MESSAGE FROM
Nikolaj Sörensen, CEO of Orexo AB

Let me take this opportunity to introduce you to Orexo, which I recognize as a new company to many of you. Orexo US, Inc. is a specialty pharmaceutical company fully dedicated to the science and treatment of opioid dependence. Orexo is a publicly traded company (Nasdaq OMX: ORX or US OTC Market: ORXOY (ADR)) with the largest shareholder being Novo AS.

At Orexo, we have identified opioid addiction as one of the areas with the largest unmet medical need today. My vision for Orexo is that we will be recognized as a leader in the field of addiction medicine. I believe investments in research and partnering with patients and physicians will be key to ensuring we can intervene earlier in the devastating cycle of opioid dependency to enable improved treatments and help patients with addiction restore their lives. To that end, I am excited to introduce the first edition of Resolv – The Orexo Healthcare Professional Newsletter.

The aim of this newsletter is to share the latest clinical updates from Orexo on the treatment of addiction and highlight resources available for you and your patients.

With our launch of ZUBSOLV sublingual tablet (CIII) for the maintenance treatment of opioid dependence in September 2013, we offered physicians and patients a new medication option for opioid dependence that addressed concerns such as slow dissolve time and poor taste.

ZUBSOLV, developed using Orexo’s advanced proprietary sublingual formulation technology, addresses these concerns to provide you and your patients with a meaningful choice. However, ZUBSOLV is just a first small step to enable patients to gain control of their opioid addiction. My commitment to this disease area is to continue to invest in further advances to benefit patients and physicians.

I recognize that addiction medicine has not been a focus of the pharmaceutical industry, and that limited investments have been made in the continued clinical development of treatments for opioid dependence, even by those active in this disease area today. Orexo is striving to change this. While the US Food and Drug Administration approval of ZUBSOLV was an integral part of advancing treatment, it was only the first step. Successful treatment of opioid dependence goes “beyond the tablet,” and we will continue to identify opportunities to support patients suffering with addiction and the physicians who treat them. To this end, we have 3 ongoing clinical programs involving more than 1,100 patients, demonstrating our dedication and continued investment in enhancing and improving the treatment of opioid dependence.

I am convinced additional choice and competition between companies to develop new and improved treatments will benefit patients and physicians in terms of reasonable prices. I am looking forward to working with you to break the destructive cycle of the opioid dependence epidemic and to enable a better and brighter future for patients suffering from this devastating disease.

About ZUBSOLV® (buprenorphine and naloxone) Sublingual Tablet (CIII)

- An advanced formulation for the maintenance treatment of opioid dependence
- Contains the same active components and has comparable efficacy and safety as other approved buprenorphine/naloxone sublingual formulations
- Offers unique advantages specifically designed to meet the needs of your patients

- In two open-label, crossover studies in healthy volunteers, ZUBSOLV demonstrated:
  - Preferred menthol flavor
    - Significantly more healthy volunteers preferred the taste of ZUBSOLV sublingual tablets over Suboxone® sublingual film or tablets (P < 0.0001)
  - Fast dissolve time
    - ZUBSOLV tablets dissolved within minutes
  - Higher bioavailability
    - ZUBSOLV contains 30% less buprenorphine than other buprenorphine-containing sublingual tablets, but achieves similar systemic exposure

- Switching to ZUBSOLV
  - ZUBSOLV 5.7 mg buprenorphine/1.4 mg naloxone is bioequivalent to Suboxone 8 mg buprenorphine/2 mg naloxone

- Dosing adjustments may be necessary for patients being switched between buprenorphine/naloxone products

- The packaging of ZUBSOLV tablets is specifically designed to reduce unintended pediatric exposure and medication diversion
  - Each individually sealed unit-dose blister pack meets the highest child resistance criteria
  - Each package is serialized with unique coding to facilitate medication counts and is intended to reduce diversion

FOR MORE INFORMATION, PLEASE VISIT WWW.ZUBSOLV.COM.

Indication
ZUBSOLV (buprenorphine and naloxone) sublingual tablet (CIII) is a partial opioid agonist indicated for the maintenance treatment of opioid dependence and should be used as part of a comprehensive treatment plan to include 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).

