIII) is indicated for the maintenance treatment of opioid dependence and should be used as part of a comprehensive treatment plan, which includes counseling and psychosocial support. Treatment should be initiated under the direction of physicians who are certified under the Drug Addiction Treatment Act of 2000, and who have been assigned a unique identification number ("X" number).

Zubsolv sublingual tablets can be abused in a manner similar to other opioids, legal or illicit. Clinical monitoring appropriate to the patient's level of stability is essential. Liver function tests should be monitored before and during treatment. Children who take Zubsolv sublingual tablets can have severe, possibly fatal, respiratory depression. Emergency medical care is critical. Keep Zubsolv sublingual tablets out of the sight and reach of children.

Adverse events commonly observed with the sublingual administration of buprenorphine/naloxone sublingual tablets during clinical trials and post-marketing experience are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain and peripheral edema.

Further information on Zubsolv can be found at **www.zubsolv.com**.

Suboxone is a registered trademark of Reckitt Benckiser Healthcare (UK) Ltd.

*Orexo AB (publ) discloses the information provided herein pursuant to the Financial Instruments Trading Act and/or the Securities Markets Act. The information was submitted for publication at 08:30am CET on June 23, 2014.*