Contraindications
ZUBSOLV should not be used by patients hypersensitive to buprenorphine or naloxone, as serious adverse reactions, including anaphylactic shock, have been reported.

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On behalf of Orexo US, Inc., I would like to express our appreciation for your dedication to the treatment of opioid dependence and thank you for making a difference.

In my role as President of Orexo US, Inc., I have had the opportunity to meet and talk to both the physicians who treat addiction and the patients under their care. When interacting with patients, I saw first-hand the impact this disease has on every facet of their lives. I have heard heartbreaking stories about relationships destroyed, jobs lost, and the lengths people go to satisfy their addiction. I have also heard from patients who, despite wanting treatment, cannot find the care they need. Alternatively, I have also heard the stories of success and redemption from patients overcoming addiction and rebuilding their lives – patients who may struggle to stay in treatment, but continue to persevere. The common thread in these stories is the commitment of physicians like you.

You may already be familiar with Orexo and ZUBSOLV, but allow me a reintroduction. Our goal at Orexo is to mirror the commitment to your patients that you have shown. Orexo exists for one reason – to help patients with opioid dependence lead better lives. Every member of the Orexo team knows their priorities are 1) to support patients struggling with addiction and the physicians who treat them by providing resources to aid treatment, and 2) to invest in research to advance the understanding of opioid dependence and its treatment.

Orexo has a long-term commitment to retaining and growing a valued partnership with the addiction medicine community. Our current objective is to improve existing treatment, but in the longer-term we have a vision of changing the treatment paradigm with earlier intervention for patients at risk of developing opioid dependence. We want to partner with you to help realize that vision.

The entire Orexo organization, in partnership with the addiction medicine community, is committed to addressing the long-term challenges associated with opioid dependency, and collectively celebrating successes as we advance the treatment paradigm moving forward. To that end, we encourage you to reach out to us directly to comment or discuss any questions, insights, or concerns you wish to share.

Thank you,

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Helping Patients Gain Access to ZUBSOLV

We know that patients struggle to continue treatment and pay for their medication. To help remedy these issues, Orexo is proud to offer the following resources:

- The RISE™ program is an online patient support resource that was developed with the help of people with opioid dependence, and was designed to meet the needs of patients and their support network. RISE offers continuous access to information and resources throughout the recovery process that is strictly confidential and in accordance with HIPAA guidelines. For more information, please visit http://www.zubsolv.com/healthcare-professionals/risetm/.
- Because Orexo is committed to helping patients gain access to the treatment they need, the ZUBSOLV Patient Savings Program is available to help lower patients’ out-of-pocket costs. These cards are accessible at www.ZUBSOLV.com.
- We have successfully expanded access to ZUBSOLV with both public and private payers. We will continue these efforts to ensure ZUBSOLV is covered on as many plans as possible with a reasonable co-pay.

With each of these programs, we aim to minimize medication costs as a barrier to the treatment your patients need.

Putting Families First—Unintended Pediatric Exposure

A serious concern with buprenorphine treatment is the possibility of unintended pediatric exposure. Just one dose of buprenorphine can cause fatal respiratory depression in children who are accidentally exposed to the medication.

During the development of ZUBSOLV, we wanted to ensure that we did everything possible to help reduce the risk of accidental pediatric exposure. To help achieve that goal, we package ZUBSOLV in F1 child-resistant, unit-dose blister packaging. F1 represents the most stringent testing criteria for child-resistant packaging.

However, we know that packaging alone, even with improvements in design, is not sufficient to completely mitigate this risk. Doctors and other healthcare providers need to play a key role.

For patients with children, consider prescribing buprenorphine medications that utilize child-resistant and unit-dose packaging. In addition, counsel patients to store medications safely out of the sight and reach of children and destroy any unused medication appropriately.

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Opioid dependence is an epidemic and a major public health issue in the United States and worldwide. I am proud to be part of a company that strives to provide solutions for these issues. While the treatment of opioid dependence has continued to improve, questions remain regarding the disease and its management. As a part of our commitment to you and your patients, we will continue efforts to advance the treatment of opioid-dependent patients.

To date, Orexo has invested over $50 million in clinical programs of patients with opioid dependence. Orexo has initiated 3 clinical studies which will include more than 1,000 patients at more than 50 clinical sites across the United States. Ongoing Orexo-sponsored studies include a phase 3, randomized, non-inferiority study, which was designed to assess treatment efficacy and patient adherence with ZUBSOLV versus Suboxone film, and a 24-week follow-up study, which was designed to assess long-term safety and efficacy of ZUBSOLV. Please visit the following links for more information:

https://clinicaltrials.gov/ct2/show/NCT01908842
https://clinicaltrials.gov/ct2/show/NCT01903005

In addition to generating clinical trial data on ZUBSOLV, Orexo supports independent research through our Investigator Sponsored Trials (IST) program. The goal of the IST program is to fund physician-led research that progresses the understanding of the science of opioid dependence. We have also supported non-product educational roundtable meetings, which provide the opportunity for addiction practitioners to discuss clinical issues related to the use of buprenorphine for opioid use disorder. The forum is an opportunity for experts in the field of opioid dependence and community practitioners to gather and share experiences. There is no formal presentation – each roundtable has a chairperson responsible for facilitating the discussion. Topics commonly discussed include patient management challenges, role of urine drug screens, prevention of abuse, misuse, and diversion, and optimal dosing.

As a demonstration of our long-term commitment, Orexo will continue to invest a sizeable portion of revenues to improving the treatment of patients with opioid dependence and identifying other opportunities to help patients coping with addiction.

DIVERSION OF BUPRENORPHINE
A Public Safety Issue

Orexo designed ZUBSOLV with attributes that may help to deter diversion and misuse.

- ZUBSOLV provides equivalent systemic exposure with approximately 30% less buprenorphine compared with Suboxone when taken sublingually.
  - While sublingual administration yields similar blood levels, patients who abuse the medication via intravenous injection (which allows 100% bioavailability) will be exposed to 30% less buprenorphine.

In addition, ZUBSOLV is packaged in serialized unit doses that can be easily recorded in physicians’ offices to facilitate medication counts.

- ZUBSOLV 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. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits.
- ZUBSOLV can cause serious, life-threatening, respiratory depression and death, particularly when taken by the intravenous route in combination with benzodiazepines or other central nervous system (CNS) depressants (eg, sedatives, tranquilizers, or alcohol). Patients should be warned against self-administration or misuse of these combinations.

Please see additional Important Safety Information on back and accompanying full Prescribing Information and Medication Guide.
IMPORTANT SAFETY INFORMATION FOR ZUBSOLV

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• Dose reduction of CNS depressants, ZUBSOLV, or both should be considered in situations of concomitant prescription.

• Children who take ZUBSOLV can experience severe, possibly fatal, respiratory depression.

• Intravenous misuse or taking ZUBSOLV before the effects of full-agonist opioids (eg, heroin, hydrocodone, methadone, morphine, oxycodone) have subsided is likely to cause opioid withdrawal syndrome.

• Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy.

• ZUBSOLV should not be used as an analgesic. There have been reported deaths of opioid-naïve individuals who received a 2-mg sublingual dose of buprenorphine.

• For more important safety information, please visit www.ZUBSOLV.com.

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Use in Specific Populations
The use of ZUBSOLV sublingual tablets in pregnant women or during breastfeeding should only be considered if the potential benefit justifies the potential risk. Buprenorphine passes into breast milk. The safety of buprenorphine/naloxone in breastfeeding has not been established.

Adverse Reactions
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.

This is not a complete list of potential adverse events associated with buprenorphine/naloxone sublingual tablets. Please see full Prescribing Information for a complete list: http://www.zubsolv.com/pdf/zubsolvFullPI-patient.pdf#1

To report an adverse event associated with taking ZUBSOLV sublingual tablet, please call 1-877-ZUBSOLV (1-877-982-7658). You are encouraged to report adverse events of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

REFERENCE